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ZOONOSIS

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PREFACE

The well-being of humans and animals is pretty much interdependent. It's impossible to ensure human health, without considering animal health and vice versa.

The need to enhance the collaboration between animal health workers and medical professionals, researchers and academicians has moved the editors to develop this publication. The book takes into account the major threats of animal and human health. This book provides the core concepts of Zoonosis with a critical focus on the key challenges and their effective management. The objective is to cover epidemiological interactions of various infectious diseases and their ecological implications as an emerging threat.

It is anticipated that this book would be of great use to a variety of readers. University students, graduates, practitioners, animal healthcare providers and health professionals would definitely find this book of great importance. The language of book has been intentionally kept easier for a non-technical person to grasp the concepts on interdependence of animal and human health. The editors wish to publish a series on the subject keeping in view the urgency to highlight these areas for awareness, research and development.

Editors

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Influenza: Importance on Public Health and in other Species

01

Catalina Tufiño-Loza[1], Fernando Diosdado-Vargas[2] and Luis Gómez-Núñez[2*]

ABSTRACT

Influenza is a highly contagious disease that causes various outbreaks in different regions as a result of the interaction between humans and reservoirs. Due to its zoonotic and pandemic potential, this chapter reviews the importance of the disease in public health and in other species. We begin with understanding key aspects of its biology, genetic characteristics, structural and non-structural proteins, antigenic shifts and antigenic drift. Likewise, the ability of the virus to cross the barrier between species, its adaptation to the host and the migration and interaction of wild migratory waterfowl, as a natural reservoir of almost all subtypes of influenza type A, its dissemination, transmission and establishment will be addressed, in domestic birds and mammals. Subsequently, the emerging and re-emerging subtypes and lineages that caused outbreaks with different degrees of severity throughout human history are described. Finally, we summarize the diagnostic techniques applied, as well as the prevention and control measures. Although a century has passed after the most serious influenza pandemic, this disease continues to cause high rates of morbidity and mortality, mainly seasonally, and vaccination remains the most effective measure to control and prevent it. There is currently a global epidemiological surveillance system dedicated to the identification and characterization of the various antigenic variants circulating in different regions of the world. Therefore, it is important to continue monitoring its evolution and distribution, in addition to continuing to generate new diagnostic tools that, together with existing ones, lead us to a better determination of effective virus control strategies in human and animal populations.

Keywords: Influenza virus, public Health, surveillance, zoonotic, pandemic, reservoirs

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1. INTRODUCTION

Every day, the World Health Organization (WHO) and the World Organization for Animal Health (OIE-WOAH) report outbreaks of this disease in different regions. As a result of the interrelation between humans and reservoirs, it has given rise to the appearance of new subtypes and lineages, genetically and antigenically different from each other, which cause conditions in different degrees of severity depending on the host. Due to its zoonotic and pandemic potential recorded throughout history, society and governments from different countries have joined efforts to understand the infection dynamics of this disease.

2. INFLUENZA VIRUS OVERVIEW

The influenza virus is made up of four types, A, B, C and D. Type A influenza viruses (AIV, *Alphainfluenzavirus*) cause the greatest number of infections in humans and animals each year and have the potential to generate subtypes with pandemic potential. Types B and C (*Betainfluenzavirus* and *Gammainfluenzavirus*) mainly affect humans, although type C circulation has been reported in pigs and type D (*Deltainfluenzavirus*) also affects cattle, pigs, goats, and sheep (Long et al. 2019; Kuchipudi and Nissly 2018). These viruses belong to the family *Orthomixoviridae*, they can have a spherical or pleomorphic shape (~80-100 nm), they have a lipid envelope and their genome is made up of 8 segments of single-stranded RNA of negative polarity, which code for 10-17 proteins. Types C and D express 9 seven-segment proteins (Szewczyk et al. 2014; Hao et al. 2020; Skelton and Huber 2022). The complete genome contains about 14,000 nucleotides (Szewczyk et al. 2014). Each segment contains at least one open reading frame (ORF) that expresses a protein, and some segments may encode accessory proteins. Their names and functions are listed below in Table 1.

Two genes encode the viral envelope proteins haemagglutinin (HA) and neuraminidase (NA), which play crucial roles in the interaction between the virus and cellular receptors (Kuchipudi et al. 2021). Eighteen different antigenic subtypes of HA and eleven subtypes of NA have been described in the AIV. Each influenza virus contains, in any combination, only one HA subtype (H1-H18) and only one NA subtype (N1-N11), which can lead to a large number of possible subtypes, almost all of which are found in wild waterfowl, with the exception of subtypes H17N10 and H18N11 which have only been identified in bats (Tong et al. 2012; Tong et al. 2013; Kuchipudi et al. 2014; Puryear et al. 2016). The recognition of sialic acid receptor molecules on the surface of the host cell through the HA glycoprotein, leads to the initiation of the infection cycle with receptor-mediated endocytosis of the virus for the formation of an endosome, where the decrease of pH changes the structure of the HA and allows the fusion of the viral envelope and the endosome membrane, leading to the release of the viral segments into the cytosol (Dou et al. 2018). The viral segments are transported to the cell nucleus where their replication and transcription take place. Subsequently, the messenger RNAs (mRNA) are transported to the ribosomes to initiate the synthesis of viral proteins and form new vRNPs, as well as the proteins that make up the virus envelope and allow the generation of new viral progeny (Szewczyk et al. 2014; Zhu et al. 2022). Although AIVs lack the molecular mechanisms to repair errors that occur during their replication, this feature has allowed them to adapt genetically and antigenically, so that the existing strain can be replaced by a new variant. These continuous and permanent genetic changes are known as "drift" or "antigenic drift" (Webster and Govorkova 2014). Another feature of these viruses, which is of public concern, is their ability to exchange genetic material by recombination. This exchange process, known as "antigenic changes" or "shift", results in a new subtype different from that of both parent viruses. Due to this situation, the host lacks immunity to the new subtype and there is no vaccine that can confer protection. Historically, antigenic shift has resulted in highly fatal pandemics. For this to happen, the new subtype needs to have genes from influenza viruses of human origin that would make the infection easily

transmissible from person to person for a sustainable period of time (Webster and Hulse 2004; Webster and Govorkova 2014). The study of these pandemics has been of great interest; however, it is still not possible to predict those (Saunders-Hastings and Krewski 2016). Another key characteristic of influenza viruses that allows them to expand their genetic diversity is their ability to replicate in non-natural hosts, where the generation of these new variants that can reach pandemic potential can occur (Poole et al. 2014). For this, sialic acid (SA) receptors in the host cell play an important role in the evolution of these viruses. As previously mentioned, through the recognition of these receptors by the HA the infection cycle begins, and the differences in the structure of these glycoconjugates between species will determine the species-specific susceptibility to infection of the influenza virus (Kuchipudi et al. 2009; Long et al. 2019). AIV of avian origin bind preferentially to SAα2,3-Gal receptors, whereas viruses of human and porcine origin show preference to SAα2,6-Gal receptors. Therefore, those species that express both types of receptors, SAα2,3-Gal and SAα2,6-Gal, can be "mixing vessels" in which recombination of different subtypes of the AIV can occur (Kuchipudi et al. 2009; Nelli et al. 2010).

Table 1: Genes and proteins of influenza viruses.

Segment	Protein	Viral function
1	PB2[1]	RNA-dependent RNA polymerase complex (RDRP)
2	PB1[1]	RDRP complex
	PB1-F2[2,3]	Regulation of the immune response, apoptosis
	PB1-N-40[2,3]	Regulates expression of the PB1 protein
3	PA[1]	RDRP complex
	PA-X[2,3]	Degradation of messenger RNA, facilitates viral expression, and regulates the immune response
	PA-N155[2,3]	Unknown functions
	PA-N182[2,3]	Unknown functions
	P3[4]	RDRP complex
4	HA[1]	Recognition of host receptors and membrane fusion
	HEF[4]	Recognition of host receptors and membrane fusion, facilitates virion release and esterase activity
5	NP[1]	Packaging of the viral genome and assembly with the RDRP
6	NA[1]	Neuraminidase, facilitates the release of virions from the host cell
	NB[5]	Unknown function
	M1[4]	Packaging of the viral genome and assembly with the RDRP
	M2[4]	Ion channel, facilitates the release of virions
7	M1[3,5]	Packaging of the viral genome and assembly with the RDRP
	M2[3,5]	Forms the ion channel, facilitates the release of virions
	M42[1]	Forms the ion channel
	NS1[4]	Immune response evasion, interferon antagonist
	NS2[4]	Nuclear export protein for the synthesis of vRNPs
8	NS1[3,5]	Immune response evasion, interferon antagonist
	NS2/NEP[3,5]	Nuclear export protein for the synthesis of vRNPs

1: present in all four types of influenza viruses: A, B, C and D; 2: accessory protein; 3: present only in type A influenza viruses; 4: present only in influenza viruses type C and D; 5: present only in type B influenza viruses; 6: vRNPs: viral Ribonucleoprotein Complex

3. HOSTS

Wild migratory waterfowl such as ducks (*Anseriformes*), geese (*Passeriformes*), gulls and swallows (*Charadriformes*) are identified as the natural reservoir of almost all identified AIV subtypes, with the exception of bats, which are also natural reservoirs of some subtypes (García and Ramos 2006). This, together with the ability of the virus to cross the inter-species barrier, its adaptation to the host, and the

migration and interaction of these birds with other species, has favored its dissemination, transmission and establishment in domestic birds and land mammals, such as the human, pigs, horses, cattle, dogs, cats, and marine mammals, such as seals and whales, creating host-specific lineages in birds, humans, pigs and horses (Cauldwell et al. 2014; Kessler et al. 2021).

3.1. POULTRY

Avian influenza viruses (aAIV) cause serious economic losses in poultry. According to the severity in the clinical presentation of the virus, strains with two forms of presentation have been identified, in low pathogenicity viruses (LPAIVs) a mild clinical picture is observed, compared to highly pathogenicity viruses (HPAIVs), that result in death in two or three days, due to the severity of the clinical picture (Jeong et al. 2009). This will depend on the species, type of bird, and age, as well as the various environmental conditions in which they occur. Clinical signs caused by HPAIVs can range from sudden death with no obvious clinical signs to variable clinical presentations, including respiratory signs, such as ocular and nasal discharge, cough, dyspnea, decreased vocalization, marked reduction in food intake and water, cyanosis of the skin devoid of feathers, wattles and comb, incoordination and diarrhea (Swayne et al. 2020). High morbidity is usually accompanied by inexplicably high and rapidly increasing mortality. The LPAIVs viral strains commonly affect chickens, turkeys, and other birds of economic importance, and are associated with the H5 and H7 subtypes, causing respiratory diseases, reducing egg production, and low mortality (Cox et al. 2017; WOAH, 2022). Low virulence viruses can mutate to highly virulent strains after circulating for (sometimes short) periods in a poultry population. For example, during a 1983-1984 epizootic in the United States of America, the H5N2 virus initially caused low mortality, but within six months it became highly virulent, with approximately 90% mortality. Control of the outbreak required the destruction of more than 17 million birds at an approximate cost of $65 million dollars. In Italy (1999-2001) due to the H7N1 virus initially had low virulence and later transformed into a highly virulent form within 9 months. More than 13 million birds died or were culled (Monne et al. 2014). aAIVs are also a concern for public health due to the fact that sporadic cases have been identified in the human population, mainly of the H5, H7 and H9 subtypes, as well as the generation of possible pandemics in the event of additional mutations that favor sustained person-to-person transmission, such as the infection caused by an Eurasian lineage HPAI H5N1 with a case fatality rate greater than 50% (Nelli et al. 2012; Cox et al. 2017).

3.2. PIGS

Currently, the disease is widely distributed in all pig-producing countries, where China is the world leader (Borkenhagen et al. 2019). The H1N1, H1N2 and H3N2 subtypes of influenza viruses are the most frequently reported worldwide, with H1N1 being the most widely disseminated (Zell et al. 2013). However, the origins and the genetic and antigenic characteristics of these viruses differ depending on the continent or region in which they are isolated, due to both the phenomenon of recombination and genetic drift (Nelson and Vincent 2015). These differences are especially evident in the case of the H1N1 subtype, the virus present in America (classical swine) originated directly from the H1N1 that caused the "Spanish influenza" of the year 1918 (Kessler et al. 2021), while the Eurasian H1N1 has an avian origin and was first isolated in the late 1970s in Italy. Both viruses have different genetic and antigenic characteristics (Van Reeth and Vincent 2019). In the case of the H3N2 subtype, it is a triple recombinant that is characterized by containing the genes that code for HA and NA of human origin, while the genes belonging to the internal viral proteins are of avian origin in the European strain (Ruiz-Fons 2017), and are of avian and porcine origin in the case of the North American subtype (Nelson and Vincent 2015). Finally, the H1N2 subtype, isolated in Europe in 1994 (Brown et al. 1995),

is a recombinant that contains all the genes of porcine H3N2 with the exception of the HA gene, which comes from an H1N1 of human origin. However, in some countries, H1N2 has been detected with HA of avian origin, as is the case in Denmark and France (Hjulsager et al. 2006; Kyriakis et al. 2011). Other influenza virus subtypes have also been isolated, although less frequently and have not become widely established in the swine population. These include the H1N7, H4N6, H3N3 and H3N1 subtypes (Brown et al. 1994; Karasin et al. 2000, 2004; Lekcharoensuk et al. 2006). The swine influenza virus has been found primarily in pigs, but has also been found in humans, turkeys, ducks and dogs (Ma et al. 2015, 2017). It has been associated with the 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 2009 (H1N1) pandemics (Easterday, 2003; Crosby, 2003; Krueger and Gray, 2012; Mena et al. 2016; Taubenberger et al. 2019). The global transport of infected animals has also been implicated in the movement of various virus strains across countries and continents. In China, there are viruses of North American and Eurasian lineages co-circulating, suggesting that international trade and agricultural fairs may have facilitated the introduction of these viruses (Bowman et al. 2014, 2017; Duwell et al. 2018; Schicker, 2016; Gray et al. 2012; Trovão and Nelson 2020).

4. OTHER HOSTS

4.1. HORSES

This species is mainly affected by the A/H3N8 subtype, severely affecting the respiratory tract, with a fatality rate of 20%, in unvaccinated animals (Sack et al. 2017; Singh et al. 2018). Various epidemic outbreaks have been registered, which caused great economic losses to the affected countries, mainly in meat production and in the racing industry, as it was in Mongolia and Australia (Cowled et al. 2009; Sack et al. 2017). Various studies have shown the ability of these viruses to produce clinical and subclinical infections in horses and humans, and possibly in dogs and cats (Borkenhagen et al. 2019; Sack et al. 2019). Through an archaeo-immunological study, it was possible to detect neutralizing antibodies against the A/Equino-2/63 virus in individuals born in 1870 and 1900 (Chambers 2022). Although various data have been reported evidencing human exposure to these viruses, the risk of infection is low (Larson et al. 2015; Xie et al. 2016).

4.2. DOGS

In recent years, a high susceptibility of dogs to influenza virus infections has been frequently observed, mainly in those that are found in places with a high population density such as shelters, races or kennels (Voorhees et al. 2018). This species has been affected by the H3N8 subtype of the equine influenza virus in 1999, as well as by an avian type H3N2 virus in 2005 or 2006, among others (H1N1, H5N1, H6N1, H9N2) (Parrish et al. 2015; Jang et al. 2017; Sun et al. 2013; Songserm et al. 2006; Lin et al. 2015). Although dogs have been shown to be susceptible to infection with influenza viruses of human origin, there have been no documented cases of canine influenza virus infections in humans or in personnel assigned to work in places such as shelters or kennels (Chen et al. 2018; Krueger et al. 2014).

4.3. CATS

Reports of infection with the influenza virus in this species have been documented since 2004; its susceptibility to infection with viruses of human, avian, canine and equine origin has been demonstrated (Borkenhagen et al. 2019). Infection with the pandemic A/H1N1 virus was observed in Italy in 2011, and during 2016-2017, more than 500 shelter cats were infected with the H7N2 subtype in New York, USA

(Fiorentini et al. 2011, Hatta et al. 2018). The veterinarian who treated the infected cats developed symptoms and A/H7N2 virus infection was confirmed (Lee et al. 2016). An employee from another shelter was also confirmed to have the same subtype by serological testing (Poirot et al. 2018).

4.5. BATS

The H17N10 and H18N11 subtypes of influenza A virus have been identified in fruit bats, respectively, in the yellow-shouldered bat (*Stunira lilium*) in Guatemala, and in the flat-faced fruit bat (*Artibeus planirostris*) in Peru. In addition, serological studies have shown a high seroprevalence among bat populations from Central and South America. The little brown bat may be a source of new genetic variants, due to the co-expression of receptors that recognize avian and human-type viruses (Tong et al. 2012; Tong et al. 2013; Chothe et al. 2017).

5. EMERGING AND RE-EMERGING VIRUSES

Various pandemics caused by influenza viruses have been reported throughout human history. The first, in 1580, identified as “wind sickness” due to its rapid spread, originated in Asia, spread to Europe, Africa, and the American continent through trade routes (Rafeek et al. 2017). There are records of approximately thirty-one subsequent events, including three that occurred in the last century, in 1918-19, 1957 and 1968, and six in the 19th century: 1800-1801, 1837, 1843, 1857, 1874, and in 1889-92 (Miller et al. 2009; Tognotti, 2009). The most severe of the pandemics on record was the Spanish flu. Various scientists estimate that it caused 40-50 million deaths. The disease spread through North America, Europe, Asia, Africa, Brazil, and the South Pacific. According to the molecular analyzes carried out on the tissues of the 1918 victims, the RNA fragments detected suggest that it was a virus with an A/H1N1 avian-human rearrangement introduced into the population approximately 6 months before the start of the pandemic (Taubenberger et al. 2019). Subsequently, two less severe pandemics originated in Asia but spread throughout the world. In 1957, the “Asian flu” occurred in China, which spread rapidly, replacing the circulating A/H1N1 with A/H2N2. Likewise, in Hong Kong, in 1968, an A/H3N2 virus emerged that spread throughout the world until 1969, and in 1976-1977 the A/H1N1 subtype reemerged (Kilbourne, 2006). In 1997, a highly pathogenic A/H5N1 virus of avian origin acquired human infectivity in Hong Kong; from 1999 to 2003, in Italy, seroconversion of individuals who were in contact with birds infected with A/H7N1 and A/H7N2 viruses was demonstrated, and in Japan, infection and seroconversion of workers in production units affected by the low pathogenic A/H5N2 virus were described (Campitelli et al. 2004; Puzelli et al. 2005; García and Ramos 2006; Tognotti, 2009). Other subtypes of avian origin have also affected humans such as A/H9N2 in China, A/H7N7 in the Netherlands, and A/H7N3 in Canada (Stegeman et al. 2004; Hirst et al. 2004; Kemink et al. 2004; Tweed et al. 2004; Gu et al. 2017). The most recent influenza pandemic recorded originated in Mexico in April 2009 due to a triple recombinant A/H1N1 virus (porcine-avian-human), and in August 2009 it was declared by the WHO as the first pandemic of the XXI century (Franco-Paredes et al. 2009). The main subtypes identified as candidates to generate a pandemic are: A/H5Nx, AH7N9, A/H9N2 and A/H10Nx (Sutton, 2018; Taubenberger et al. 2019). For this reason, WHO has developed tools for risk analysis (WHO, TIPRA) (Global influenza Programme WEP, 2020) as well as the Center for Disease Control and Prevention (CDC, IRAT) (Centers for Disease Control and Prevention, 2020). These programs analyze the phenotypic properties of the virus (specific recognition receptors, transmission between species, etc.), characteristics of the susceptible population (signology, immune response, etc.), the ecology of the virus, and its epidemiology in non-human hosts.

6. DIAGNOSIS

Due to its importance in public health, early and opportune diagnosis should be considered. In typical flare-ups, a provisional diagnosis can be made based on clinical and pathologic findings. But it must be confirmed by virus isolation or by detection of its specific antibodies. The virus can be isolated from nasal secretions during the febrile phase or from lung tissue (3 to 5 days) during the early acute stage (Torremorell et al. 2012). The isolation is done by inoculation in the chorioallantoic membrane of a chicken embryo of 9-11 days, free of specific pathogens (SPF). The virus isolation technique is considered the standard for virus detection through which the viability and infectivity of the virus can be determined, information that cannot be obtained with molecular amplification and antigen detection techniques. For its detection, the specific hemagglutination technique is used (Van Reeth and Vincent 2019; Ravina et al. 2020). Another option is to use the *Madin Darby Canine Kidney* (MDCK) cell line for influenza isolation (Ravina et al. 2020). A retrospective diagnosis can be made, starting from serum samples taken during the acute and convalescent stages of the disease, demonstrating the presence of specific antibodies, using the hemagglutination inhibition test. It is one of the most widely used tests in countries where the disease is endemic, since it recognizes HA that is specific for each subtype and does not present cross-reactions (Truelove et al. 2016). Other methods to detect the virus, viral antigen, or specific antibodies are direct and indirect immunofluorescence techniques. It is frequently used for the diagnosis of influenza in humans. It can be used both in clinical samples and in cell cultures. There are other tests such as neuraminidase inhibition, viral seroneutralization, and ELISA (Jin et al. 2004; Woolcock and Cardona 2005; WHO, 2005). The high similarity of the pandemic H1N1/2009 virus to other H1N1 of porcine origin made viral identification highly dependent on nucleic acid sequencing. Currently, in addition to the CDC protocol for specific diagnosis by real-time RT-PCR recommended at the very beginning of the H1N1/2009 pandemic, laboratories in various countries have refined the specificity of this assay and various protocols. The real-time RT-PCR technique from nasal swabs has been the commonly used method for the detection of type A influenza viruses as part of surveillance (Ellis et al. 2009), and it is based on the detection of the matrix gene (M), a highly conserved region of influenza A viruses, so that it allows the detection and quantification of practically all influenza viruses (Spackman and Suarez 2008; Slomka et al. 2010). In addition, other RT-PCRs (conventional and real-time) are capable of amplifying porcine (H1, H3, N1 and N2) and avian (H5 and H7) haemagglutinins and neuraminidases (Lee et al. 2008; Mallinga et al. 2010; Shi et al. 2014; Lee et al. 2021). Another test that is used, and that has been widely accepted, is the One-Step-Real-Time-Multiplex RT-PCR, which has already proven to be fast, sensitive, and specific when applied during H5N1 influenza outbreaks (Payungporn et al. 2006).

7. PREVENTION AND CONTROL

A century after the most severe influenza pandemic, this disease continues to cause high morbidity and mortality rates, mainly during the winter, and vaccination continues to be the most effective measure to control and prevent it. Today, there is a global epidemiological surveillance system dedicated to the identification and characterization of the various antigenic variants circulating in different regions of the world (Holloway et al. 2014; Hay and McCauley 2018). The CDC, in Atlanta, Georgia, in the United States, houses the WHO Center for Disease Surveillance. Led by health professionals dedicated to analyzing the annual reports of morbidity and mortality caused by the different circulating strains, they recommend which strains should be included in the preparation of vaccines for the following winter season in the northern and southern hemispheres (Malik et al. 2020). Vaccines can significantly reduce the incidence of infection with the influenza virus and other medical complications (Bosaeed and Kumar 2018).

Inactivated vaccines, split-virion vaccines, subunit vaccines, virosome vaccines, live-attenuated vaccines, and recombinant vaccines are available (Rajao and Pérez 2018). Another way to mitigate the effects of this disease is through the use of antivirals, which are classified as those that block the ion channel (M2) of the virus, and also neuraminidase (NA) inhibitors (Schnell and Chou 2008; Gubareva et al. 2010; Ison et al. 2017). Unfortunately, various studies and results on practice have shown the development of resistance against this therapeutics, in addition to the high cost of treatment, which ranges between 30 and 70 dollars a day for 10-15 days. The main preventive action that can help limit the spread of the virus in the human population is to avoid as far as possible contact with sick people; but in the case of sick people, they should stay at home for at least 24 hours after initiation of the classic symptoms (cough, runny nose, muscle pain, fever, among others), cover nose and mouth, clean and disinfect surfaces and wash hands frequently, avoiding touching the mouth, nose and eyes (Lancet 2018). Biosecurity practices and vaccination are preventive measures that minimize the transmission of influenza virus in pigs and from pigs to other species. Other prevention measures are: applying a quarantine period to newly introduced animals, avoiding contact with wild birds, limiting and/or excluding movements of people, such as the use of clothing and boots exclusive to the production unit, having a control in the access of personnel or restrict the entrance to visitors, limit the entrance of sick personnel, the obligation to shower before the entrance and exit of any person who has access to the production unit, have a personnel vaccinated against influenza, restrict access to animals and vehicles from other production units, establish adequate cleaning, and disinfection methods for all areas including vehicle entrances (CDC, 2012; Van Reeth and Vincent 2019). The application of therapeutic treatment in animals is unaffordable. The application of antibiotics is common but only to prevent the presentation of secondary infections, these are added to water. Expectorants and antipyretics are also used (Van Reeth and Vincent 2019). Knowledge of the serological status is essential, since depending on this we will decide both the application and change of a vaccination protocol (Salvesen and Whitelaw, 2021). Knowing well the dynamics of the influenza virus in the population can help in the determination of effective strategies for the elimination of the virus (Torremorell et al. 2012).

8. CONCLUSIONS

Worldwide, outbreaks caused by influenza viruses cause great economic losses. Therefore, it is extremely important to continue with active epidemiological surveillance throughout the world, monitoring its evolution and distribution, in addition to continuing to generate new diagnostic tools that, together with the existing ones, lead to better control of the virus in human populations and animals.

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Animal Influenza: An Eco-Health Outlook

02

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ABSTRACT

Animal influenza is a contagious respiratory disease caused by influenza viruses of the family Orthomyxoviridae that are further classified into types A, B, C and D. Influenza viruses can infect many species of mammals including humans and birds. They pose a significant threat to public health considering their zoonotic potential. The influenza viruses, mainly type A, tend to rapidly evolve through antigenic drift and shift resulting in viral miscellany that can potentially give rise to novel strains with zoonotic and pandemic potential. The trait of genetic reassortment and versatility of these viruses make it challenging to understand their transmission patterns, genetic modifications, vaccine development, and control measures. Avian influenza viruses and Swine influenza viruses have epidemiological significance because of their history of endemic and pandemic outbreaks. The effects of animal influenza outbreaks on economics, and agriculture, together with the potential for zoonotic transmission, highlight the importance of comprehensive monitoring, vaccination strategies and combined efforts among veterinary, public health, and research communities to address the challenges effectively. This chapter provides a detailed analysis of the key aspects of animal influenza following recent research, covering its etiology, transmission dynamics, viral ecology, host-pathogen interactions, epidemiology, zoonotic potential, and acquittal strategies for the well-being of animal and human populations.

Keywords: Animal Influenza, Zoonotic Potential, Influenza A viruses, Epidemiology

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1. INTRODUCTION

Animal influenza is an infectious, transmissible respiratory disorder of global importance in mammals and birds caused by influenza viruses. Influenza viruses belong to the Orthomyxoviridae family. Due to their zoonotic potential, they are liable to cause a severe and significant threat to global public health in both animals and humans. Influenza viruses cause infection in humans and many species of animals such as birds, horses, dogs, pigs, etc. Interspecies transmission of their viral strains can occur which may lead to the spread of endemic or pandemic influenza virus infection among populations (Usman and Maimuna 2009).

The evolving nature of influenza viruses leads to the constant emergence of new variants and strains. This constant genetic variation of influenza viruses is considered to be their unique trait among respiratory tract viruses (Webster 2002). This behavior of influenza viruses results in the rise of epidemics and sometimes pandemics of varied intensities. There is a recommended system of nomenclature by World Health Organization according to which viral strains of the influenza viruses are named based on name of the species they are isolated from, their year of isolation, and their genus (Mostafa et al. 2018; Memorandum 1980).

2. OVERVIEW OF ANIMAL INFLUENZA VIRUSES

2.1. ETIOLOGY

Influenza viruses belong to the family Orthomyxoviridae, Order Articulavirales, and Phylum Negarnaviricota Influenza viruses are classified into four genera Alphainfluenzavirus, Betainfluenzavirus, Gammainfluenzavirus, and Deltainfluenzavirus based on the antigenic differences of their surface proteins, i.e., nucleoproteins (NP) and matrix 1 (M1) proteins. Each of these genera has only one species, which are named influenza A virus (IAV), influenza B virus (IBV), influenza C virus (ICV), and influenza D virus (IDV), respectively (Kuhn et al. 2020; Mostafa et al. 2018).

2.2. MORPHOLOGY AND STRUCTURE

Influenza viruses are observed to be pleomorphic. They exhibit elliptical, spherical or filamentous shapes with a diameter of 80–120 nm and a length up to 20 µm. The influenza virus is enveloped with a lipid-bilayer membrane. The outer layer of virion possesses matrix protein M2 ion channels and embedded spike-like projections of viral proteins. Influenza viruses A and B are almost similar in structures. IAV and IBV have spikes of hemagglutinin and neuraminidase (Vijayakrishnan et al. 2013). While ICV and IDV have distinguished spike-like reticular structures known as hemagglutinin esterase fusion (HEF) glycoprotein, arranged in hexagonal patterns. They have chimeric M2 (CM2) instead of M2 in their outer layer. CM2 is closely related to M2 of IAV (Su et al. 2017).

The inner layer of the virion is an envelope of matrix protein M1 that provides firmness to the outer layer. Underneath the inner layer, nuclear export protein (NEP) is attached to M1 layer. Center of the virion comprised eight viral ribonucleoprotein (vRNP) structures organized as one central long vRNP surrounded by seven vRNPs. vRNPs are single-stranded RNAs connected with polymerase complex and lined with nucleoprotein. Unlike IAV and IBV, the core of ICV and IDV have seven vRNPs instead of eight (Fig. 1) (To and Torres 2019).

2.3. GENOMIC CONFIGURATION OF INFLUENZA VIRUSES

Influenza viruses have basically their genomes structured as segmented, single-stranded RNA molecules enveloped in nucleoprotein. They are pleomorphic, negative - sense viral RNA viruses (Barnard 2009).

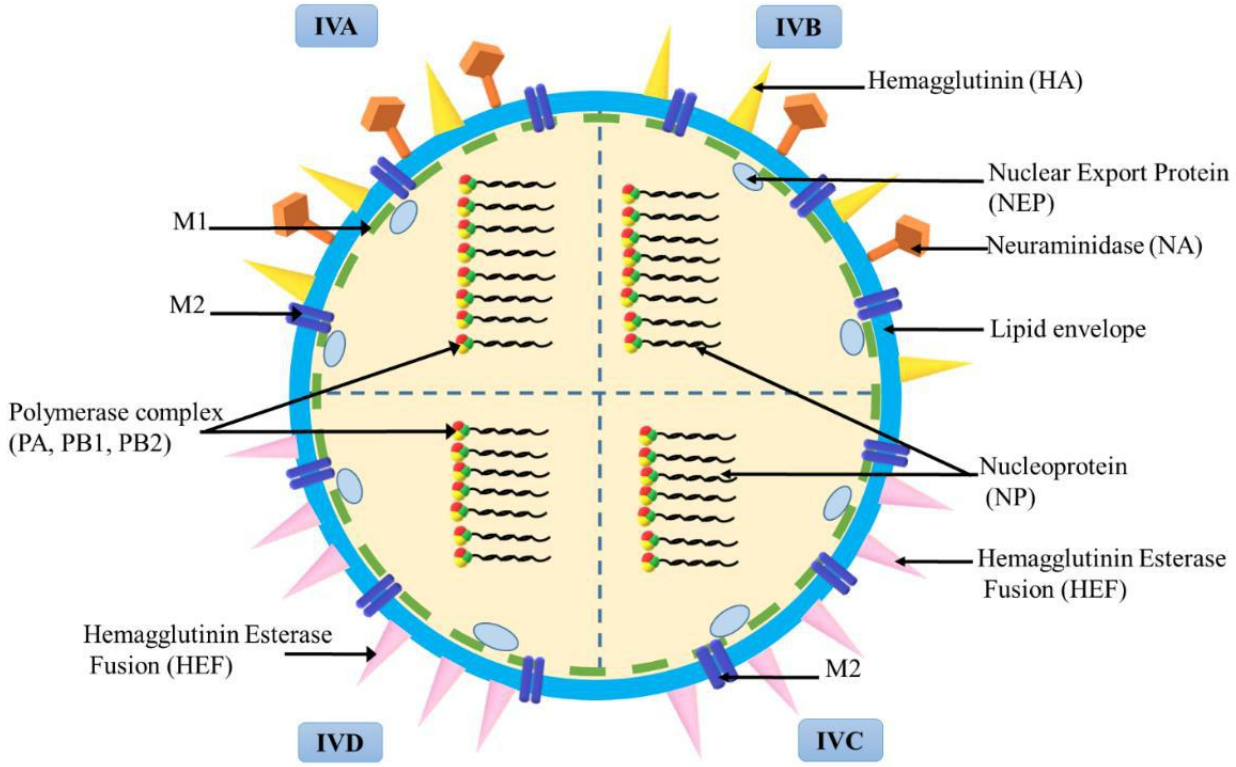

Fig. 1: Structure of Influenza viruses A, B, C and D.

The eight segments of the influenza A and B viruses can encode more than 10 proteins, named Matrix proteins (M1 and M2), Nucleoprotein (NP), Hemagglutinin (HA) glycoprotein, Neuraminidase (NA) glycoprotein, Polymerase acidic protein (PA) subunit, Polymerase basic protein1 and 2 (PB1 & PB2) subunits, and Nonstructural proteins (NS1 and NS2). These segments are named on the basis of the main proteins they encode (Parvin et al. 2022). Influenza C and D viruses contain seven segments of RNA. Three longest segments form the trimeric polymerase complex, encode polymerase basic proteins (PB1), polymerase basic 2 protein (PB2) and polymerase acidic (PA/P3) proteins. Other four segments encode hemagglutinin esterase fusion (HEF) glycoprotein, nucleoprotein (NP), matrix proteins (M1 and chimeric M2 protein (CM2)), and non-structural proteins (NS1 and NS2), respectively (Wolff and Veit 2021). Genomic sequence of the influenza D virus varies from that of the influenza C virus by 50%. There is no genetic interaction that occurs between influenza viruses C and D to form recombinants. There is also no cross-reaction recorded among their antibodies (Hause et al. 2014).

2.4. LIFE CYCLE AND PATHOGENESIS

Influenza viruses take the path of receptor-mediated endocytosis to enter the host cells. Sialic acid (SAα2,6-Gal/SAα2,3-Gal) adhered to the glycolipid and glycoproteins of the outer cell surface of most of the host cells is the binding receptor for influenza viruses. They are specified to target the epithelial cells of the upper or lower respiratory tract. However, the receptor on the targeted host cell used by the influenza C virus is 9-O-acetyl-Nacetylneuraminic acid which is an acetylated derivative (Wolff and Veit 2021). Hemagglutinin plays a significant role in receptor binding and membrane fusion during viral entry into host cells. A low pH environment is important for the initiation of fusion and M2 ion channel activation (Bedi and Ono 2019). The acidic nature of the endosome induces changes in the conformation of

hemagglutinin molecules to initiate the process of fusion of membranes i.e., membranes of virus and membranes of endosomes. This fusion of membranes then results in the release of viral ribonucleoproteins (vRNPs) in the cytoplasm of the host cell. After entering the nucleus from the cytoplasm through nuclear pores, these vRNPs act as transcription templates (Dadonaite et al. 2019). Viral polymerase complex (polymerase basic 1, polymerase basic 2 and polymerase acidic subunits) transcribes the viral RNAs to messenger RNAs for the production of viral proteins (Neumann and Kawaoka 2015). Replication of viral RNA and transcription of mRNA occurs in the nucleus, while the translation of viral protein takes place in cytoplasm. Newly generated vRNPs are then actively released in the cytoplasm with the help of non-structural proteins 2 (NS2) or nuclear export protein (NEP). Hemagglutinin, neuraminidase, M1 protein, M2 protein and vRNPs are needed to be transferred to the plasma membrane for the assemblage of new virus and budding (Su et al. 2017). Lipid raft domains located in plasma membranes of the host cells are used as replication sites by viruses. Neuraminidase plays an enzymatic role in the release of new viruses from the infected host cells by cleaving the binding receptors (Rossman and Lamb 2011). Non- structural proteins 1(NS1) play a vital role in the immune system circumvention of the host (Dou et al. 2018). In the case of influenza viruses C and D, instead of HA and NA, hemagglutinin esterase fusion protein (HEF) plays role in the viral entry of viral RNA in the host cell by membrane fusion, receptor binding, and cleavage of binding receptors during the exit stage of the newly produced virus (Hause et al. 2014).

After their release from the host cell, they start to invade other surrounding cells. Temperature sensitivity of influenza C viruses reduces the production of their new virions at higher temperatures. That is why they infect the upper respiratory tract more than the lungs where the temperature is high. Influenza D viruses are found to be more temperature stable than influenza A, B, and C type viruses (Wolff and Veit 2021).

Apoptosis of infected host cells by influenza virus occurs after the exit of newly produced viruses from host cells through direct triggering of NS2 and PB1-F2 viral protein. The incubation period of influenza virus is 1 to 4 days (Peaper and Landry 2014). Influenza virus infection causes oxidative stress which leads to neutrophil infiltration and high production of reactive oxygen species resulting in tissue damage. There is a rapid production of cytokines by epithelial cells and immune cells of respiratory mucosa as an immune response in severe influenza virus infection. Their overexpression results in high level lung tissue edema, pneumonia, hemorrhage of alveoli or may result in multiple organ failure (Luo et al. 2023). Influenza A virus infection escalates levels of metabolites in plasma and urine (Francis et al. 2019) (Fig. 2).

3. AN ECO-HEALTH OVERVIEW OF ANIMAL INFLUENZA VIRUSES

3.1. INFLUENZA A VIRUS

Influenza A viruses are considered to be the most common and highly pathogenic among all the other influenza viruses. They display high levels of morbidity and mortality in birds and mammals. IAVs are also zoonotic in nature, i.e., they can transmit from animal hosts to humans. Aquatic birds are naturally the host reservoir of the influenza A viruses. Mammals in which influenza A viruses have been reported include pigs, horses, dogs, bats and humans (Wille and Holmes 2020) (Fig. 4).

3.1.1. SUBTYPES

Influenza A viruses are further categorized into different subtypes on the basis of their antibody response and their surface proteins, hemagglutinin and neuraminidase (Usman and Maimuna 2009). These proteins have their role in host cell entry and exit of virion during the replication process. Eighteen known hemagglutinins (H1- H18) and eleven neuraminidases (N1- N11) are there. Viruses containing H1 to H16 hemagglutinin and N1 to N9 hemagglutinin appeared to cause infection in birds (Capua and Munoz 2013).

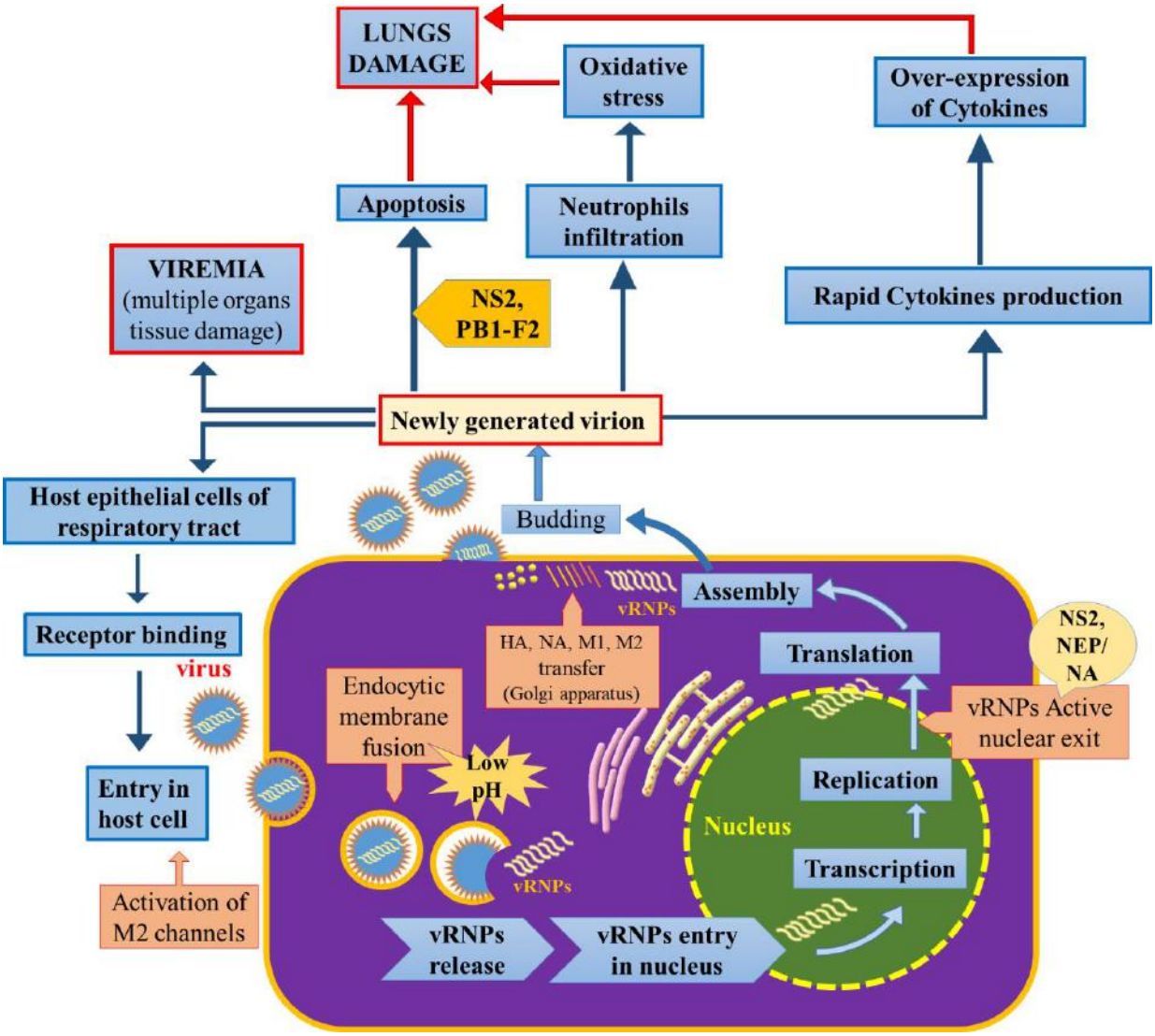

Fig. 2: Schematic representation of life cycle and pathogenesis of influenza virus.

3.1.2. ANTIGENIC SHIFT AND DRIFT

Influenza A viruses show phenomenon of "antigenic drift" that refers to a gradual change in hemagglutinin and neuraminidase of virus. This process results due to influenza A virus's ability of enduring minor to major variations in its genome. Major changes in hemagglutinin and neuraminidase proteins lead to the nullification of existing immune responses of host against that virus. The changes will be major and rapid if virus undergoes genetic reassortment (Collisson et al. 2007). It can even result in a whole new hemagglutinin and/or neuraminidase. These sudden and major changes in virus result in emergence of novel influenza viruses. This process is referred to as "antigenic shift" (Heinen 2002; Spickler et al. 2008) (Fig. 3).

3.1.3. AVIAN INFLUENZA A VIRUSES

Avian influenza A viruses (AIVs) are very diverse and heterogenic in nature, with highly variable sixteen hemagglutinin and nine neuraminidases. Among the subtypes of avian influenza, the H9N2 subtype is

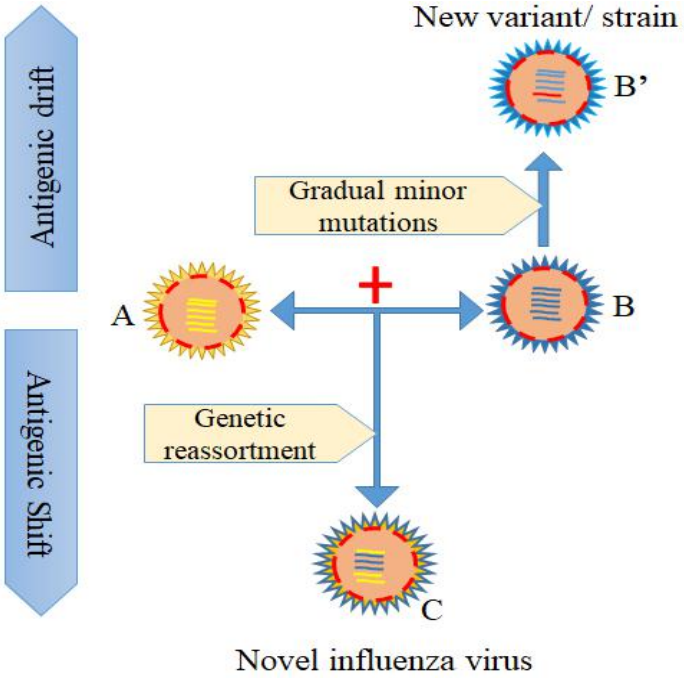

Fig. 3: Antigenic shift and antigenic drift.

considered to be the most prevalent and appears to be causing infection globally (Xu et al. 2018). AIVs target α2,3-SA receptors for binding. Although α2,6-SA receptors are abundant in respiratory and intestinal tracts of birds but very few AIV H16N3 (gull), in poultry H9N2 and H7N2, and H6N6 from duck showed binding potential for these receptors (Liu et al. 2023). Over the past twenty years, the sporadic zoonotic spread of the avian influenza virus has instigated concern regarding the incidence of the virus in poultry and poultry products. This concern was raised due to the occurrence of widely fatal pandemics and infectious outbreaks of avian influenza viruses reported in humans. These outbreaks are the cause of intense socio-economic losses (Naguib et al. 2019).

3.1.4. SUBTYPES

Avian influenza A viruses are categorized into two groups on the basis of their virulence in poultry i.e., Low pathogenic avian influenza viruses (LPAI) and high pathogenic avian influenza viruses (HPAI).
HPAI and LPAI viruses have a structural difference in their hemagglutinin protein and its cleavability. LPAI virus hemagglutinin cleavage is mediated by trypsin-like enzymes. These enzymes are present in respiratory secretions and epithelial cells. Therefore, usually, LPAI viruses remain at the sites present in the gastrointestinal and respiratory tracts. While HPAI viruses undergo cleavage of their hemagglutinin with the help of furin enzymes which can be found in the whole body. Therefore, HPAI virus infection involves multiple organs and systems of the body resulting in severe infections in the host (Swayne 2007). They can show high mortality and morbidity rates. Birds already infected with other pathogens, sick or stressed due to external factors are more likely to get infected by LPAI viruses (Spickler et al. 2008). Most of the avian influenza viruses are low pathogenic. They cause mild infections in birds. Low pathogenic viruses having hemagglutinin H5 or H7 may undergo mutational changes and turn themselves into high pathogenic viruses (Naguib et al. 2019). Low pathogenic influenza viruses can stay in their hosts for long periods, reassorting and producing novel variants. Some HPAI viruses are not highly pathogenic or non-pathogenic in chickens. These viruses can eventually undergo evolution and become more virulent (Patapiou et al. 2022).

3.1.5. CLINICAL SIGNS AND SYMPTOMS

Clinical signs and their intensity during HPAI infection normally vary with the virus. It is said that avian influenza viruses have a high mortality rate and cause the instant death of birds. The mortality rate can reach up to 100% (Alexander 2000). Therefore, leaving very narrow chances to observe birds for the onset of clinical signs. Reportedly, the death of the infected birds was observed within 48 to 7 hours after the onset of early clinical signs. Calculating the time between onset of infection and initial mortality is difficult. This can be calculated in experimentally infected birds by measuring the average time to death. This average is known as mean death time (MDT) which depends on route, dose and subtype of virus (Swayne and Pantin 2006). Avian influenza virus has an incubation period of 48 hours up to 4 days (Khan et al. 2021). Early signs observed were tremors, nervous signs, lethargy and anorexia. Some birds reportedly showed mild respiratory signs such as petechial hemorrhages on the hock and cyanosis of wattles and comb. Respiratory signs included inflammation of the trachea, hemorrhages in the trachea, coughing, reduced vocalization, and rales were heard during clinical examination of sick birds. Nervous signs that were observed included incoordination, torticollis, paralysis and depression. Other clinical signs include severe diarrhea or greenish fecal matter, conjunctivitis, excessive lacrimation, decreased quantity and quality of eggs, huddling, ruffled feathers, haematochezia, and facial edema (Spickler et al. 2008).

3.1.6. ROUTE OF TRANSMISSION

The natural route of transmission in humans and birds for avian influenza viruses is the respiratory route. Avian influenza virus tends to zoonotically transmit through direct interaction with infected birds, respiratory secretions, or corpses of infected birds. Respiratory transmission of the virus by respiratory droplets through the conjunctiva and nostrils is an important route in humans (Sun et al. 2020). The virus sheds out of the host bird through body secretions and feces. The virus is then transmitted by air through water vapors when they come in contact with dried fecal material or feathers of infected birds. Fine droplets can pass the virus to the lower respiratory tract causing severe infections. Transmission of the virus from poultry products to the host e.g., meat and eggs is also a viable and concerning route (Rimmelzwaan et al. 2006).

3.1.7. EPIDEMIOLOGY

Avian influenza virus, because of its diversity and zoonotic significance, results in major epidemic outbreaks. These outbreaks are life threatening and eventually result in huge economic losses. Over the years, many outbreaks of the avian influenza virus have been reported displaying worldwide severe respiratory signs and a very high mortality rate. H9N2 (1998), H7N3 (1995, 1998, 2001-2002) and H5N1 (2006-2008) in Pakistan, H4N8 outbreak in Alabama in 1975, H5N2 (1983 to 1984) Pennsylvania, 1999 to 2000 H7N1 outbreak in Italy, H5N1 outbreak in Thailand (2005), H7N7 in The Netherlands in 2003, H6N2 LPAI outbreak in California 1985, H7N7 outbreak in Australia (Spickler et al. 2008; Siddique et al. 2012).

3.1.8. ZOONOTIC ASPECT

A number of avian influenza viruses made a successful way through the species, causing zoonotic infections. H10N7, H10N8, H9N2, H7N9, H7N7, H7N4, H7N3, H7N2, H6N1, H5N8, H5N6, H5N1 and H3N8 subtypes are of high significance regarding zoonosis, reportedly. They cause mild to fatal infection and in some cases, there is no display of symptoms during infection (Pusch and Suarez 2018). Sneezing and fever are mild infection symptoms in humans that are normally self-limiting. Severe illness can occur if the individual has a

compromised immune system or the attacking virion is highly pathogenic such as H7N9. Animal Influenza viruses spread pandemically when their novel virion attains the capability to transmit to humans efficiently (Sun et al. 2020). Avian influenza viruses possess the potential to become a pandemic threat if they go through some mutations so that they can replicate in mammalian cells efficiently. The three worldwide influenza pandemics; H1N1 AIV 'Spanish flu' (1918 –1919), 'Asian flu' (1957–1958) and 'Hong-Kong flu' (1968 –1969) caused by the H3N2 virus caused high morbidity and mortality, depression and socio-economic losses globally. Widespread low pathogenic H9N2 in Asia and highly pathogenic H5N1 in poultry can result in a zoonotic situation (Zowalaty et al. 2013). Co-infections with avian influenza viruses have been reported often, such as H5N1 with H9N2 and Newcastle disease and H5N1 with Newcastle disease (Channa et al. 2021).
The relation of live bird markets with the spread of avian influenza viruses is quite evident. These markets provide a stable environment for the growth, stability and transmission of different viruses. The presence of multiple species at such places provides enough opportunities for genetic exchange and mutations among viruses for the emergence of novel viruses. In keeping all the factors in view, live bird markets play a vital role in zoonotic transmission (Ali et al. 2021). It is not necessary that a virus show low pathogenicity for both birds and humans. Some avian influenza viruses can be fatal in humans but show low pathogenicity in chickens e.g., H7N9. A rare human-to-human transmission of avian influenza virus occurs. In cases of H5N1, H7N9 and H7N7 a very limited transmission of poultry-based viruses among humans has been reported (Abdelwhab and Mettenleiter 2023).

3.1.9. TREATMENT AND PREVENTION

Prevention of the spread of highly pathogenic avian influenza viruses in birds and mammals is a huge assignment. Implementation of stern rules and regulations for poultry import and export across borders,

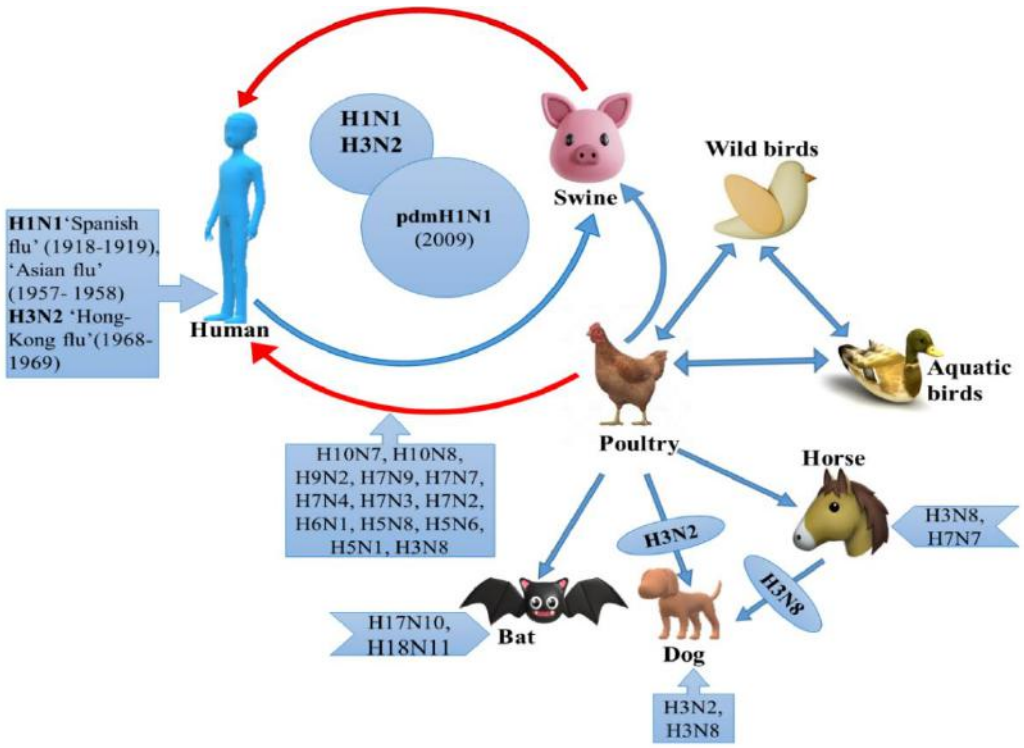

Fig. 4: Schematic flow chart for transmission pattern of influenza A viruses.

proper handling of birds, sanitization, personal hygiene, reducing direct contact with birds using safety gadgets, and vaccination are crucial precautionary steps. H5 vaccines are used in poultry to prevent virus onset, but H5 vaccines are not yet licensed in humans. Vaccine development for humans and animals is under process. Because of their evolving nature, the new pandemic strain would be antigenically modified, requiring a new type of vaccine to develop for its control. Antiviral chemoprophylaxis can be used during outbreaks for protection in high-risk individuals (Wong and Yuen 2006).

3.1.10. SWINE INFLUENZA A VIRUS

Swine influenza A viruses have vast and diverse strains. The diversity of strains is because of repeated reassortments due to the interaction of swine influenza A virus with avian influenza A virus and human influenza A virus. The genetic constitution is still restricted to subtypes H1N1, H1N2, and H3N2. Ancestral European avian-like (EA) H1N1 swine influenza A virus showed affinity for both sialic acid receptors, unlike the human H1N1 virus, due to their evolved antigenic difference (Liu et al. 2023). Pigs are hosts for the swine influenza A virus, where these viruses reassort with avian influenza viruses and human influenza A virus. This reassortment results in the emergence of novel viruses and pandemics e.g. pdmH1N1 contains gene segments from the avian influenza virus, human influenza A virus and swine influenza A virus (Abdelwhab and Mettenleiter 2023).
Swine have both types of sialic acid receptors distributed in the respiratory tract that are possessed by avian and humans. α2,6-SA receptors in the trachea and bronchus are more than α2,3-SA, while both are equally distributed in the bronchioles and alveolar region. Both receptors were also found to be sited in other organs, including the digestive tract, kidneys, liver, heart, brain and skeletal muscles. Therefore, they can infect multiple systems in the body (Nelli et al. 2010).

3.1.11. ROUTE OF TRANSMISSION

Swine influenza A viruses can be transmitted zoonotically through direct contact between pigs and humans. However, the globally reported infection rate in humans of swine influenza A virus is lower than that of avian influenza viruses. Transmission of human influenza A virus to pigs leads to the formation of a reservoir for influenza A viruses of zoonotic significance in pigs (Abdelwhab and Mettenleiter 2023).

3.1.12. CLINICAL SIGNS

Humans and pigs showed almost similar clinical signs for swine influenza A virus infection. Therefore, pigs can effectively be used as study models for influenza viruses. Fever, lethargy, anorexia, respiratory distress, nasal discharge, coughing, conjunctivitis, and sneezing are common characteristic symptoms of swine influenza A virus (Heinen 2002). The incubation period of the virus is 1 to 3 days. The onset of infection is usually sudden. Swine influenza is characterized by almost 100% morbidity but has low mortality in pigs (Vincent et al. 2008).
Swine have receptors for both humans and birds; therefore, they are considered to undergo reassortment between human influenza viruses and avian influenza viruses. That is the reason swine are generally termed as potential mixing vessels for reassortment (Abdelwhab and Mettenleiter 2023).

3.1.13. EPIZOOLOGICAL ASPECT

Swine influenza viruses prevalent in pigs can transmit zoonotically and cause severe pandemics. Swine influenza A virus presence in pigs was first identified in 1918 during the Spanish flu pandemic. In 1930 first

swine influenza virus was isolated by Shope in 1930 was from the H1N1 lineage now known as classical swine H1N1. In 2009, the first 21st century pandemic occurred involving the global spread of swine-origin H1N1 influenza A virus infection. H1N1 swine influenza A virus is a blend of swine, human and avian influenza A viruses due to multiple reassortment between them (Zowalaty et al. 2013).

Classical swine H1N1 can be widespread among the major pig populations of the world, getting 25% of the population infected. In Europe, in 1979 antigenically distinct from classical swine H1N1 viruses, avian-like swine H1N1 viruses were recognized. H3N3 human influenza virion appeared in pigs during 'Hong Kong flu' pandemic around 1970. This human influenza virus after reassortment with avian-like H1N1 swine virus generated a new human-like swine H3N2 influenza virus with structural and genomic properties of human and avian. This virus can cause serious illnesses and can spread rapidly. The H1N1 virus pandemic in 2009, caused sporadic infections (Heinen 2002; Garten et al. 2009).

Due to sporadic infections, vast diversity and frequent reassortments among viral strains in swine, and low immunization of populations towards new strains, the chances of an outbreak of a pandemic are always higher. Several organizations are working as a unit to identify new forming strains of swine influenza viruses pre-pandemic (Rambo-Martin et al. 2020).

3.1.14. EQUINE INFLUENZA A VIRUS

Equine influenza A viruses cause respiratory tract infections in horses and other equines. H3N8 and H7N7 are two subtypes of equine influenza A virus that kept on causing infections in equines. But after 1970s, no known cases of H7N7 have been reported. H3N8 viruses are still prevalent in horses causing sporadic infection and keep on evolving to form new lineages. H1N8, H5N1, H7N1, and H9N2 are the other influenza A viruses that have been found in horses. Zoonotic transmission of equine influenza A viruses has never been confirmed. However, the presence of viruses in humans with no notable infection has been reported several times worldwide i.e., in 1959, 1965, 1960s, 1963, 1965, 2005, 2008 to 2013, 2014 and 2015 (Abdelwhab and Mettenleiter 2023). It has been reported that there is a limited transmission of the H3N8 equine influenza A virus in other mammals like dogs, cats, pigs and camels. Fever, mild flu-like symptoms and seroconversion have been observed in equine Influenza virus-infected individuals (Borkenhagen et al. 2019).

3.1.15. CANINE INFLUENZA A VIRUS

H3N8 and H3N2 canine influenza A virus subtypes, isolated in 2000s, were observed to infect only dogs. But dogs are not natural hosts for influenza A virus. The outbreak of the H3N8 canine influenza virus in dogs which was related closely to the equine influenza H3N8 virus, was reported for the first time in 2002 in UK (Abdelwhab and Mettenleiter 2023). H3N8 canine influenza virus is a genetic divergent of the equine influenza virus and is avirulent towards horses. Several outbreaks of canine influenza viruses have been reported over the years. In 2005 another subtype H3N2 having avian-origin gene segments was isolated from dogs. H3N2 canine influenza virus can be transmitted to cats. Zoonotic transmission of H3N8 or H3N2 canine influenza virus is considered to be very low (Borkenhagen et al. 2019).

3.1.16. BAT INFLUENZA A VIRUS

H17N10 and H18N11 viruses were isolated in 2009 to 2011 from bats. These viruses do not infect other species. They are unique in their hemagglutinin H17 and H18 structure and binding properties. Their

internal genes are unique from other influenza A viruses. To date, no zoonotic transmission of bat influenza viruses has been confirmed (Abdelwhab and Mettenleiter 2023).

3.2. INFLUENZA B VIRUS

Influenza B viruses (IBV) primarily infect humans. There are two IBV strains Victoria and Yamagata. This strain can genetically reassort and have limited antigenic cross-reactivity. Other animals prone to IBV are seals *(Phoca vitulina).* They show low rates of evolution. Clinical symptoms displayed by IBV are flu-like symptoms. IBV are not much genetically diverse, due to which level of immunity can be attained. Therefore, the potential of IBV to cause a pandemic is very low. But they are known to cause seasonal outbreaks. IBVs can be efficiently prevented by vaccination (Wolff and Veit 2021).

3.3. INFLUENZA C VIRUS

Influenza C viruses have humans as primary hosts but they are also found in farmed pigs. ICVs infections are asymptomatic or may cause mild respiratory distress, Inflammation of the upper respiratory tract, fatigue, cough and fever. In pigs, the infection can be sustained for a month approximately (Hause et al. 2014).
ICVs are distributed worldwide. The transmission of the virus occurs through respiratory route. Human-to-human transmission of ICVs is efficient. They can cause persistent infections in human populations. Isolation of influenza C virus from an infected human in 1947 revealed that ICVs do not show cross-reactivity against IAV or IBV antibodies. ICVs are not life-threatening. Therefore, vaccines have not been developed for ICVs (Wolff and Veit 2021).

3.4. INFLUENZA D VIRUS

Influenza D virus (IDV) in 2011 was identified in swine showing influenza-like clinical signs and then subsequently in cattle. Cattle is the only reservoir of IDV. IDV is the first identified influenza virus in cattle (Hause et al. 2014). IDV and ICV having genetic similarities emphasize IDV being a descendant of ICV for 300 to 1500 years. IDV also infect other mammals naturally such as horses, sheep, goat, camel and pigs (Ferguson et al. 2016). Interspecies transmission of IDV can occur through direct contact. Distribution of IDV is worldwide. There is no indication of zoonotic transmission of IDV. IDV infects ferrets, which are the favored human alternate animal models for influenza virus studies. In vitro analysis of IDV revealed their ability to grow and replicate on human airway cell culture (Abdelwhab and Mettenleiter 2023). Also, IDV has a broad cell tropism because of its HEF glycoprotein's open receptor-binding cavity. These characteristics of IDV point towards its potential for zoonosis (Ferguson et al. 2016).

4. EVOLUTION OF ANIMAL INFLUENZA VIRUSES

Influenza viruses have segmented genomes that allow genetic exchange among different strains. This property is considered helpful in the evolutionary process (Wolff and Veit 2021). The emergence of new subtypes and strains of animal influenza remained a significant concern for global health (Lowen 2017). One of the major concerns with animal influenza is the potential for reassortment, a process in which genetic material from different influenza viruses combines to form a new subtype with the potential to cause a pandemic if it gains the ability to spread efficiently among humans. Vigilant surveillance and rapid identification of emerging subtypes and strains are crucial for early detection and response (Wille and Holmes 2020).

Monitoring high-risk areas and animal populations, especially those in close proximity to humans, is essential for detecting emerging subtypes and strains. Genetic sequencing and characterization of the viruses provide insights into their pathogenicity, antigenicity, and potential for human transmission. Continuous monitoring of viral evolution and the identification of genetic markers associated with increased virulence or adaptation to new hosts can guide the development of targeted interventions (Reperant et al. 2012).

5. ONE HEALTH APPROACH TO ANIMAL INFLUENZA

Human development has increased carbon emissions, causing a rise in global temperature. The rise in temperature, deforestation, increased humidity, pollution, and overpopulation destroyed the lifecycles and diversity of ecosystems. These factors, along with increased direct contact with animals due to urbanization enhanced threats of zoonotic transmission of diseases (Yasmeen et al. 2022). Environmental considerations play a significant role in the emergence, spread, and persistence of the virus (Naguib et al. 2019). Key aspects include:

- Wild bird ecology: Wild birds, particularly waterfowl, are natural reservoirs of avian influenza viruses and play a crucial role in the virus's ecology and transmission. Studying their migratory patterns, habitats, and interactions with domestic birds is important for understanding the dynamics of virus circulation.
- Environmental contamination: The virus can persist in the environment, such as in water bodies or contaminated surfaces. Environmental monitoring and assessing the survival and transmission potential of the virus in different settings help inform control measures and risk assessment.
- Climate change and land-use changes: Environmental changes, including climate change and land-use changes, can impact the distribution and behavior of avian influenza viruses and their hosts. Understanding these dynamics helps anticipate and mitigate the risks associated with changing environments.
- Environmental health interventions: Implementing environmental health interventions, such as proper waste management, water treatment, and hygiene practices, can reduce the risk of environmental contamination and transmission of the virus.

5.1. DIAGNOSIS

Detection of viral strain is important in the diagnosis of influenza viruses to take essential clinical steps to prevent the virus. Samples in the form of swabs or tissue collected for testing. Reverse transcription-polymerase chain reaction (RT-PCR) is considered a strong and preferred diagnostic test for influenza viruses (Khan et al. 2021). Other detection tests include rapid influenza diagnostic tests, ELISA, hemagglutination inhibition test for antibodies detection, Immunofluorescence method for antigen detection, fluorescent antibody staining assays, and viral culture method (Patapiou et al. 2022).

5.2. TREATMENT, PREVENTION AND CONTROL STRATEGIES

Virus propagation in a population depends on host species, viral subtype, season, geographical location, and vaccine efficiency (Zaman et al. 2019).

5.3. VACCINATION

Vaccination is an essential tool for preventing and controlling animal influenza. Vaccines can be developed for specific strains of influenza viruses to reduce the risk of infection and disease in both animals and

humans. Vaccination programs are commonly used in domestic poultry to minimize the spread of avian influenza viruses and protect bird populations (Patapiou et al. 2022). Vaccination strategies include the use of inactivated vaccines, live attenuated vaccines, or recombinant vaccines. Inactivated vaccines are typically administered via injection and provide protection against specific strains of the virus. Live attenuated vaccines are administered orally or by aerosol and mimic a natural infection, stimulating an immune response. Recombinant vaccines use genetic engineering techniques to produce viral antigens and stimulate an immune response. Vaccination of poultry can reduce the severity of the disease, decrease viral shedding, and limit transmission to humans (Dey et al. 2023). However, vaccination alone is not sufficient and should be combined with other control measures such as biosecurity practices and surveillance.

5.4. ANTIVIRAL MEDICATIONS

Antiviral medications can be used as a control strategy for animal influenza, particularly in situations where vaccination is not feasible or as a complement to vaccination. Antiviral drugs, such as neuraminidase inhibitors (e.g., oseltamivir, zanamivir), can help reduce the severity and duration of illness, as well as limit viral replication and transmission (Luo et al. 2023). Antiviral treatment is typically recommended for infected individuals or individuals with a high risk of exposure, such as healthcare workers caring for patients with confirmed cases of zoonotic influenza. Antiviral drugs may also be used for outbreak control in animal populations. Indiscriminate use of antiviral drugs can contribute to the development of drug-resistant strains of the virus.

5.5. BIOSECURITY MEASURES

Biosecurity measures are critical in preventing and controlling the spread of animal influenza. These measures aim to minimize the introduction and transmission of the virus within and between animal populations (Mak et al. 2012). Key biosecurity practices include:

- Restricted access: Implementing strict control of access to farms, live bird markets, and other animal facilities helps prevent the entry of infected animals or contaminated materials.
- Hygiene protocols: Promoting good hygiene practices, such as hand washing, disinfection of equipment and surfaces, and proper waste management, reduces the risk of virus transmission.
- Separation and isolation: Isolating infected or potentially infected animals from healthy animals minimizes the spread of the virus. This includes separating sick animals, implementing quarantine measures, and segregating different animal species.
- Poultry production systems: Improving the design and management of poultry production systems can reduce the risk of virus introduction and spread. Measures such as improved ventilation, separate production zones, and proper waste management can enhance biosecurity.
- Surveillance and early detection: Implementing active surveillance programs to monitor animal populations for signs of infection allows for early detection and rapid response, limiting the spread of the virus.
- Slaughter and quarantine policies are crucial control measures during zoonotic outbreaks of animal influenza. These measures aim to contain the spread of the virus and prevent further transmission to humans or other animals.

5.6. PUBLIC HEALTH EDUCATION AND AWARENESS

Public health education and awareness campaigns play a crucial role in preventing and controlling zoonotic influenza. These campaigns aim to educate the public, animal handlers, healthcare professionals, and

other stakeholders about the risks of zoonotic influenza and preventive measures (Mak et al. 2012). Key components include:

- Information dissemination: Providing accurate and up-to-date information about animal influenza, including modes of transmission, signs and symptoms, and preventive measures, helps raise awareness and promote responsible behavior.
- Hygiene practices: Promoting good hygiene practices, such as regular hand washing, proper cooking of poultry products, and respiratory etiquette, helps reduce the risk of transmission.
- Risk communication: Clear and effective communication during outbreaks helps build public trust and understanding. Providing timely information about outbreaks, control measures, and recommended actions helps individuals make informed decisions.
- Stakeholder engagement: Collaborating with various stakeholders, including farmers, veterinarians, healthcare professionals, and public health authorities, ensures a coordinated response and effective implementation of preventive measures.

6. CONCLUSION

Animal influenza is a multifaceted threat with the zoonotic potential, impacting the balance of the ecosystem. This is a contagious viral respiratory disorder, considered important globally. Continuous emergence of new strains and interspecies transmission of influenza viruses may result in outbreaks. Vaccination is a vital key for the prevention and control of animal influenza. Public health education and awareness campaigns, vigilant monitoring, continued research, early detection, and rapid response are the preventive strategies for fostering an Eco- Health approach, emphasizing the interconnectedness of animal, human, and environmental health and mitigating the risks of potential zoonotic influenza endemic or pandemic among populations.

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Zoonotic Potential of Avian Influenza Virus: Knowns and Unknowns

03

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ABSTRACT

Avian influenza viruses (AIVs) are one of the leading causes of economic losses to the poultry industry around the globe, and owing to their zoonotic and pandemic potential, AIVs present a considerable threat to animal and human health. Waterfowl are the natural reservoirs of the AIVs. Different species of birds vary considerably in their susceptibility to AIV infection. Genetic changes such as mutation, antigenic drifting, and reassortments in the different AIVs can develop new strains with increased transmission and pathogenicity. Due to the interrelation of the AIV and previous pandemics in humans, there is a dire need to perform molecular epidemiology studies. In humans, AIVs can cause eye irritation, flu-like symptoms, respiratory disease and even death, but its severity varies with the strain of the virus, age, dietary habits, and health status. For the prevention and control of AIV infection, definitive diagnosis, strict biosecurity, and vaccination are recommended. Many antiviral drugs, such as Dextran sulfate, DSA181, arbidol, etc., are effective against influenza viruses.

Keyword: Avian influenza virus, transmission, human health implication, biosecurity, vaccination

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1. INTRODUCTION

Avian influenza viruses pose significant risks to human and animal health and global food security due to their zoonotic and pandemic nature. Avian influenza viruses (AIV) cause avian influenza, commonly known as bird flu, and can infect Wild waterfowl, including ducks, geese, turkeys, chickens, and other avian species. These viruses belong to the influenza A virus category and are divided based on their surface proteins.

Frequent outbreaks of avian influenza and domestic poultry can lead to profound economic repercussions for the global poultry industry. Culling of the infected birds, market restrictions, and imposition of trade limitations can lead to considerable financial losses to poultry farmers and economies. Being the major source of animal protein, influenza outbreaks within poultry can lead to a decrease in poultry meat and egg production, significantly impacting nutritional well-being and food security. Waterfowl is a major source of influenza viruses that can transmit these viruses to migratory birds. These migratory birds can carry these viruses to longer distances and transmit them to animals and humans.

Avian influenza viruses can carry significant health ramifications due to human infections. Specific strains of AIVs having zoonotic potential can result in severe respiratory disorders and have caused outbreaks, even pandemics.

The genetic architecture of the avian influenza viruses makes them vulnerable to mutations and recombination, which facilitates them to leap the species barrier. The possibility of zoonotic transmission raises concerns regarding the emergence of novel strains that can cause widespread illness in humans. Previous outbreaks of the different influenza viruses like H5N1 and H7N9 have provided different basis for the virus evolution, transmission, and global response strategies. Dealing with the challenges posed by these zoonotic viruses necessitates collaborative efforts in the different sectors.

Future studies should be based on understanding the viral genomes that can lead to the transmission of viruses from animal hosts to humans and developing novel vaccines. These insights will be beneficial for pandemic preparedness and response.

2. HISTORICAL PERSPECTIVE

Many non-bacterial outbreaks in household birds causing high mortality were recorded during the nineteenth century and those outbreaks were named ‘‘fowl plague’’ (Alexander and Brown 2009). In 1955, Schafer concluded that the ‘fowl plague virus’ was in fact a type of Avian Influenza virus, having internal antigens similar to influenza viruses of humans & swine (Schäfer 1955). Several sequencing studies confirmed that the H7 subtype of the influenza A virus was responsible for those outbreaks (Röhm et al. 1995).

The Spanish flu pandemic caused by the influenza virus (H1N1) has been guessed to cause around 50 million deaths in humans in 1918 (Johnson and Mueller 2002). Three other major human pandemics have occurred since then: Asian flu caused by H2N2 (1957), Hong Kong flu caused by H3N2 (1968), and swine flu caused by H1N1 (2009). In all cases, Influenza A virus strains having RNA segments coding for novel HA or NA proteins quickly disseminated through a human population. In 1967 Pereira et al. outlined the connection between human influenza, avian influenza, and fowl plague and suggested the human H2N2 and H3N2 pandemic viruses could have had an avian origin on the basis of antigenic cross-reactivity (Pereira et al. 1967). Several other studies unequivocally established the avian virus origin of the human 1957 and 1969 pandemics (Fang et al. 1981). The pandemic of swine flu in 2009 occurred as a result of reassortment between diverse influenza A virus strains that had been circulating in pigs for the last few years but these pig-origin strains exhibited evidence of genomic segments that could be traced back to avian origins (Smith et al. 2009). There have been reports that many sporadic infections of humans

occurred directly from avian sources with a number of avian virus subtypes like H5, H6, H7, H9 & H10, but without leading to sustained human-to-human transmission as yet (Yuen et al. 1998).

3. AN OVERVIEW OF AVIAN INFLUENZA VIRUS

Avian influenza viruses belong to class *Insthoviricetes,* order *Articulavirales, family Orthomyxoviridae, Genus Alphainfluenzavirus* (ICTV 2022), previously known as influenzavirus A. These have a single standard, negative sense, and segmented RNA genomes (Wille and Holmes 2020). There are eight gene segments in their genomes and encodes ten different proteins (Perez et al. 2019). The surface proteins of the virus include membrane channel (M2) neuraminidase (NA) and hemagglutinin (HA). The viral RNAs encode proteins, including polymerase basic protein 1(PB1), polymerase basic protein (PB2), polymerase acidic protein, matrix proteins (M1, M2), and nucleoprotein (Shaw and Palese 2007). The influenza viruses produce two other non-structural proteins namely non-structural protein one (NS1) and non-structural protein two (NS2), also known as nuclear export proteins (Lee and Suarez 2005). The transcription of the alternative open reading frames can produce several accessory proteins, and most of these proteins' functions are unclear (Vasin et al. 2014). The HA plays a major role in the pathogenicity and initiation of the infection process by attaching to the host cells. There are 18 different HA subtypes of avian influenza viruses. The NA protein's basic function is to release the newly formed viruses from the infected cells, and there are 11 different subtypes of avian influenza viruses based on the NA gene. Different strains with distinct pathogenicity and characteristics are formed, such as H5N1 and H7N9, based on the various combinations of the HA and NA proteins.

The AIVs are categorized into highly pathogenic (HPAIV) and low pathogenic avian influenza viruses (LPAIV) based on their pathogenicity in chickens (Swayne and Suarez 2000). For the classification of the HPAI and LPAI and pathogenicity in poultry, the arrangement of multiple basic amino acids at the cleavage site of the HA serves as a pivotal factor (Medina and Garcia-Sastre 2011). HPAIV causes significant mortality in chickens, whereas LPAI causes a decrease in reproductive performance, depression, and respiratory signs.

4. UNDERSTANDING VIRAL GENETICS AND VARIABILITY

Genetically reassortments can occur in avian influenza viruses due to their segmented genome. It can lead to the shifting or exchange of the different genes, leading to the differences in the pathogenicity and immunogenicity of the newly formed viruses. This antigenic shift due to reassortments can lead to antigenic change known as antigenic shift. This antigenic shift may result in pandemics. Another way the antigenic drift alters the antigenicities of the receptor-binding HA and NA is the selection pressure of immune responses. It may be due to the non-proofreading ability of polymerase in influenza A viruses (Boivin et al. 2010), due to which there is a higher chance of base mutations leading to antigenic drift.

5. NATURAL RESERVOIRS, HOSTS RANGE, AND TRANSMISSION DYNAMICS

Influenza A viruses predominantly reside within wild waterfowl, particularly those belonging to the orders Anseriformes (ducks, geese, and swans) and, to a lesser degree, Charadriiformes (gulls, terns, sandpipers, and plovers), serve as their natural reservoirs (Caron et al. 2017; Neumann et al. 2010; Nishiura et al. 2009). Migratory species within these orders play a crucial role in expanding the geographical spread and perpetuation of these viruses (Verhagen et al. 2015; Viruses 2016). Conversely, influenza A prevalence remains low in other bird orders, like passerine songbirds, implying their status as spillover hosts, often

infected via contact with poultry or waterfowl (Fuller et al. 2010). It's worth noting that certain peri-domestic species including house sparrows (*Passer domesticus*) might still contribute to viral movement between poultry farms or even between wild birds and farms (Bahl et al. 2016; Hassan et al. 2017; Prosser et al. 2013).

Domestic poultry, including chickens, ducks, and turkeys, exhibit varying degrees of susceptibility to infection, each displaying a range of clinical signs and severity levels. Additionally, avian influenza strains can infect various avian species, encompassing both captive and wild birds, resulting in sporadic outbreaks. Recently sporadic cases or outbreaks of H5 HPAIV have been reported in different mammals like foxes, otters, minks, and sea lions (Aguero et al. 2023; Huang et al. 2023; Kupferschmidt 2023; Sidik 2023) which raise a lot of concerns for human. There are several factors that influence the distribution of Avian Influenza viruses like wild bird populations, migratory patterns, climatic conditions, human interaction, and live bird trading. The outbreaks of AIV are reported in the Middle East, Africa, Bangladesh, India, Pakistan, Europe, and America indicating its global distribution.

Influenza virus can be transmitted from the natural host that is aquatic birds to domestic poultry or pigs (Long et al. 2019). The AIV spread is influenced by the complex combination of factors among birds, human and other species. Primarily AIV is transmitted through direct contact between infected and susceptible birds. This can occur in various ways, such as through close interactions, sharing of feeding and drinking sources, or mating behaviors. Indirect transmission can occur from the contaminated environment, equipment, feed, water, etc. In the areas with higher population of commercial or domestic poultry airborne transmission is possible for short distances. The direct or indirect contact of the infected birds, their dropping or contaminated environment can lead to zoonotic transmission and it is observed in the outbreaks in Egypt and Asia (Li et al. 2019).

Novel strains with higher pathogenicity and transmissibility can arise from genetic changes such as mutation and reassortments in the different AIVs. Migratory birds can shed these viruses in the environment and waterbodies leading to their contamination and transmit the viruses to the longer distances due to their ability to carry in their digestive and/or respiratory system. Across continental migration of birds can transmit viruses to those continents. Rearing of the ducks at the interface of domestic poultry and migratory birds in different countries like China, Indonesia, Vietnam and Bangladesh provide a significant role in the spread and ecology of AIVs (Cappelle et al. 2014). Many environmental factors such as water bodies, temperature, and humidity influence the movement of migratory birds and viral survivability (Bozó et al. 2018; Brown et al. 2009; Brown et al. 2007). In the similar way live poultry transportation and live bird markets can transmit the AIVs to the domestic poultry (Gilbert et al. 2014).

6. FACTORS INFLUENCING ZOONOTIC POTENTIAL OF AIV

The zoonotic potential of the AIV is influenced by the different factors like viral genetics, antigenic drifting, reassortments, and virus evolution. The glycoprotein HA binds to the sialic acid receptors and enables virus attachment to host cells. The human influenza viruses primarily replicate in the upper respiratory tract (URT) glycans, which are rich in terminal α2,6-linked sialic acid (SA). On the other hand, AIVs preferably binds to the α2,3-linked SAs which are commonly present in the gastrointestinal and respiratory tracts of birds (Pillai and Lee 2010). Selected mutations in the HA gene of the AIVs can lead to their ability to bind to α2,6-linked SA effectively which is necessary for successful infection and transmission in humans (Peacock et al. 2021). Reassortments occur when viruses of two different strains/lineages infect the same host. During replication, these viruses can exchange/mix their RNAs leading to the formation of new viruses which may have the characteristics of both the parents. This type of formation of new viruses increases the cross-species transmission

of AIV and may result in zoonotic transmission (Hoye et al. 2021) or potential pandemics. During replication and transmission within the birds, AIV can mutate resulting in the emergence of new strains with altered genetic and pathogenic characteristics, increasing their genetic potential (Lee et al. 2010).

7. HUMAN HEALTH IMPLICATIONS

The AIVs can cause illness in humans, spanning from mild flu-like symptoms or eye irritation to critical, sudden respiratory disease and even potential fatality. The severity of the condition hinges on the specific strain of the virus and the particularities of the infected individual such as age, genetics, dietary habits, health status, variation in the immune system, etc. Influenza symptoms typically manifest approximately 2 days following exposure to the virus. These symptoms encompass an abrupt onset of fever, a typically dry cough, headaches, muscle and joint discomfort, pink eye, a profound feeling of unwellness, a sore throat, and a runny nose (Wong and Yuen 2006; Yuen et al. 1998). The cough can persist intensely for a span of 2 weeks or more. For the majority, recovery from the fever and other associated symptoms generally occurs within a week, necessitating no medical intervention. However, influenza has the potential to provoke severe illness or even fatalities, particularly in individuals classified as high-risk. Additionally, it can exacerbate symptoms of pre-existing chronic ailments. In more critical instances, influenza can lead to complications such as pneumonia, acute respiratory distress, respiratory failure, or sepsis. Individuals with underlying medical conditions or experiencing severe symptoms should promptly seek medical attention. On rare occasions, instances of gastrointestinal and neurological symptoms have been documented.

8. PREVENTION AND CONTROL

8.1. ANTIVIRALS

Monoclonal antibodies against specific AIVs have shown promising results in clinical treatment and post-exposure prophylaxis. In addition, polypeptide drugs have also been developed (Saito et al. 2021; Zhao et al. 2020), but their efficacy is challenged by the continual mutation of AIVs (Baz et al. 2010), necessitating the exploration of new antiviral strategies (Huang et al. 2023).

Various small compounds have been created to combat influenza viruses by targeting different stages of their life cycle (Figure 1). These include inhibitors of the HA protein, which can hinder virus adsorption or fusion. HA1 inhibitors like Dextran sulfate and DSA181 (Belser et al. 2007) obstruct the binding of HA1 to cell surface receptors, while HA2 inhibitors such as BMY-27709 (Luo et al. 1997) and arbidol (Boonma et al. 2022) prevent virus entry by impeding HA2-mediated membrane fusion. The viral fusion process relies on host enzymes like proteases and endosomal acidification indicating the role of the enzyme inhibitors like aprotinin (Zhirnov et al. 2011) and bafilomycin A1 (Ochiai et al. 1995) can be used as antiviral drugs. Inhibitors like rimantadine and amantadine block the release of the viral RNA in the cytoplasm of the host cell by targeting the M2 ion channel (Bright et al. 2006). Similarly, NA inhibitors such as zanamivir, peramivir, and oseltamivir can prevent the release of newly formed viruses from infected cells (De Clercq 2006; De Clercq and Neyts 2007). But resistance to NA inhibitors can be seen due to the mutations in the NA protein (Burnham et al. 2014). Antiviral agents include a variety of substances that target different stages of viral replication, such as NP inhibitors (Correa-Padilla et al. 2023), PB2 inhibitors (Li et al. 2023), PA inhibitors (Govorkova et al. 2022), and RNA-dependent RNA polymerase inhibitors (Shiraki and Daikoku 2020) can be used as antiviral agents (Huang et al. 2023).

8.2. BIOSECURITY

Strict biosecurity measures are the most significant means of preventing avian influenza outbreaks in poultry, preserving the food supply chain, and reducing the probability of outbreaks in human. Thus, controlling and preventing the spread of AI expects strict biosecurity protocols and excellent hygiene standards. These procedures have a direct effect on reducing the risks of contamination related to workers and equipment. Direct of contact of the wild birds from the domestic poultry should be prevented because wild birds are the primary source of infection to the domestic poultry (Peiris et al. 2016). Poultry production facilities and flocks need to strictly regulate vehicles, employee, and equipment access, as well as ensure thorough cleaning and disinfection. It is crucial to put in place the proper educational initiatives to guarantee that people who interact with poultry species are aware of the risks associated with avian influenza (AI), know how to prevent it, and know how to report, monitor, and handle possible outbreaks. This level of knowledge is crucial to enable the farmers and employees to identify the disease's clinical symptoms and mortality patterns, and report to Veterinary Services and the appropriate authorities right away. If disease is revealed within a flock, the OIE Terrestrial Animal Health Code prescribe that affected animals be culled together with any animals that are in touch with them (or within a specified radius of affected premises), and that carcasses and animal products be disposed of appropriately. It is also advised to impose movement limitations and implement quarantine procedures to mitigate the spread of the disease. There are several ways to successfully reduce the environmental contamination of the virus in live bird markets. These include forbidding the sale of live aquatic birds (Figure 1), separation of water fowl and poultry species, and introduction of monthly rest days when markets are cleared and thoroughly disinfected before introduction of the new birds (Peiris et al. 2016). Poultry workers involved in the culling and disposal of the infected or dead birds must use protective wears and receive antiviral drugs as preventive measures. Moreover, high risk individuals such as the staff of poultry live markets, poultry farm workers, and poultry veterinarians should get the seasonal vaccinations to lessen the chances of the infection and co-infection of the different AIVs leading to the reduction in the risk of genetic reassortments.

8.3. PROTECTIVE MEASURES AND OPTIONS FOR PUBLIC HEALTH RESPONSE

Most of the influenza viruses exhibit limited host range but in the last decades AIVs have caused zoonotic infections by the direct transmission from birds to humans. Certain strains of HPAIV and LPAIV commonly isolated from the poultry have shown their abilities to initiate zoonotic outbreaks. These occurrences of zoonotic transmission are of substantial concern for public health due to the seriousness and mortality associated with the diseases they cause. There is also a significant apprehension that a novel virus with competent human-to-human transmission might prime to a pandemic. It's essential to recognize that all influenza pandemics over the past century resulted from viruses with genetic components originating from animals, with avian species being the main source (Taubenberger and Morens 2009). Terrestrial birds, such as quail, chickens, turkeys, and similar species, have been known as the hosts capable of amplifying avian/human reassortant influenza viruses (Makarova et al. 2003; Perez et al. 2005; Perez et al. 2003; Pillai et al. 2010). Hence, biosafety is a paramount concern for individuals who come into contact with the virus. Those at risk of virus exposure can be categorized into two groups. The first group comprises those engaged in controlling outbreaks and AI eradication, with responsibilities such as culling infected birds, disposing of carcasses, and sanitizing premises. The second risk group involves laboratory personnel working with contaminated specimens and samples containing the virus (Capua and Alexander 2009). Following are the different recommendation for the individual involved in the handling of birds and field outbreaks of AIVs.

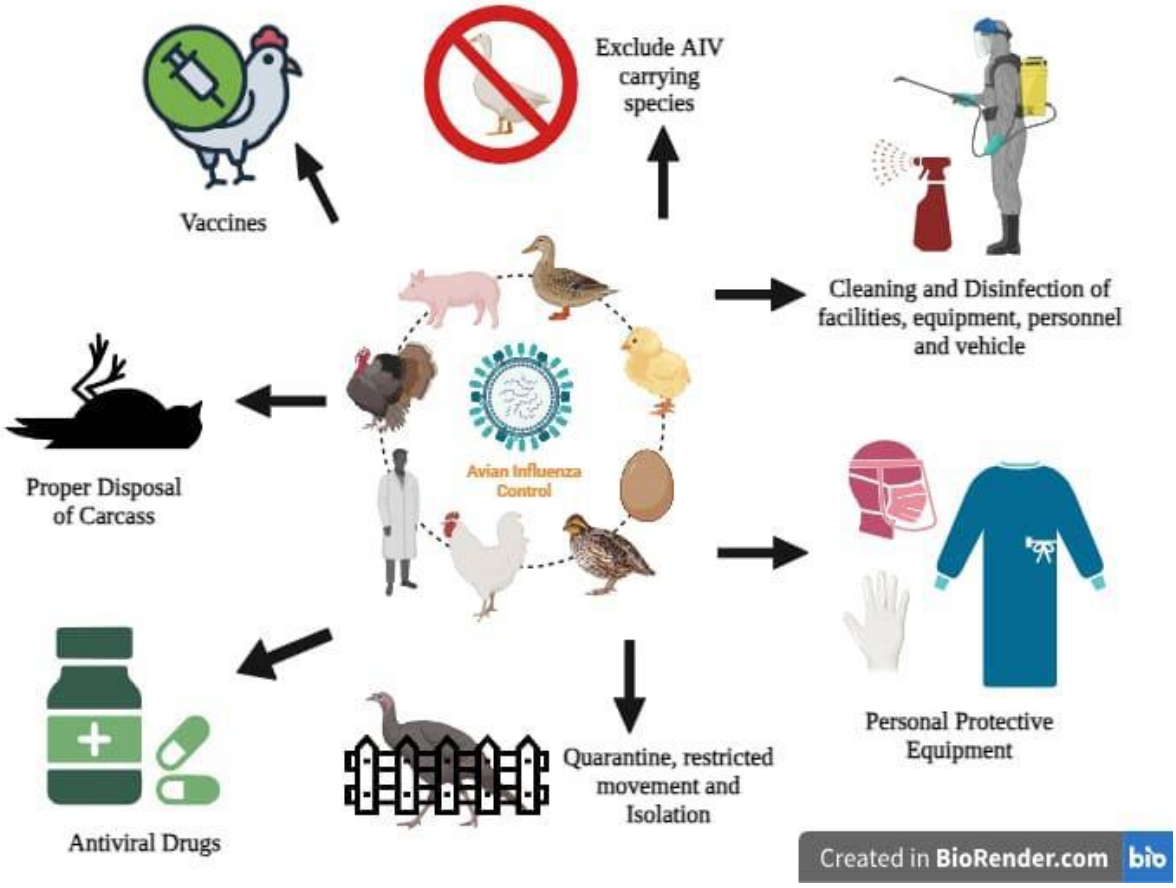

Fig. 1: Control strategies for Avian influenza. Avian influenza virus can infect chicken, turkey, waterfowl, pigs, human etc. For the prevention of the outbreaks of the Avian influenza, cleaning, disinfection and strict biosecurity measures should be adopted to prevent the movement of poultry, wild birds, and other potential carriers at the sites of poultry farming. Individuals should use protective measures to prevent contamination and proper disposal of the dead birds is important to spread the viruses. Poultry farmers should vaccinate their flocks against the avian influenza viruses and antivirals should be used in case of outbreaks.

- Decrease the number of personnel engaged in depopulation and stamping-out activities.
- Efficient management of AI outbreaks within affected flocks reduces the risk of virus transmission to personnel.
- Personnel should strictly follow effective biosafety protocols to prevent further virus dissemination and personal exposure.
- Eating and smoking are strictly forbidden in work areas, and any contact between potentially contaminated hands and the nose, mouth, and eyes should be prevented.
- Once depopulation and stamping-out operations are finished, all PPE needs to be disposed of properly or cleaned and disinfected completely.

Individuals who are in close proximity to potentially infected birds or who could be at risk of infection should wear the designated personal protective equipment including disposable head cover, facemask, protective goggles, waterproof apron, long sleeved overalls, rubber gloves and boots.

Whenever possible, individuals working in the poultry field should be vaccinated against the seasonal influenza viruses to decrease the risk of co-infection and genetic reassortment between avian and human

viruses. Individuals that come into close touch with diseased poultry or their secretions should take appropriate antiviral medication daily, continuing for 5–7 days after the potential exposure to the virus. All the personnels working with the infected poultry should observe their health closely and report any clinical symptoms such as fever, conjunctivitis, and respiratory issues for one week following any possible exposure.

Personnel protective equipment should be taken off after use, hands should be washed and disinfected in the subsequent order.

1. Start with the gloves.
2. Remove the overalls.
3. Wash and disinfect hands.
4. Take off the protective goggles.
5. Remove the visor and face mask.
6. Finish by washing and disinfecting hands.

8.4. TESTING AND DIAGNOSIS

The definitive diagnosis of avian influenza requires serological and virological techniques to distinguish it from other diseases that can manifest similar symptoms, such as avian pneumovirus, Newcastle disease virus, chlamydia, mycoplasma, infectious bronchitis virus, fowl cholera (*Pasteurella multocida*), infectious laryngotracheitis virus, E. coli, and various bacteria. Concurrent infections with avian influenza are common among poultry. Samples like cloacal, fecal, or tracheal swabs obtained from birds are employed to detect AIVs through conventional methods like virus isolation, or by identifying components of the viral particle such as nucleic acids or proteins. Post-exposure assessment is typically carried out by checking for antibodies against specific viral proteins. With advancing technologies, there is ongoing development of more specific, sensitive, and cost-effective diagnostic assays. The gold standard for the identification of avian-origin AIVs is still viral isolation (VI) in specific pathogen-free (SPF) embryonated chicken eggs (Hirst 1941).

The method involves the inoculation of the samples into the allantoic cavity of chicken embryonated eggs at the 9 to 11 days of incubation. Allantoic fluid will be harvested after 48 hours of incubation and hemagglutination inhibition assay (HAI) assay should be performed for subtyping AIVs isolates hyperimmune sera specifically prepared for different HA subtypes and NDV. Similarly, subtyping of the basis of the NA can be performed through the neuraminidase inhibition assay (NI) by using the sera specific for different NA subtypes.

Other methods to detect the influenza antibodies involve the agar gel immunodiffusion (AGID) assay and the enzyme-linked immunosorbent assay (ELISA). According to OIE, AGID holds the "gold standard" status for anti-influenza antibody detection. It is cost effective and sensitive in detecting anti-influenza NP or M1 antibodies in the sera of chickens and turkeys but it is less consistent for other avian species (Spackman et al. 2009). Real-time reverse transcription polymerase chain reaction (RRT-PCR) is commonly utilized to diagnose AIVs due to its high sensitivity, specificity, and fast detection ability.

8.6. VACCINATION

Vaccination can be regarded as the third line of defense against avian influenza. However, there is often hesitancy surrounding poultry vaccination because these vaccines typically protect against clinical signs rather than infection. Consequently, they can mask outbreaks and facilitate the spread of HPAIV. Vaccination has proven effective in countries where standard stamping-out protocols are insufficient for controlling the spread (Figure 1), when an irrevocable impact on the poultry industry may occur, or when

there is a risk to the food supply (Naeem and Siddique 2006; Villarreal 2007). Routine vaccination is implemented in certain nations as a preventive strategy to limit the spread and protect susceptible populations when avian influenza viruses have become endemic. This approach is commonly used to target H5, H7, and H9 viruses (Domenech et al. 2009; Spackman and Pantin-Jackwood 2014). Most vaccine doses administered in real-world situations have been in Mexico (H5N2 and H7N3) and China, Egypt, Vietnam, and Indonesia (H5N1) in response to outbreaks. Nevertheless, avian influenza remains entrenched in these regions (Swayne et al. 2011). Most avian influenza vaccines used in practical applications comprise inactivated whole virus formulations, enhanced with powerful oil-based adjuvants, and administered through intramuscular injection in multiple doses (Swayne et al. 2011). Numerous inactivated avian influenza vaccines have obtained licenses in the USA and other nations, alongside live recombinant vectors, including fowl pox, Avian paramyxovirus type 1 - NDV, Duck enteritis virus, and Turkey Herpesvirus.(Halvorson 2002; Swayne et al. 2001; Swayne et al. 2000). Recombinant vector vaccines against avian influenza are less prevalent in poultry than inactivated vaccines. Nevertheless, this vaccine category holds the potential for automated mass immunization methods like spray or drinking water administration, offering a speedy, efficient, and cost-effective means of immunization.

Significantly, vaccines that use NDV as a vector for H5 and H7 have demonstrated their ability to induce significant levels of HI antibodies and provide protection to chickens when exposed to challenges from H7N9 or HPAI H5N1 viruses, respectively (Liu et al. 2015).

However, the practical use of these vectored vaccines may be hindered by pre-existing immunity to the NDV vector (Spackman et al. 2014). An alternative strategy involves a chimeric NDV vector in which the F and HN ectodomains are replaced with avian paramyxovirus serotype-2 viruses. This alternative vector is safe and does not cross-react with NDV. It partially protected chickens immunized at one day of age against challenges from the highly pathogenic avian influenza virus H5N1 (Kim et al. 2017).

Moreover, a recombinant vaccine employing a turkey herpesvirus vector to express the HA gene of the H5N1 HPAIV consistently demonstrated robust protection against the same strain. It conferred cross-protection against various clades of the H5N1 highly pathogenic avian influenza virus (Gardin et al. 2016). Unconventional strategies for developing avian influenza vaccines are HA proteins, DNA-based immunization, and live vaccines (Bright et al. 2003).

9. CONCLUSION

Avian influenza viruses pose a multifold threat for animal and human health, as well as global food security. The continuous outbreaks in domestic poultry along with the competence of these viruses to undergo genetic reassortment, pose a constant threat to the poultry industry and raise apprehensions about the emergence of novel strains with pandemic potential. Previous outbreaks of the AIVs highlight the interrelationship between the avian and human influenza viruses which emphasize the need for a thorough interpretation of their evolution and transmission dynamics. Furthermore, continuous surveillance is necessary to predict the future outbreak and viral characteristics circulating in the field.

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Dissemination of Highly Pathogenic Avian Influenza through Wild Migratory Birds

04

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ABSTRACT

Avian influenza viruses (AIVs) pose a significant threat to both poultry and human populations due to their ability to cross species barriers. This review explores the genetic diversity and factors influencing the pathogenicity of Influenza A viruses, focusing on the H5N2 subtypes currently circulating in China. The viral subtypes are determined by Neuraminidase (NA) and Hemagglutinin (HA) genes, with H5N2 variants dominating recent outbreaks. The presence of polybasic cleavage sites in the HA molecule is a key indicator of high pathogenicity. Notably, the NP, PB1, and PB2 proteins contribute to increased pathogenicity. Outbreaks are classified based on cytotoxicity and the presence of polybasic cleavage sites in the HA. The dissemination of AIVs is closely linked to wild birds, especially migratory species. HPAI spread through migratory flyways, raising concerns about cross-continental transmission. The study addresses the role of migratory birds, exploring questions regarding their ability to carry infections while migrating and the involvement of illegal exotic bird trade in viral spread. Surveillance measures are crucial for early detection and preparation, necessitating updated kits and knowledge about wild bird behavior. The global impact of AIVs on the poultry industry is profound, affecting both small and large-scale farmers. Economic losses, culling practices, and societal impacts are discussed, emphasizing the vulnerability of small-scale farmers in developing countries. Prevention strategies involve understanding migratory patterns, implementing effective surveillance, and preparing management protocols. Coordination among organizations and heightened situational awareness are vital components of proactive measures against AIV outbreaks.

Key words: Avian influenza, Genetic diversity, Migratory birds, Viral reassortment, Surveillance

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1. INTRODUCTION

The Influenza A virus (IAV) has the broadest range of hosts and carries extraordinary gene diversity compared to the other two influenza virus types (Zhang et al. 2013). The subtypes of influenza viruses are determined by their Neuraminidase (NA) and Heam-agglutinin (HA) genes, of which there are 18 and 11 forms, respectively. These viruses have a history of infecting avian hosts, as evidenced by analysis of their viral genomes using phylogenetic link. Although the presence of a site for polybasic cleavage on the HA of H5 viruses is an indicator of their high pathogenicity, experiments in chickens have shown that the introduction of polybasic genes into the LPAIV HA does not necessarily produce a fatal phenotype (Bogs et al. 2010). NP, PB1, and PB2 Influenza proteins may make it more pathogenic to an influenza virus.

Classification of Low pathogenic AIV or High Pathogenic AIV outbreaks in poultry often relates to the cytotoxicity of the infectious agent during illness and if the virus possesses a site for polybasic cleavage in its HA molecule (as mentioned above). However, other proteins, including NA, can increase the virus's pathogenicity. Currently, the H5N6, H5N8, and H5N2 viruses of type H5Nx are the newly circulating AIV strains in China. As a result of these viral re-assortments (Lee et al. 2017). A dominant NA molecule may emerge, increasing the pathogenicity and viral particle release. Viral modifications in the Hemag-glutinin proteolytic cleavage site, such as the mutation of numerous non-basic amino acids to basic amino acids, replication of essential amino acids, or mutation with insertion of viral or cellular amino acids, have led to the emergence of high-pathogenic avian influenza (HPAI) viruses from low-pathogenic avian influenza (LPAI) viruses (Swayne et al. 2016). The first cases of the highly pathogenic avian influenza virus in poultry birds were discovered in northern Italy in 1878 (Swayne et al. 2016). Six people died in Hong Kong in 1997 after being infected with the H5N1 strain of the highly pathogenic avian virus (HPAIV), which was first discovered in 1996 in China. The H5 clade 2.3.4.4 (HPAI) subtype H5N8 virus was first identified in chickens in South Korea in 2014. In Europe, North America, and Asia, by the middle of 2015, it has spread to domestic and wild birds (Hall et al. 2015).

2. SUBTYPES

At present, AI viruses can contain surface proteins from any of the nine different neuraminidase subtypes (N1-9) and the 16 different Hemag-glutinin subtypes (H1-16) (Swayne et al. 2016).

2.1. AVIAN INFLUENZA A(H5) VIRUSES

There are nine different subtypes of the A (H5) virus including (H5N1), (H5N2), (H5N3), (H5N4), (H5N5), (H5N6), (H5N7), (H5N8) and (H5N9) (Swayne et al. 2016).

2.2. AVIAN INFLUENZA A (H6) VIRUSES

A (H6) viruses have several subtypes, including LPAI A (H6N1) and A (H6N2). The first known human LPAI A (H6N1) virus infection was reported in Taiwan in 2013 (Swayne et al. 2016).

2.3. AVIAN INFLUENZA A (H7) VIRUSES

The nine subtypes of AIV
A (H7N1), A (H7N2), A (H7N3), A (H7N4), A (H7N5), A (H7N6), A (H7N7), A (H7N8) and A (H7N9) are all currently recognized (Swayne et al. 2016).

2.4. AVIAN INFLUENZA A (H9) VIRUSES:

There are nine recognized subtypes of AIV: A (H9N1), A (H9N2), A (H9N3), A (H9N4), A (H9N5), A (H9N6), A (H9N7), A (H9N8) and A (H9N9). All A (H9) viruses seen in wild birds and poultry across the world are LPAI viruses (Swayne et al. 2016).

2.4.1. AVIAN INFLUENZA A (H10) VIRUSES

A (H10) viruses come in a variety of subtypes, including:
A (H10N3), A (H10N4), A (H10N5), A (H10N6), A (H10N7) and A (H10N8). In 1984, a mink was reported to have A (H10N4), and in 2008, swine (pigs) were found to have A (H10N5). A (H10N3), A (H10N7) and A (H10N8) are the A (H10) virus subtypes reported to have infected humans (Swayne et al. 2016).

3. RECENT OUTBREAKS

When it affects the poultry population, the avian influenza virus (AIV) can lead to severe epidemics (James 2000). However, it occasionally infects people who come into contact with infected birds. A particular illness that has spread beyond its expected endemicity is said to be an epidemic when there are more instances than typical (King et al. 2021). A specific number of cases, meanwhile, is not necessarily required for there to be an epidemic (Bellouet al. 2013). Aside from that, identifying an epidemic also heavily depends on the moment and location of occurrence. So, an epidemic belongs to a particular group of people (community), in a specific place (geographical area) and at a special moment in time (season) (Marchenkoet al. 2011). Since the Gs/GD HPAI viruses first emerged (in 2002), in the outbreaks of HPAI, East Asia has played a significant geographic role that frequently affects aquatic birds in the wild and in captivity (Marchenkoet al. 2015).
Russia, Japan and South Korea are among the nations in East Asia that have frequently been impacted by previous HPAI epidemics in wild birds (Sakodaet al. 2012). In the 20th century, in 1918, 1957, and 1968, three influenza pandemics occurred, resulting in about 0.5 million, 1 million and 05 million fatalities. AIV subtype H5N1 is still the most prevalent subtype. Additionally, the most common region for the geographic scope of epidemics is Asia. A number of the most significant pandemics between 2010 and 2016 were counted in Taiwan, South Korea, China, Japan, India, Israel, and Vietnam. It's due to enhanced clinical and laboratory programs conducted in all of these nations over the past few years, or it may be because these nations have a distinctive environment with plenty of lakes, rivers, creeks, ponds, and creeks that serve as wintering grounds for migratory birds (Jeonget al. 2014).
Cases with a more significant percentage were recorded in Egypt (including Cameroon, Nigeria, Africa, Togo, Libya, Tunisia, Ghana, Burkina Faso, and Cote d'Ivoire). The Spread of the virus in Europe, particularly HPAI H5N8 emergence in Germany, has reinforced the intimate connection between the habitats of wild birds and the pathogen dissemination through their migration (King et al. 2021). The greatest H5N2 epidemic ever documented in the United States occurred between 2014 and 2015, and to stop the expansion of the disease, almost 51 million birds were depopulated. Twenty-five million birds, or 409,836 every day or 284 per minute, were killed between May and June 2015 in the United States (Chatziprodromidouet al. 2018).
The government spent a total of US$879 million during the 2014–2015 H5N2/H5N8 epidemic, while more than US$3 billion was paid by the United States egg and poultry industries to stop the disease from infecting poultry. In the USA, this HPAI outbreak was the most expensive. Due to the new wave of HPAI H5N8 viruses in numerous European nations saw severe outbreaks of wild and poultry birds in the first half of 2020 (Jacobs 2022).

There were many bird flu outbreaks reported in Europe before the end of 2020. (HPAI) High-pathogenic avian influenza virus outbreak has been detected in numerous European nations since mid-October, primarily in wild birds, including Germany, France, Belgium, Sweden, Denmark, Ireland, the United Kingdom and Netherlands (Hall et al. 2015). Other poultry and captivity birds tested positive as well. Three different types of Highly pathogenic avian influenza viruses, A(H5N1), A(H5N5), and A(H5N8), were discovered, with H5N8 being the most often found, declared by the European Center for Disease Prevention and Control (ECDC). To stop the H5N8 virus from spreading, 29,000 hens were slaughtered in Germany (Lee et al. 2020).

4. UNITED STATES 2022–23 OUTBREAK

All Health Monitoring Agencies working for the betterment of public health in the United States collaborated and worked on the pandemic wave. Data came on board revealing that a single wave of the viral activity resulting in deaths of many birds following the second wave which came around the end of 2022 which impacted the major Nine areas of the America (Merced-Morales et al. 2021). Despite strict prevention strategies put in place by the sector following the 2015 outbreak, the most recent outbreak has cost about $661 million to the government, and there is no control to the outbreak in sight (Cox et al. 2000).

4.1. AFRICA 2023 OUTBREAK

In Early December 2020, in the poultry shed rearing, the total number of birds was almost more than 0.1 million. In a small village area of Africa, suddenly, this poultry farm showed numerous mortalities, which created an alarming situation in the Area. The clinical signs and symptoms reported in the birds affected by that infection were swelling of the neck, the pale coloration of the body parts, and congestion in the respiratory (Lo et al. 2022). Given that wild birds in North America that are a carrier of Gs/GD HPAI viruses gives some amount of health danger to people who interact with domestic and wild animals, it is essential for efficient coordination to occur across management organizations and agencies for wildlife, agriculture, and public health (Sleemanet al. 2017).

5. DISSEMINATION THROUGH MIGRATORY BIRDS

In the research and studies conducted on the widespread of highly pathogenic AIV, there is a critical talk about its dissemination through the migratory routes of the wild birds. The burning issue is H5N1 spread to the European countries and is thought to be due to the fly routes of the birds (Kilpatrick et al. 2006). Whenever there is a talk about the pandemic of HPAI strain H5N1 from Asia to the countries of Europe, the only culprit is not the wild birds. We also need to shed a light on the illegal movement of exotic and wild birds and the movement of poultry products through international trade routes (Salzberget al. 2007). Wild birds, which have the nature of migration in their life from Europe to Asia and other countries like Russia and North America, are the central spreading element of the H5N1 virus in pandemics (Feare2007; Gauthier-Clercet al. 2007).

Two significant concerns arise here, which are required to be addressed first, as wild birds are the most discussed element of dissemination for HPAI, but if they get infected with the virus, are they still able to migrate to carry infection? Till now, the answer to this question is not available, as supporting research is silent (Flint 2007). In some studies, it was seen that HPAI infection, especially the Asian strain, does not cause mortality in some wild bird species, like water-fowls (Brown et al. 2006; Keawcharoenet al.

2008). The second question that needs to be answered is that the fly routes of the wild migratory birds are really involved in the dissemination of highly pathogenic types of AIV between the continents and causes pandemics in Europe and North America. There is another point to be noted that many outbreaks of the HPAI virus in wild birds were not the dissemination root cause, which revealed that the new areas where the HPAI pandemic occurs is not linked with the migration behavior of the wild birds which carry H5N1 Infection (Kalthoffet al. 2008).

Various zoonotic infections are disseminated over long distances and change their shape to pandemics through the wild migratory birds when they carry them during their migration from one place to another (Reed et al. 2003). During the regular fly pattern between continents, the most spreading agent is AIV, which is transmitted to long distances via these wild birds (Olsen et al. 2006; Lam et al. 2012).

Low pathogenic type of AIV is usually transferred to long distances during the migration of wild water-fowls (Webster et al. 1992), and these birds carry this low pathogenic strain to other continents like Africa and America (Cappelleet al. 2012). One question still requiring attention: as is there any regional spread of the AIV virus through these wild types of flying birds in the regions? (Normile2005; Hill et al. 2012). The first case of HPAI was reported in Asia in the last of 1995 (Li et al. 2004), which was then seen to spread through the migration of wild birds in other continents, causing many economic losses and taking human lives as well. It was seen that the rate of transmission of HPAI type of H5N1 from birds to Humans and then its transmission from humans to humans itself was not that significant.

The mortality rate was higher, which is why it was widespread among the wild birds and was a serious issue for the human health committees (Webster et al. 2006). Qinghai Lake was the breeding ground for many wild birds that migrate towards other continents, and that's why the particular strain of HPAI H5N1 transmitted to other areas through the wild birds from the lake area (Brown et al. 2008). It was also noted that many birds, after carrying the infection, sometimes don't show any infection as they migrate and shed the virus without showing any signs and symptoms of H5N1 (Keawcharoenet al. 2008). The take-home message was that large-scale transmission of HPAI infection through migratory birds isn't that easy to detect (Gaidetet al. 2008).

6. INFLUENZA THROUGH WATERBIRDS

Many water birds carry infectious viruses, which may be zoonotic, as dabbling ducks and mallards carry avian influenza virus (Olsen et al. 2006). Almost all the antigenic different types, including Hemag-glutinin and neuraminidase, are seen in the dabbling ducks (Fouchier et al. 2005; Olsen et al. 2006; Krauss et al. 2004; Latorre-Margalefet al. 2009). The incidence of occurrence of infection of avian influenza virus in the mallards ranges from 10% in the hot season while it can vary to 60% in the fall season, and this is seen in both nearby continents like Asia and Europe and the northern side of America (Olsen et al. 2006; Krauss et al. 2004; Latorre-Margalefet al. 2009; Wallenstenet al. 2007). This kind of variation may be due to many factors which influence the viral spread and its survival. Factors including the breeding season and the other environmental elements which harbour the viral replication and its widespread are made possible (Stallknechtet al. 1990).

6.1. INFLUENZA THROUGH SHOREBIRDS

Charadriiformes is the class of birds which is found to be a habitat on many continents. Which may be many types of birds named as gulls and terns. It is also seen that the frequency and prevalence of the HPAI type of influenza is little different in Charadriiformes than in the Anseriformes (Kawaokaet al. 1998).

The unique point about the Charadriiformes is that two subtypes are only seen in those birds, which are H13 and H16 (Krauss et al. 2004). Another unique point is the shore birds show HPAI infection most of the hot summers (Kawaokaet al. 1998). Ducks have a different pattern of moving to their breeding grounds compared to other shore birds. While most shore birds migrate during the summer, ducks migrate during the fall season. This leads to a higher transmission of infections during this time for ducks (Stallknechtet al., 1988). Hence, the purpose of this talk is the type of birds living in shore areas of the world are seen to be more important in breeding grounds and for longer periods the presence of infection in the wild type of birds may be important as the transmit the infection during their migration to the northern areas of the world in spring (Lee, et al., 2015).

Many studies conducted on the prevalence and frequency of infection in the Charadriiformes and Anseriformes showed different patterns of infection in both (Tian et al. 2015). In a study conducted, a total of 63 subtypes with the HA and NA genes were detected in more than 13 thousand samples of shore birds in almost 15-16 years (Tian et al. 2015). Two different orders of birds including Anseriformes (geese, swans and ducks) and Charadriiformes (gulls and shorebirds), are the names of wild birds. For the low pathogenic type of HPAI virus type A, wild birds are major dissemination elements (Leeet al. 2017). Ruddy shelducks, great black-headed gulls, great cormorants, bar-headed geese, brown-headed gulls, and common coots in Qinghai Lake are common wild birds (Tian et al. 2015).

When the wild birds migrate on their usual fly routes, it is seen that there are some stopover places for their preparation for next migration (Kim et al. 2009), and they seem to get infected in those places by the domestic poultry in nearby places (Tian et al. 2015). Sanmenxia Clade type 2.3.2.1c-like HPAI virus seemed to spread through this way of migration of wild birds (Li et al. 2014). Countries in Europe and Asia, including Japan, China, Korea and Eastern Europe (Eurasia), are best breeding grounds for wild birds like whooper swans (Uchida et al. 2008). numerous whooper swans which have their breeding ground in China and complete their wintering on that ground (Almost 20,000 birds). More than 10000 birds from the total during their migration breed on the grounds of Sanmenxia, where ducks of East Asian sides also stay and breed. Their migration isn't complete on those grounds, but after arriving in October on Sanmenxia lake, they fly back to their native grounds in Mongolia and Siberia for next spring breeding (Aoet al. 2020).

In Russia and other neighboring countries like Kazakhstan, Genetic re-assortment of highly pathogenic avian influenza virus created new research grounds that linked the pandemics of the H5N8 virus in Europe (in late and early 2020) with these re-assortment strains (Liang et al. 2021).In Asia the studies show that the spread as the pandemic of HPAI, specially the strain, is due to the wild migratory birds that disseminate the H5N1 strain (Tian et al. 2015), .and then these migratory birds take the route to Europe (Xu et al. 2016). Research focusing on the transmission of AIV revealed that the gene flow usually occurs between the routes of the same region, and usual gene flow occurs through them (Lam et al. 2012). In another study, it was seen that migratory flyways of individuals or the partial type may be associated with the gene flow or transmission of AIV through the migration networks (Zhang et al. 2023).

In Early 2015 near the Sanmenxia Lake which is the breeding ground for many migratory wild birds, including whooper swans and other birds, for example ducks from china and nearby countries like Siberia and Mongolia. These birds take their migratory route from Qinghai Lake to Sanmenxia reservoir area. Deaths of more than 100 birds in this area created alarming conditions as it seemed another HPAI virus outbreak, and this outbreak was connected with the fly routes of the following discussed wild birds(Swayne et al. 2020).

In the wake of pandemics, dissemination of the virus through wild birds usually occurs, and it is required to take strict measures about their movement to make surveillance on the virus (Bi et al. 2015). This

kind of early surveillance is helpful in early preparation for such widely spreading viruses. For testing purpose, an updated surveillance kit containing required reagents is needed. Also, new updated knowledge about the wild bird's movement and their virus-shedding behavior can answer the questions about the HPAI ecology, epidemiology, spatial and temporal spread (Fouchier et al. 2005). In a study conducted in 1997, a total of more than 27 thousand samples were collected in the form of cloacal swabs and fresh samples of bird droppings. These samples were tested for the presence of the RNA of HPAI virus type A (Fouchier et al. 2000; Munster et al. 2005). There were two different types of distribution of samples on the basis of the collection as the majority of the samples were taken from the different geographical areas of Sweden and the Netherlands. At the same time, other type of collection was done from the 40 different locations of the world for a pilot study. Wide samples were from the Seagulls, Water geese, Ducks and from shorebirds but these were not the only species as the samples were collected from the 250 different species of birds for HPAI surveillance. Samples from the Greylag Goose, Eurasian Wigeon, Northern Shoveler, Northern Pintail, Common Teal, Black-headed Gull, Mallard, Common Guillemot and Greater White Goose were seen positive. Overall positive surveillance ratio for the HPAI virus was 2.1% in wild birds, but it is noted that it may rise to 60% in the specific geographical areas or the stay points of the wild birds in specific months (Fouchier et al. 2005).

In a study conducted on Northern Pintails (usually takes a fly route between Asia and Northern-areas of America, and it is evident it has shown higher Asian HPAI lineages frequency in areas of Alaska) very little evidence of Asian lineage parts was seen even the study was performed on their areas of breeding (Keawcharoenet al. 2008). It is seen that the genetic base studies done on the Low Pathogenic type of Avian Influenza can be useful for the decision-making in the area wise study or specie-related spread of the Highly Pathogenic type of Avian Influenza. It can be understood that if a route of migration of wild birds or species isn't found to be the culprit for the spread of Avian Influenza of low pathogenic type, it will be very unlikely otherwise for the High Pathogenic type. The same if a species or the migration route seems to support the spread of LPAI, there will be higher Chances of HPAI spread from the same route or the same bird species. Very high chances of genetic re-assortment of two important genes (HA and NA) make it very hard to study the normal pattern. Therefore, the recommended way is complete genetic sequencing, which will open up the surveillance ways for the spread of HPAI pandemics as it will tell us the normal patterns of genetic re-assortment of the LPAI genes (Koehler et al. 2008).

7. GLOBAL IMPACT

The poultry industry as a major part, capturing the 20% share of total protein source in developing countries (Alders et al. 2014). In the recent past, due to the Highly Pathogenic type of Avian Influenza spread across the borders, the killing of millions of birds was practiced to limit the pandemic. Several control measures in Vietnam resulted in the culling and disposal of over 50 million poultry birds in the wake of the HPAI pandemic (McLeod et al. 2005). Economic downfall in the year 2005 estimated by the Food and Agriculture Agency were over billions of Dollars in the East side of the South Asia continent (McLeod et al. 2005). It is seen that these pandemics have great negative impact on both small and large-scale farmers, but small-scale farmers raising poultry in the domestic form in villages are affected greatly than the industrial scale. Industrial-scale farmers face temporary downfall in the form of asset losses or Market worth. The compensation scenario is different in developing and developed countries as many get more than their Market. On the contrary, countries like Cambodia provide no support for affected Farmers (Alders et al. 2014).

In recent past due to the influenza pandemics domestic poultry faced many crises, and the most affected element of the industry was lower-scale poor farmers (Porter 2012). In developing countries

like Vietnam, total losses to the poultry industry, especially to small-scale farmers, were over a hundred Dollars. Production was also hampered for an average of 2-3 months due to the HPAI pandemic in those areas where per-day earning is less than the USA $2 (McLeod et al. 2005). Stunted growth is a major setback in children seen in those areas of Egypt affected by HPAI pandemics. In many countries, small-scale flocks of poultry are reared by women, and they are impacted by these losses (Bagnol2012). In Turkey, it was noted that due to widespread cases of HPAI, culling practices in small-scale village areas rearing domestic poultry resulted in a lower number of school enrolment for girls (Alders et al. 2014).

8. PREVENTION

Highly Pathogenic avian influenza is reported to spread across borders of Europe to Asia. Due to this widespread circulation, it is necessary to understand the mechanism of its propagation in the form of a pandemic across Eurasia. During their flight from Europe to Asia, many birds gather at different stay points, making these geographic regions hot points (Lee, et al., 2015).

Different management strategies by the agencies dealing in hot areas of migratory birds are necessary to obtain the development and application of action protocols to limit the widespread HPAI outbreak. Managers of these agencies should be well aware of the migratory patterns and the stay behavior of wild birds. They should keep a close eye on the type and number of mortality or morbidity during the migration in order to get prepared for any alarming situation. They should maintain proper surveillance of the health of these birds on a territorial or provincial level (Leeet al. 2017).

A second possible step towards determining whether and how to develop and apply management actions to mitigate damages incurred through the dissemination of HPAI via wild birds is to be prepared. Preparations include numerous elements such as coordination and communication within a management organization and with external agricultural and public health agency partners, consideration of the appropriate use of personal protective equipment (PPE) during outbreak events, determining whether and how to document the geographic extent of HPAI outbreaks in wild birds, evaluation of management options to mitigate the dissemination or effects of HPAI viruses, and elevating situational awareness as determined to be appropriate (Lee et al. 2017).

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Prion Zoonoses

05

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ABSTRACT

Prions are strange, unconventional pathogens composed exclusively of protein. They propagate by templating conversion of a brain protein, PrPC, into an alternative conformation, PrPSc. PrPSc is an amyloid. Prions cause fatal neurodegenerative diseases with exceedingly long incubation times to economically valuable domestic animals: scrapie of sheep and goats, bovine spongiform encephalopathy (BSE, popularly known as “mad cow disease”) of cattle, chronic wasting disease (CWD or “zombie deer disease”) of cervids, or camel prion disease (CPrD). While transmission of prions between different species is restricted by barriers whose molecular underpinnings we are beginning to understand, zoonotic transmission of animal prions to humans has occurred at least once, during the BSE epizootic that ravaged European cattle in the 1980´s. In contrast, no cases of zoonotic transmission have been ever associated to scrapie or CWD. The zoonotic potential of CPrD is still unknown. However, factors such as adaptation of PrPSc prions through intermediate species that cohabit with the primary hosts might result in unexpected breaches of transmission barriers. Implementation of active surveillance programs is an urgent necessity. In this chapter, the main biological and pathological features of animal prion diseases are summarized, together with a brief presentation of the analytical techniques used to diagnose them. A description of the current understanding of the mechanism of prion replication, at the molecular level, is also presented.

Keywords: prions, scrapie, bovine spongiform encephalopathy, chronic wasting disease, camel prion disease.

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1. INTRODUCTION

1.1. PRIONS: STRANGE PATHOGENS MADE ONLY OF PROTEIN

The term *prion* was introduced in 1982 by Stanley Prusiner and defined as a "proteinaceous infectious particle" (Prusiner 1982). Prion is pronounced "/*priːɒn*/" (Prusiner SB, many public communications); if pronounced "/*praɪɒn*/", the word refers to a bird, a small petrel of the *Pachyptila* or *Halobaena* genera (Anonymous 2013). Prusiner proposed, and eventually demonstrated, that the pathogen responsible for the infectious neurodegenerative disease scrapie, that affects sheep and goats, is a prion. In 1936, Cuille and Chelle had proven that scrapie was caused by a pathogen with a size typical of a virus (Cuille and Chelle 1938). Given the long period of time, measured in years, between its experimental inoculation and the emergence of clinical signs, it was described as a "slow virus", a taxonomic category created *ad hoc*. However, all efforts to isolate and identify such virus during the following decades were fruitless. Furthermore, evidence accumulated showing that procedures that destroy nucleic acids, such as irradiation with UV light, did not affect scrapie infectivity titers, whereas manipulations that modified proteins, such as treatment with guanidine, did (Prusiner 1998). Prusiner concluded that the agent had to be composed of protein alone, a notion that seemed heretical at the time: how could a pathogen propagate without DNA or RNA? In the following two decades the prion concept gained support and eventually, full acceptance (Prusiner 1998; Aguzzi and De Cecco 2020). Key milestones in this process were the demonstration that knock-out (KO) mice not expressing the prion protein in their brain were completely resistant to prion disease (Prusiner 1998) and the generation of totally recombinant prions (Aguzzi and De Cecco 2020).

Besides ovine and caprine scrapie, prions cause and transmit bovine spongiform encephalopathy (BSE), popularly known as "mad cow disease", chronic wasting disease (CWD) of cervids, and camel prion disease (CPrD). BSE showed the zoonotic potential of prions, as it transmitted in the 1980´s through 2000´s to humans, generating variant Creutzfeldt-Jakob disease (vCJD). About ~300 people died of vCJD and likely many more were silently infected (Requena et al. 2016). Finally, spontaneously generated human prions (*vide infra*) causing a sporadic form of prion disease termed sporadic CJD, have been shown to transmit iatrogenically (Requena et al. 2016) and to cause a localized prion epidemic in Papua New Guinea in the 1950´s termed kuru (Aguzzi and Calella 2009).

2. THE MECHANISM OF PRION PROPAGATION

A mammalian prion is a misfolded conformer of a brain protein termed PrP (prion protein). The normally folded conformer of the prion protein, termed PrP^{C} (cellular isoform of the prion protein) is expressed in many mammalian cells, particularly in the brain. Its function is not fully understood, although it is known to participate in myelination of nervous fibers (Aguzzi and De Cecco 2020). PrP^{C} is a cell membrane protein, tethered to it through a C-terminally attached glucosylphosphatidylinositol (GPI) anchor. It is quite conserved among mammals. Mature PrP^{C} is composed of residues 23-230: the N-terminal 22 residues are cleaved off during maturation. PrP^{C} has two large domains, one globular, in turn made up of three α helices and a short β sheet, and another one highly flexible if not disordered (Aguzzi and Calella 2009). Each of these two domains comprises approximately one half of PrP^{C}. The prion form of PrP, termed PrP^{Sc} (scrapie isoform of the prion protein) has a completely different fold: its C-terminal domain has refolded to a completely flat succession of short β strands connected by short loops (Caughey et al. 2022). These flat domains stack to form a "parallel in-register beta stack" (PIRIBS), forming long amyloid fibrils (Fig. 1). Both PrP^{Sc} and PrP^{C} are variably glycosylated, featuring two, one or no glycans attached to the protein (Prusiner 1998).

Prion propagation consists of a PrP^{Sc}-templated conversion of PrP^{C} into PrP^{Sc}. From the perspective of PrP^{C}, the outermost surface of a PrP^{Sc} is a template. The PrP^{Sc} stack features hydrogen bonds between -C=O and HN- groups in residues located in stacked β strands. But in the outermost surface there is a deficit of such hydrogen bonds, rendering it a "velcro-like" template ready to trap and mold any isosequential PrP stretch coming close to it. And that is precisely what the ~95-124 unfolded stretch of PrP^{C} is (Fig. 1), so templating and conversion of that stretch occurs easily. Once this templating event has concluded, the remaining ~125-230 globular domain of PrP^{C} has to unfold and then refold onto the PrP^{Sc} templating surface.

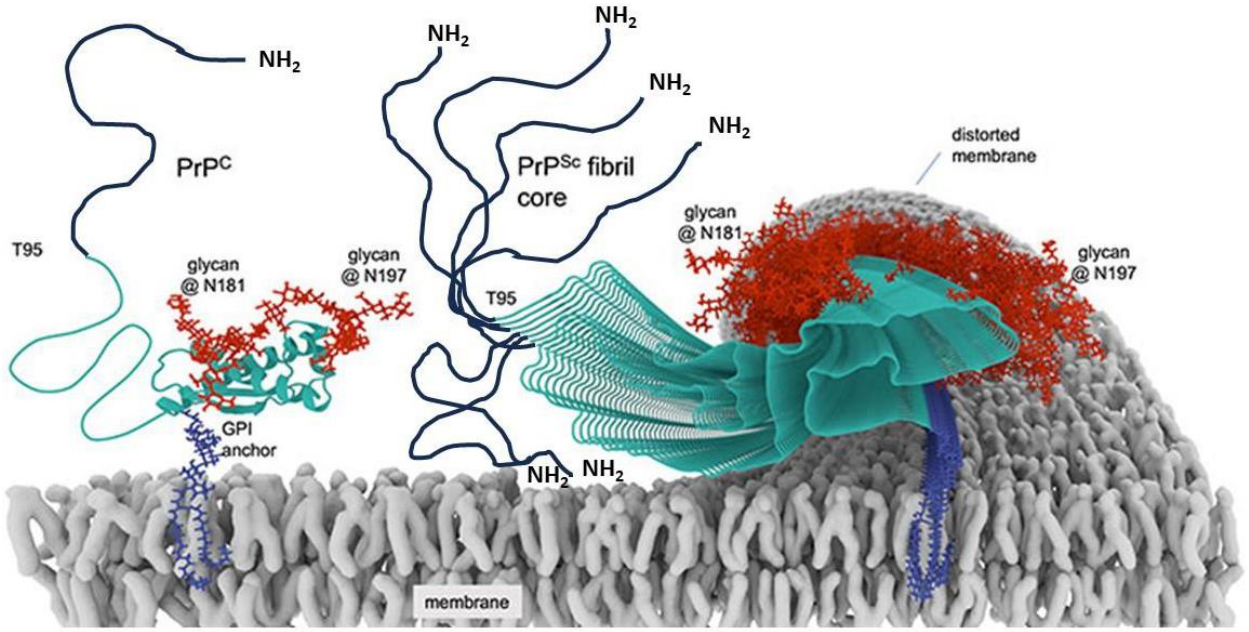

Fig. 1: Propagation of prions: conversion of PrP^{C} to PrP^{Sc}. PrP^{C} (left) encounters a PrP^{Sc} assembly (right) on a neuronal membrane. The amyloid core of PrP^{Sc} (cyan) consists of stacked ~95-230 sections bound together by hydrogen bonds. Each flat, extended PrP^{Sc} monomer is "sandwiched" between two identical PrP^{Sc} monomers, in which each amino acid residue lies on top of and under an identical residue. The extreme N-terminal stretch of PrP^{C} (23-124) which contains many Pro and Gly residues, incompatible with a β-sheet, does not change its conformation and remains highly flexible (in black). GPI anchors are depicted in blue and glycans in red. Modified with permission from Kraus et al. (2021).

Details of how this takes place are still not known. An atomistic model of the entire conversion process was proposed, but it was based on an inaccurate structural model of PrP^{Sc} (Spagnolli et al. 2019). However, its main features are likely to be correct. Once a PrP^{C} unit has been transformed into PrP^{Sc}, the templating cycle can continue *ad infinitum* as long as there is a supply of PrP^{C}. This is why PrP KO mice are refractory to prion infection (Prusiner 1998).

PrP^{Sc} is very resistant to proteases; to be more precise, its compact ~95-230 amyloid core is. Thus, when experimentally treated with proteinase K (PK), the flexible N-terminal ~23-94 tails "dangling" from the amyloid core stack (Fig. 1) are destroyed, but the core itself resists the treatment, remaining as a truncated form of PrP^{Sc} termed PrP27-30 (Aguzzi and Calella 2009) (Fig. 2).

Such unusual resistance to PK is used as the basis to detect prions in animal samples. Resistance to proteases is also key for propagation of PrP^{Sc} prions between animals. When an infected animal dies, PrP^{Sc} prions in its carcass resist autolysis, and being resilient to high temperatures and desiccation, they remain

in the soil and grass, from where they can be ingested by other members of the herd. Ingested prions partially resist enzymes in the digestive tract (Aguzzi and Calella 2009).

From the gut, prions traverse into the subendothelial space, particularly in Peyer patches, via transcytosis across M cells (Fig. 3). Some are transferred to cells of the secondary lymphatic organs (SLO). Conventional dendritic cells play a key role in transfer of prions to follicular dendritic cells. These cells express PrP and provide a first site for PrP^{Sc} replication. Eventually, some can transfer to nerve endings. Then, by retrograde transport, they can move to the brain (Fig. 3). All this takes a substantial amount of time, and propagation in and across the brain, an additional portion, until damage to the brain becomes apparent through clinical signs. During this last phase, propagation is exponential. When the infected animal dies, the cycle begins again.

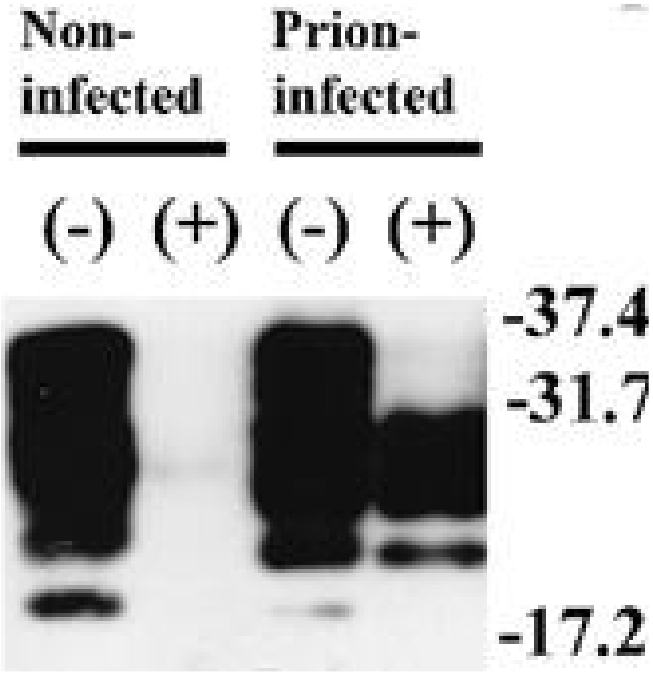

Fig. 2: Western blot of brain homogenate samples from animals not infected or infected with a prion disease. Samples were (+) or not (-) treated with PK and probed with a PrP-specific antibody. Approximate molecular masses are shown. The appearance of different bands is the consequence of di-mono- and nonglycosylated populations of PrP. PrP^{C} exhibits some degree of spontaneous fragmentation in the absence of PK. Adapted, with permission, from Sakudo and Onodera (2011).

Of note, in some prion diseases involvement of cells of the SLO is particularly important, and peripheral, extra-encephalic prions can reach into milk, urine and feces, which become additional sources of infectivity (Mabbott 2017).

3. PRION STRAINS AND TRANSMISSION BARRIERS

While a given PrP sequence results in a single PrP^{C} conformation, dictated by Anfinsen´s principle, it can result in not one but several PrP^{Sc} conformations, all sharing the same basic architecture but exhibiting minor structural nuances (Hoyt et al. 2022). Such PrP^{Sc} variants are known as strains. They maintain their unique structural characteristics as they propagate and give rise to distinct biological properties and pathological phenotypes (*vide infra*). Why different PrP^{Sc} strains cause diseases with distinct phenotypes is not fully understood, but it is a fact that different strains accumulate in different brain areas. Transmission of prions between species involves mismatches between a sequence of PrP^{Sc} and that of the host PrP^{C}. This often leads to steric hindrances, v.g., if the mismatch involves a larger or charged residue in the host´s PrP^{C} that will just not fit into the PrP^{Sc} template (Kraus et al. 2021). This creates a transmission barrier. Since different PrP^{Sc} strains of a given species exhibit conformational differences, transmission barriers with other species can be mitigated or accentuated for different strains (Aguzzi and Calella 2009).

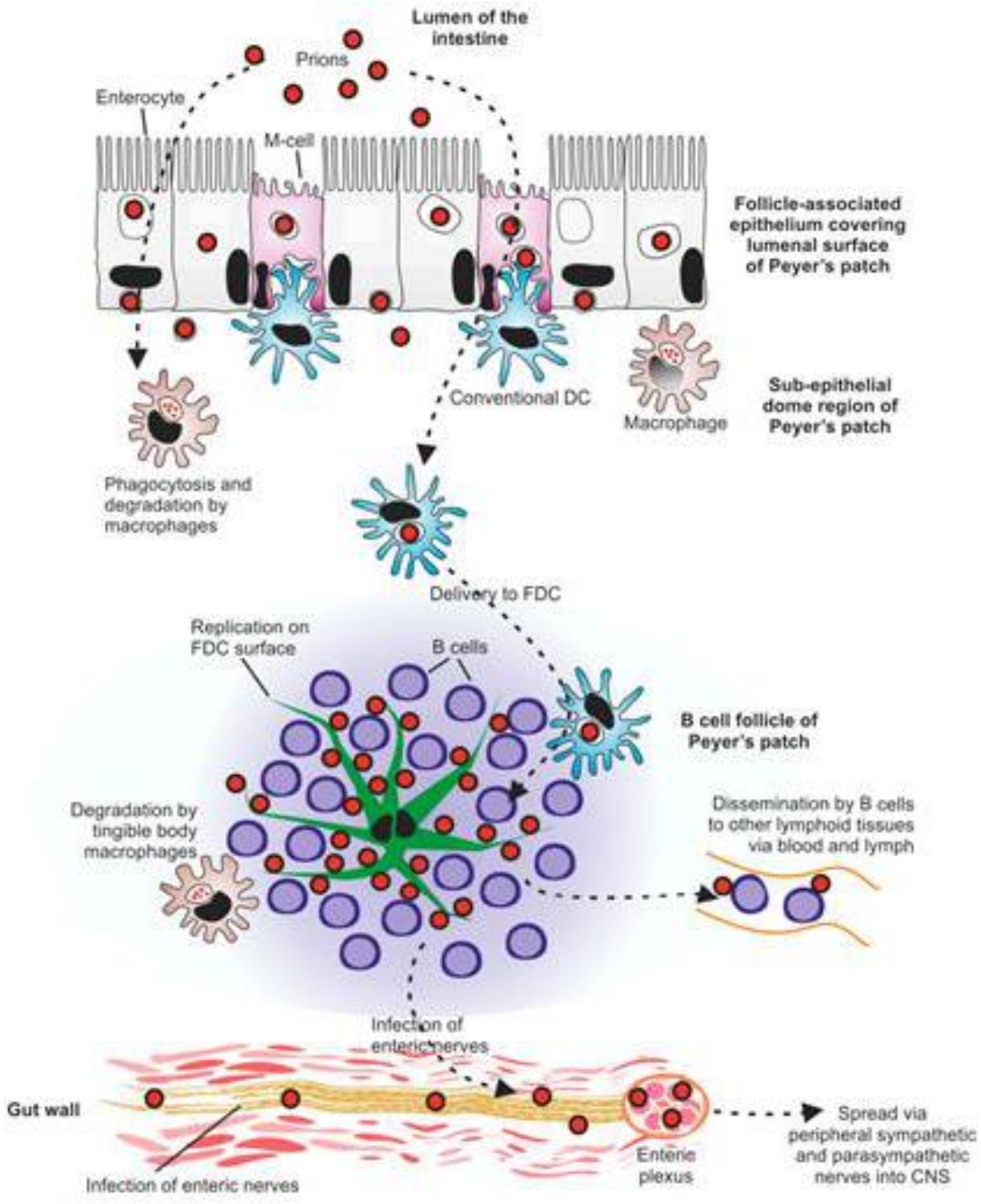

Fig. 3: Passage of prions from the gut to the brain. Prions traverse the intestine mainly by transcytosis through M cells located in Peyer patches. They are subsequently phagocytosed by conventional dendritic cells, that deliver them to other cells of the SLO, including follicular dendritic cells, where prions propagate and accumulate. Eventually, prions reach enteric nerves and are transported to the central nervous system. Reproduced with permission from Mabbott (2017).

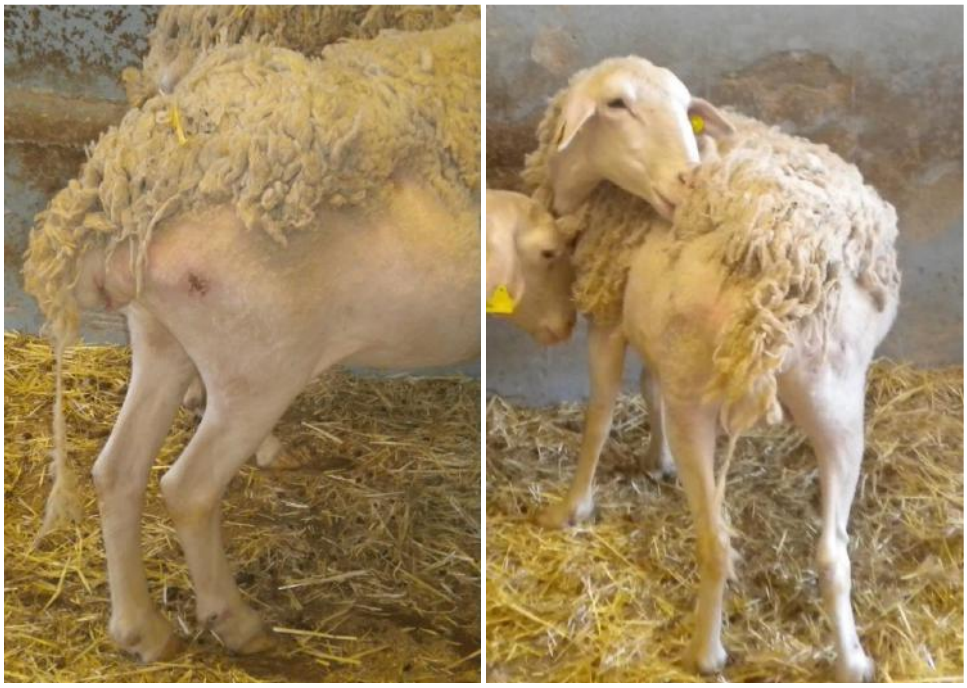

Fig. 4: Clinical manifestations of scrapie. Left: alopecia and cutaneous lesion. Right: scratching. Images by Centro de Encefalopatías y Enfermedades Transmisibles Emergentes, University of Zaragoza, Spain.

4. SCRAPIE

Ovine and caprine scrapie was first documented in England in 1732. Since then, it has spread to become the most widely distributed prion disease worldwide. Nowadays, it is considered as the prototype and model for the study of other prion diseases (Aguzzi and Calella 2009).

Transmission of the classical form of scrapie occurs mainly horizontally, through environmental contamination (Andreoletti et al. 2002) and possibly vertically, via intrauterine transmission (Foster et al. 2013). Animals affected naturally by classical scrapie are usually between 2 and 5 years, with a life expectancy after the onset of the first clinical signs of 1 to 6 months (Collinge and Clarke 2007). Most frequent clinical signs are changes in behavior, such as separation from the herd, loss of body condition, exaggerated response to external stimuli, bruxism with constant lip movements, changes in locomotion patterns (ataxia), head tremors, and the appearance of intense pruritus leading to wool loss (Fig. 4) (Clark and Moar 1992).

In 1998 an atypical form of scrapie, named Nor98, was observed in Norway (Benestad et al. 2008). It differs clinically and epidemiologically from classical scrapie and has its own biochemical and histopathological characteristics. It is also distributed worldwide and has a similar incidence to classical scrapie. Animals suffering from atypical scrapie are usually individuals over 5 years of age and it is common to see isolated cases in the herd (Fediaevsky et al. 2008). Due to its epidemiology, it is considered a non-infectious form of the disease in which a characteristic strain of PrP^{Sc} appears spontaneously in the brain, an extremely rare occurrence of spontaneous misfolding of PrP^{C} to PrP^{Sc} (Benestad et al. 2008; Vidal et al. 2022). Atypical scrapie has been confirmed in areas considered free of classical scrapie, such as Australia (Cook et al. 2016). Common atypical scrapie clinical signs include progressive ataxia, tremors, loss of body condition, circular movements and visual impairment (Simmons et al. 2009). No pruritus and therefore no alopecia have been documented (Acin et al. 2021; OIE, FAO 2022).

Numerous polymorphisms of the PRNP gene (which encodes the PrP^C protein) have been described in different species and have a major impact on the development of naturally occurring prion diseases (Hunter 1997), likely influencing the conversion of PrP^C to PrP^{Sc} (Bossers et al. 1997). Polymorphisms in codons 136, 154 and 171 play an important role in the susceptibility to scrapie. Codon 136 can encode the amino acids valine (V), alanine (A) or threonine (T); codon 154 encodes arginine (R), histidine (H) or leucine (L) and codon 171 can code for arginine, histidine, glutamine (Q) or lysine (K). However, out of all possible alleles, only five of them appear with a high frequency: A136R154Q171 (original gene variant, abbreviated as 'ARQ'), ARR, ARH, AHQ and VRQ (Hunter 1997; Goldmann 2008).

Ewes expressing the VRQ or ARQ alleles have a high vulnerability to classical scrapie, whereas the expression of the ARR allele confers resistance. In addition, the ARR haplotype has a dominant effect, and both homozygous and heterozygous animals are at lower risk for this prion disease (Belt et al. 1995). This genetic knowledge has been used for years to genetically select sheep flocks to achieve greater natural resistance to classical scrapie and thus reduce its incidence. But it should be noted that no fully resistant genotype has been detected. Additionally, it has been observed that atypical scrapie appears more frequently in sheep with genotypes associated with a higher resistance to classical scrapie along with homozygosity for phenylalanine at codon 141, while individuals carrying the VRQ allele rarely develop the disease (Tranulis et al. 2011).

Several polymorphisms associated with scrapie susceptibility have also been reported for the goat PRNP gene. Specifically, polymorphisms H143R, R154H, R211Q and Q222K represent an increase in the resistance to classical scrapie, although R154H has been associated with increased susceptibility to atypical scrapie (Holko et al. 2005; Lacroux et al. 2014). Detailed PRNP sequence studies of Pakistani goats have been carried out, given the economic importance of these animals as sources of milk and meat in this country (Hassan et al. 2016).

5. BOVINE SPONGIFORM ENCEPHALOPATHY

BSE was first diagnosed in the United Kingdom in 1986 (Wells et al. 1987). Shortly after, it spread and caused one of the most significant food crises in Europe in recent decades. Animals infected with BSE have incubation periods of 4 to 5 years and exhibit clinical signs similar to those observed in sheep with scrapie, including emaciation, alopecia, apprehension, lethargic or aggressive behavior, hypersensitivity to stimuli, and abnormal movements (Kobold et al. 2006).

Several hypotheses have been formulated regarding the origin of BSE, but the most widely accepted one has been the practice of feeding cattle with meat and bone meal contaminated with infectious prions (Wilesmith et al. 1991). This led to the implementation of a series of measures by different countries to break the transmission cycle of this disease. Thanks to these efforts, its incidence was drastically reduced, although it has not been completely eradicated.

The presence of PrP^{Sc} in animals infected with BSE, unlike scrapie, is mainly limited to the nervous system. However, low infectivity has been described in the small intestine (Peyer's patches), distal ileum, jejunum (Hoffmann et al. 2011), and tonsils (Wells et al. 2005). Moreover, infectivity has been detected in skeletal muscles due to the centrifugal spread of the agent through nerves via motor and/or sensory pathways to muscle tissues. It was important to define specific risk materials to prevent the entry of BSE-contaminated materials into the food chain (Okada et al. 2014).

BSE has demonstrated a great capacity for transmission to other species (Bruce et al. 1994). During the 1980s, it spread to humans, leading to the emergence of vCJD (Bruce et al. 1997). It was also detected in cats and zoo animals, resulting in feline spongiform encephalopathy (FSE), and exotic ungulate encephalopathy (EUE) (Sigurdson and Miller 2003). In 2005, the first case of natural BSE in goats was detected in France (Eloit et al. 2005), repeated a year later in the United Kingdom (Jeffrey et al. 2006).

These studies suggested that goat BSE could pose a potential risk to human health, necessitating improvements in control strategies.

In 2004, two new neuropathological and molecular phenotypes of BSE were detected, classified into two groups based on their biochemical and biological characteristics. The L-type BSE or L-BSE was detected for the first time in Italy (Casalone et al. 2004). Affected animals showed significant differences in the distribution of the encephalic lesions compared to animals infected with classical BSE (C-BSE). On the other hand, H-type BSE (H-BSE) was described for the first time in France (Biacabe et al. 2004). Currently, atypical BSE cases are still reported in several European countries (OIE, FAO. 2022). These cases are diagnosed in adult cattle and their origin is unknown, although it has been proposed that they could be sporadic, as proposed for atypical scrapie. Polymorphisms of the PRNP gene described in cattle (W84R, G100S, K113R, V115M, H143R, S146N, and N177S) have little impact on susceptibility or resistance to BSE (Seuberlich et al. 2010).

6. CHRONIC WASTING DISEASE

CWD affects different members of the Cervidae family, especially elk, moose, and various species of deer. CWD was first identified in captive mule deer (*Odocoileus hemionus*) and black-tailed deer (*Odocoileus hemionus columbianus*) in the late 1960s in Colorado, United States (Miller et al. 2000). Soon after, the disease was identified in contiguous Wyoming, Nebraska, and South Dakota, affecting captive and free-ranging populations (Williams and Miller 2002). Surveillance programs suggested that CWD was endemic among free-ranging deer and elk in this region of North America, indicating that CWD had been spreading through wild cervid populations within this endemic area for decades before its detection. The high prevalence of CWD in some states of the U.S. is a major cause for concern (DeVivo et al. 2017). CWD cases have been reported in twenty-six U.S. states, three Canadian provinces (Rivera et al. 2019), three Scandinavian countries (Tranulis et al. 2021) and two South Korean provinces (Lee et al. 2013). Natural migrations of free-ranging populations and commercial exports contributed to a fast geographical expansion. Epidemiological investigations revealed that CWD cases in South Korea were imported from Canadian farms. In 2016, CWD was also identified in wild reindeer and moose in Norway, followed by the detection of more cases in a semi-isolated reindeer population (Benestad et al. 2016). In an attempt to control the spread of cases in that area, the Norwegian authorities took the drastic decision to cull this entire reindeer population. Testing resulted in 18 positive cases out of 2400 post-culling samples (Tranulis et al. 2021). Intensive surveillance enabled detection of isolated cases in Sweden and Finland. Although the origin of CWD cases in Europe remains unclear, it does not seem to be related to the outbreaks in North America (Miller et al. 2000). No cases of CWD have been described in Pakistan.

Histopathological features vary among the cervid species and the geographical distribution of the populations. Overall, CWD-infected animals present extensive deposition of PrP^{Sc} in lymphoid tissues, which are detectable in the early stages of the disease, and in the central nervous system (Sigurdson et al. 1999). The incubation period and disease progression are also highly variable and are associated with the species, the route of infection, the dose of infectious agents, and the genetic background (Otero et al. 2021). During progression of the disease, animals usually show loss of body weight, hypersalivation, and behavioral changes such as dropped head and ears, and loss of fear of humans. At advanced clinical stages, animals present incoordination and a decline of the body condition (Moreno and Telling 2018).

CWD transmission is highly efficient, and horizontal transmission has been proposed as the main mechanism of infection. CWD prions have been found in saliva (Henderson et al. 2013), urine (John et al. 2013), blood (Mathiason et al. 2006), feces (Pulford et al. 2012), and lymphoid tissues (Benestad et al. 2016). CWD PrP^{Sc} prions persist in the environment for years. They contaminate the soil (Kuznetsova et al.

2014), grazing areas, and water sources (Nichols et al. 2009). Additionally, CWD prions have also been experimentally transmitted from doe to fawn, indicating that vertical transmission is also a possible route of infection (Nalls et al. 2013).

To date, no natural transmission of CWD to humans has been described. Nonetheless, experimental studies have successfully transmitted CWD to various animal species that cohabitate with cervids, such as cattle, sheep, goats, ferrets, minks, raccoons, and mice, indicating that CWD entails a potential risk of cross-species transmission and rising concern about its zoonotic potential (Kurt and Sigurdson 2016).

7. CAMEL PRION DISEASE

In 2018, a prion disease affecting dromedaries (*Camelus dromedarius*) was detected in Algeria. It is estimated that 3.1% of the dromedaries slaughtered in Ouargla between 2015 and 2016 had presented clinical signs compatible with prion disease including weight loss, behavioral abnormalities, tremors, hyperexcitability, abnormal movements of the neck and head, ataxia, falls, and difficulty getting up (Babelhadj et al. 2018). Diagnosis was confirmed following the observation of spongiform degeneration and PrP^{Sc} deposition in the central nervous system of affected animals. It has been demonstrated that the PrP^{Sc} prions causing this disease have biochemical characteristics that are different from those of BSE and scrapie (Babelhadj et al. 2018). The presence of PrP^{Sc} in lymphoid tissues of affected animals suggests the contagious nature of CPrD, although the origin of the disease is still unknown. It was suggested that CPrD could have originated from sheep scrapie since dromedaries are often raised alongside sheep and share common pastures. However, scrapie has not been reported in Algeria. The nomadic herding of dromedaries could have contributed to the spread of the disease at long distances (Babelhadj et al. 2018).

Pakistan has around 1.1 million camel heads, being one of the ten biggest camel producer countries in the world. These animals are an important source of milk, meat and transportation (Faraz et al. 2019). In Pakistan, camel production systems primarily rely on sedentary regimes, where dromedaries are raised from birth to finishing (Faraz et al. 2021). Camels are a vital species for millions of people worldwide. For this reason, attention and investigation are required when a prion disease emerges in a new species and new geographical areas. Implementing a surveillance system and improving the diagnostic capacity for prion diseases in countries where dromedaries are an important part of the domestic livestock would control CPrD and minimize zoonotic risks.

8. ZOONOTIC POTENTIAL OF PRIONS

For decades, it was known that scrapie affected sheep; however, the zoonotic potential of animal prion diseases was considered negligible. This perception dramatically changed in the 1990s, when the emergence of vCJD was associated with the outbreak of BSE in cattle. This event triggered a public health crisis in Europe and demonstrated the zoonotic potential of animal prion diseases (Will et al. 1996; Bruce et al. 1997).

As mentioned, the transmission of prions between different species is governed by a transmission barrier. This refers to a natural resistance to propagate prions from other species and arises mainly from differences in the primary structure of prion protein (Béringue et al. 2008a). It should be noted that the transmission barrier is not absolute, and under certain circumstances, prions can adapt and overcome it. This likely involves a slight conformational change in the templated product to avoid any hindrance(s) posed by PrP sequence differences.

As a result of the transmission of C-BSE to humans and the emergence of vCJD, the transmission barrier between different animal prion diseases and humans has been extensively studied to assess their zoonotic

potential (Torres et al. 2016). The use of transgenic mice expressing the human PrP enabled to relate the outbreak of C-BSE with vCJD and to study the zoonotic risk of the atypical variants of BSE. These studies showed that L-BSE presented equal or greater virulence than C-BSE, suggesting that this prion disease entails an important zoonotic risk. On the contrary, H-BSE presented a high transmission barrier, indicating that this variant poses a lower zoonotic risk (Béringue et al. 2008b).

Regarding scrapie, whereas epidemiologic studies have not associated exposure to small ruminant products as a risk factor for developing CJD, experimental transmission of classical scrapie isolates to non-human primates has raised concern about the zoonotic potential (Comoy et al. 2015). On the other hand, transmission of classic and atypical scrapie isolates to transgenic mice expressing human PrP show non-conclusive results. Successful transmission of scrapie isolates to humanized mice depends on multiple factors such as polymorphisms in the human PrP sequence. Overall, results showed subclinical infections or inefficient transmission on the first passage but clear infectivity after serial passages, suggesting some zoonotic potential of scrapie (Torres et al. 2016).

Infectivity of several CWD isolates has been tested in humanized mice expressing different human PrP polymorphic variants, and all of them failed to show clinical symptoms or accumulation of CWD prions in the brain (Kong et al. 2005; Wilson et al. 2012; Kurt et al. 2015). Transmission of CWD has also been assessed in non-human primates with contradictory results. While one experiment demonstrated transmission of CWD to cynomolgus macaques, another failed to show infectivity by intracerebral inoculation in animals of the same species (Race et al. 2014; Moreno and Telling 2018). Altogether, these data have prompted concern about the risk of CWD for public health.

9. METHODS TO DETECT PRIONS

The diagnosis of prion diseases usually involves a combination of clinical and laboratory diagnostic methods. Clinical diagnosis is not definitive, as the clinical signs are nonspecific and similar to those of other pathologies. Thus, definitive diagnosis is always postmortem (Wilesmith et al. 1992; Konold et al. 2004; Williams 2005).

Traditionally, the diagnosis of prion diseases has been based on histopathological analysis of central nervous system tissue samples by light microscopy in search of characteristic histological lesions such as vacuolization, spongiform change (Fig. 5), gliosis, neuronal degeneration and loss, and amyloidosis (Wells and McGill 1992; Ligios et al. 2002). For example, BSE is characterized by the presence of vacuolization mainly in the medulla oblongata at the level of the obex (Jeffrey and González 2004) and also in the central gray matter, rostral colliculus, and hypothalamus (Simmons et al. 1996; Ganley et al. 2015). Both classical and atypical scrapie show similar lesions, although they differ in the distribution pattern of vacuolization. Thus, while classical scrapie is usually characterized by bilateral and symmetrical vacuolization in the spinal cord, brainstem, and hypothalamus, in atypical scrapie there is no vacuolization in the brainstem, being more frequent in the cerebellar and cerebral cortices, and in the basal ganglia (Wood et al. 1997).

However, lesions are not always observed. Therefore, the most commonly used laboratory diagnostic methods are currently based on the detection of PrP^{Sc} accumulation in tissue samples, as it occurs prior to the appearance of lesions (Grassi et al. 2008). Western blot (Fig. 2) and immunohistochemistry (IHC) (Fig. 5) are two gold standard diagnostic techniques based on the detection of proteinase K-resistant fragments of PrP^{Sc} by means of specific antibodies. Western blot allows the detection of PrP^{Sc} and the characterization of prion strains by the different electrophoretic patterns as a result of their different degrees of glycosylation and sites of proteolytic cleavage (Grassi et al. 2008; Orge et al. 2021). On the other hand, IHC allows the detection of PrP^{Sc} deposits *in situ* and identification of their cellular location, tissue distribution, and morphological characteristics (Grassi et al. 2008; Orge et al. 2021). In classical scrapie,

PrP^{Sc} accumulations are mainly observed in the medulla oblongata, at the level of the obex, both intraneuronal and outside the neurons (González et al. 2003), as well as in lymphoid tissues associated with the third eyelid, palatine tonsils or rectal mucosa (Espenes et al. 2006). The PrP^{Sc} deposits in lymphoid tissue in classical scrapie can be used for the detection of preclinical non-symptomatic infected sheep (Monleón et al. 2011). However, sheep with classical scrapie-resistant genotypes hardly accumulate PrP^{Sc} in lymphoid tissues (Jeffrey et al. 2002; Ersdal et al. 2003). In atypical scrapie, on the other hand, PrP^{Sc} deposition is mainly localized in the cerebral cortex and cerebellum, at the perineuronal level, and in the neuropil (Benestad et al. 2008), without occurrence in peripheral lymphoid tissue (Moore et al. 2008).

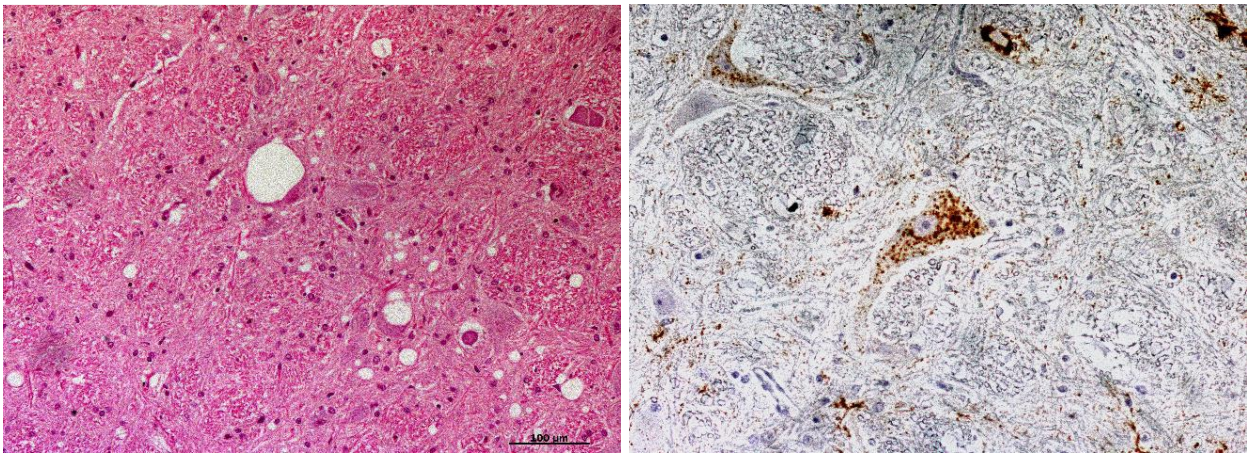

Fig. 5: Brain histopathology of prion diseases. Left: spongiform change. Right: PrP^{Sc} deposits stained with a PrP specific antibody (brown signal). Intra- and extracellular deposits are seen. Images by Centro de Encefalopatías y Enfermedades Transmisibles Emergentes, University of Zaragoza, Spain.

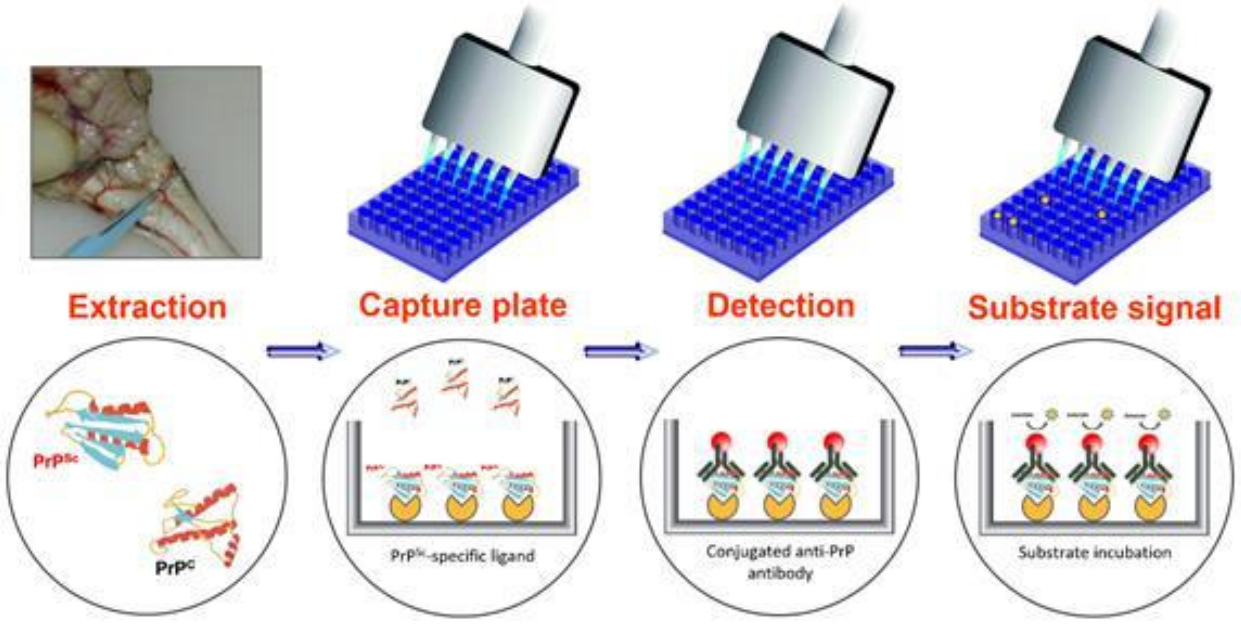

Fig. 6: Scheme of a rapid (ELISA) test to detect prion disease. After sampling, tissue is homogenized and analyzed with a commercial kit. The structure of PrP^{Sc} shown is not realistic.

There also exist rapid tests, which stand out for their usefulness in surveillance and eradication programs since they allow the diagnosis of a large number of animals in a short period due to their speed and simplicity (Fig. 6). In general, these tests are based on immunodetection of PrP^{Sc}, for which most of them include a first step of distinction between PrP^{C} and PrP^{Sc} based on their different biochemical properties, especially the relative resistance of PrP^{Sc} to digestion by PK. In addition, all rapid tests include a denaturation step of PrP^{Sc} for subsequent detection by anti-PrP antibodies. A positive result obtained with these tests is not definitive, and it is necessary to confirm it by Western blot or IHC (Esteves et al. 2021).

10. CONCLUDING REMARKS

The BSE epizootic, with transmission of prions to humans (vCJD), was a hard awakening. While epidemiological and experimental studies show that the zoonotic potentials of scrapie, CWD and CPrD are limited, factors such as adaptation of PrP^{Sc} prions through intermediate species that cohabit with the primary hosts might result in unexpected breaches of transmission barriers. Implementation of active surveillance programs is an urgent necessity.

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Status of Chemical Antibiotics Against Bacterial Zoonosis

06

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ABSTRACT

Bacterial zoonoses are a major threat to the world even if we try to control and eradicate them. This happens when we use a lot of antibiotics which can make the bacteria resistant. These diseases like bubonic plague, bovine tuberculosis, and glanders caused a large loss a long time ago. Chances to get these diseases through close contact with farm animals, treating pets like a family, and some jobs. These diseases still affect us. We diagnose these diseases through better testing techniques. In this study, we talk about relationship of bacterial diseases and resistant. We explain how diseases like anthrax, salmonellosis, bovine tuberculosis, lyme disease, brucellosis, and plague are treated with antibiotics. People with weak immune systems are at high risk. These diseases are treated by using chemical antibiotics like ciprofloxacin, levofloxacin, doxycycline and others but they are not working as well because of resistance. This section looks at global importance of antibiotics, how they work, how bacteria become resistant. Animals can carry resistant genes of bacteria and transfer to the people. This chapter explains bacterial zoonosis, how diseases spread and role of animals. We look at specific germs like Pasteurella, salmonella, brucella, campylobacter, Coxiella burnetti, laptospira, and Bordetella bronchiseptica, discussing about how they resist antibiotics and what we can done. We also discuss other ways to treat these diseases, like using phytochemicals, nanoparticals, chemothrepies and vaccines. We highlight the problems with these methods and say that still need more search and new ideas to treat these diseases and solution of antibiotic resistance.

Keywords: bacterial zoonoses, antibiotic resistance, chemical antibodies, phytochemicals, nanoparticals

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1. INTRODUCTION

Bacterial zoonoses are one of the major zoonotic diseases which could relapse meanwhile we are considering them to be eradicated or under control. The main concern behind this is the excessive or repeated control of antibiotics which leads to the culminating antimicrobial resistance and results in a lot of health problems (Paho 2001). About a century ago when there were no vaccines and a severe lack of hygiene, some bacterial zoonotic diseases caused millions of deaths and irreparable loss to farmers. Such mentionable diseases are bubonic plague, bovine tuberculosis, and glanders. Inflicted by heavy losses due to bacterial zoonotic diseases in the past, such countries are paying special heed to the issue and investing huge resources in the better screening of animal products to maintain good preventive health (Blancou et al. 2005). Surveillance programs and improved diagnostics have detected various bacterial zoonotic diseases. Very close contact with the food animals and the modern lifestyle in which the pets are treated as family members have escalated bacterial zoonotic diseases. (Glaser et al. 1994; Tauxe 1997). People such as veterinarians, abattoir workers, farmers, butchers, and lab workers are at a high risk of acquiring bacterial zoonotic diseases. Immunosuppressed people are also highly susceptible such as temporary immunosuppression in case of infancy and pregnancy while long-term immunosuppression includes chronic diseases (AIDS), diabetes, organ transplant, etc. A typical example is the bubonic plague that hit Surat, India in 1994 and it caused a huge loss of about 2 billion dollars (Marsh 2011).

Zoonotic pathogens are carriers of AMR (antimicrobial resistance). ARBs (Antibiotic-resistant bacteria) are the most common zoonotic pathogens. The emergence of ARB is directly proportional to the excessive use of antibiotics in farm animals. Such zoonotic pathogens after reaching the human gut, transfer the ARG (antibiotic-resistant gene) to the human gut's microbiome. Thus rendering the use of antibiotics useless (Hathroubi et al. 2018). Important bacterial zoonotic diseases are anthrax, salmonellosis, bovine tuberculosis, Lyme disease, brucellosis, and plague (Chomel 2009). Keeping in view the AMR, however, here we will shortly discuss the role of chemical antibiotics in treating bacterial zoonotic diseases. In the case of anthrax, the standard antibiotics used are ciprofloxacin, levofloxacin, or doxycycline. Treatment is effective if started at the initial stage of onset of the disease (Wilson 2020). For treating Salmonellosis, anti-diarrheal like Loperamide are used which reduce the pain due to cramping in diarrhea. Antibiotics are usually not prescribed in this case because they prolong the course of infection which may result in the spread to others (Hohmann 2021).

Mycobacterium Bovis which is the causative agent of bovine tuberculosis is usually resistant to Pyrazinamide but it is treated with a combination of antibiotics. First-line chemotherapies for the treatment of Bovine tuberculosis include rifampin, pyrazinamide, isoniazid, Streptomycin, and Ethambutol. While Capreomycin(CAP), Thioacetazone, and cycloserine are second-line drugs (Waters et al. 2015). For Lyme disease, antimicrobial therapy is useful if administered early after the detection of erythema multiform lesions (Asch et al. 1994). But it would be less effective after the disease has progressed, hence the treatment course should be extended (Shadick et al. 1994; Moody et al. 1994). The treatment course is 2-3 weeks in case of early diagnosis is Amoxicillin or doxycycline administered provided that the patient has no neurological abnormality (Wormser et al. 2006). The patient responds but it may be slow or incomplete (Wormser et al. 2000). The most widely studied treatment for brucellosis is the combination of doxycycline and aminoglycosides. To obtain a high therapeutic rate and less rate of relapse, this treatment duration should be eight weeks (Solís Garcia Del Pozo and Solera 2012; Hasanjani et al. 2006; Hashemi et al.2012; Solera et al. 1995; Bayindir et al. 2003; Roushan et al. 2010; Ersoy et al. 2005).

2. OVERVIEW OF BACTERIAL ZOONOSIS

The term "Zoonoses" is a combination of two Greek words, i.e. "Zoon" means "Animal" and "noses" means "illness". Bacterial diseases that are naturally transmitted from Vertebrate animals to humans with

or without vectors are called bacterial zoonotic diseases (Taylor et al. 2001). According to the older system, zoonoses are classified as Anthropozoonoses, Zooanthroponoses, Amphizoonoses, and Euzoonoses. Here, the discussion is on the bacterial diseases transferred from animals to humans known as Anthropozoonoses (Hubálek 2003). Gram-positive as well as Gram-negative bacteria can induce zoonoses 42% are bacterial pathogens among the zoonotic pathogens arising from bovine origin (Bae and Son 2011). Pathogens from animals can be transmitted to humans directly or indirectly. Direct zoonoses include diseases transmitted directly from animals to humans through any media, such as air. There is a vital role of domestic animals in the transmission of zoonotic diseases to humans. These pathogens are derived from wild animals; domestic animals then amplify these pathogens or serve as reservoir hosts (Morand et al. 2014). These animals include cattle, horses, sheep, goats, dogs, cats, and pigs (Samad 2011). More than half of humans' infectious diseases are induced from vertebrate animals (Taylor et al. 2001). The possible means of transmission are direct contact, biting, abraded skin or mucous membrane, inhalation, ingestion, and conjunctiva (Klous et al. 2016).

Animal bites and scratches induce the most commonly suffered bacterial zoonoses in humans (MMWR 1997-48). There are hundreds of pathogenic bacteria, including Pasteurella species, in the oral cavity of dogs and cats (Goldstein and Richwald 1987). A deep bite near bones and joints may result in osteomyelitis and septic arthritis. Cat scratch disease has been reported to people since a century ago. It is a clinical syndrome with the etiological agent *Bartonella henselae* transmitted through scratches and bites of cats (Stechenberg 2011). Once a person gets infected with cat scratch disease, the clinical signs appear in the form of pustules, papules, and abscessations. If not treated, it may develop into osteomyelitis, encephalopathy, and granulomatous conjunctivitis.

Infectious diarrhea in pets has also been reported to be transmitted in humans via the fecal-oral route. It is caused by salmonella species, campylobacter species, shigella species, and E.coli (Lahuerta et al. 2011). Enteropathogens induce gastrointestinal disturbances such as vomiting, diarrhea, headache, depression, and dehydration in severe cases may lead to death. Pet birds(songbirds such as parrots, finches, and sparrows) contain a smaller proportion of pets. They may have harmful impacts on human health by transmitting zoonotic diseases, which include psittacosis (chlamydophilosis), salmonellosis, and campylobacteriosis (Vanrompay et al. 2007; Wedderkopp et al. 2003; Carlson et al. 2011). *Chlamydia psittaci* is an intracellular pathogen in the respiratory tract of songbirds; it is the causative agent of Chlamydophilosis(Psittacosis) transmitted to humans by aero solar means dust, dander, and nasal secretion of birds (Circella et al. 2011; Dorrestein 2009). Flu-like illness develops which may be mild to severe. It may be misdiagnosed as influenza.

Anthrax is of significant importance in public health. Its causative agent is *Bacillus anthracis* which is a soil-borne bacteria and can produce spores. It may be transmitted by direct contact with infected animals such as cattle, goats, or their products for example meat, wool, dairy products, and bones (Goel 2015). Malignant pustules, pneumonitis, and gastroenteritis may develop in anthrax. If systemic lesions appear, death may occur. One of the most important zoonotic diseases is Bovine Tuberculosis. Its etiological agent is *Mycobacterium Bovis*. Mostly humans are infected while milking or handling unpasteurized milk products, also by inhaling the cough droplets of infected animals (Moda et al. 1996). Respiratory organs and bone marrow are severely affected.

One of the commonest bacterial zoonotic diseases is Brucellosis which is acquired by the consumption of unpasteurized milk or milk products (Corbel et al. 2006). The zoonotic species of Brucella are *Brucella melitensis*, *Brucella ovis* and *Brucella abortus*. It causes influenza-like clinical signs in humans which include pneumonia also it results in meningitis, endocarditis, headache, septicemia, fever, myalgia, and sleep hyperhidrosis (Bae and Son 2011; Rahman et al. 2006). Zoonotic diseases (bacterial zoonotic diseases discussed here) not only affect animals' health and performance but are also very harmful to

humans. Mostly they are originated from wild animals and then undergo a sylvatic or urban cycle. As far as their treatment is concerned, AMR is the burning issue.

3. IMPORTANCE OF ANTIBIOTICS

All over the world, zoonoses are a major problem. Through one health approach control the antibacterial resistance rises by zoonotic pathogens. The discovery of antibiotics during the early 1900s brought about a profound transformation in human health, saving countless lives. Antibiotics are intricate compounds that impede the growth of microorganisms through various mechanisms. These mechanisms include altering cell membranes, inhibiting cell wall synthesis, exerting antimetabolite activity, blocking nucleic acid synthesis, suppressing protein synthesis, and engaging in competitive antagonism. In addition to their crucial role in human medicine, antibiotics are also utilized in animal husbandry and livestock to safeguard against infectious diseases, thereby increasing the production of dairy products and meat. They are further employed on a large scale to promote animal growth and weight. While antibiotics offer significant benefits, their uncontrolled usage and dissemination into the environment raise serious concerns (Parmar et al. 2018).

4. MECHANISM OF ACTION OF ANTIBIOTICS

There are five mechanisms of action of antibiotics: 1) inhibit the bacterial protein synthesis; 2) inhibit the bacterial nucleic acid synthesis; 3) stop the cell wall synthesis; 4) interfere with the cell membrane function and 5) inhibition of metabolic pathway of bacteria as mentioned in Table 1 (Kapoor et al. 2017).

Table 1: Mechanism of action of different antibiotics

Mechanism of action	Drugs	Target	References
Inhibition of protein synthesis	Aminoglycosides and tetracyclines Macrolides and chloramphenicol	30S subunit of the ribosome 50S subunit of the ribosome	Krause et al. 2016
Inhibiting cell wall synthesis	Beta-lactams and glycopeptides	Block the last stage of peptidoglycan synthesis and attach to the D-Ala-D-Ala terminal, respectively	Page 2012, Wang et al. 2018
Inhibition of nucleic acid synthesis	Fluoroquinolones and rifamycin	Inhibit DNA gyrase and topoisomerase IV and DNA-dependent RNA polymerase respectively	Bhattacharjee 2016; Saito et al. 2017, Nainu et al. 2021
Inhibition of metabolic pathways	Sulfonamides and trimethoprim	Inhibits the enzymatic conversion of pteridine and PABA to dihydropteroic acid and dihydrofolate reductase respectively	Fernández-Villa et al. 2019 Akter et al. 2020 , Wróbel et al. 2020
Inhibition of cell membrane function	Polymyxins	Destroy the cell membrane by interfering with the lipopolysaccharide portion	Poirel et al. 2017; Reygaert 2018

4.1. EMERGENCE AND SPREAD OF ANTIBIOTICS RESISTANCE BACTERIA

Bacteria adapt themselves over time for replication, and survival, and spread as quickly as possible. In this way, microbes kept their existence in the environment by adjusting themselves according to surrounding conditions (MacGowan and Macnaughtan 2017). If antibiotics stop the growth of bacteria, they modify their genetic material and guarantee their survival by making them immune to drugs (Munita and Arias

2016). Bacteria have a natural process to make themselves drug-resistant but many other factors contribute to the development of resistance. For example, overuse of antibiotics, use of antibiotics without any prescription from a qualified doctor, poor medication environment, self-medication, poor hygienic conditions, and not completing medication course, etc (Chokshi 2019; Mahmoud et al. 2018; Sreeja et al. 2017). Alteration within the bacteria is the main reason for the development of bacterial resistance (Ventola 2015). During replication, one or few amino acids of the target site are replaced which introduces new base pairs in the bacterial and makes them a new resistant strain. Mostly antibiotic-resistant genes are present in the plasmid. This plasmid shares these resistance genes with other non-resistant bacteria and these genes become a part of non-resistant bacterial DNA and make them antibiotic-resistant bacteria (Von Wintersdorff et al. 2016). when we treated the bacteria with antibiotics, if they survive, they replicate and develop new resistant strains and occupy the population as a dominant form as quickly as possible (Zhao et al. 2018). In the Asia region, most people use antibiotics without any proper prescription from a professional doctor. These drugs may mask the signs of disease and develop resistance in the bacteria (Nepal and Bhatta 2018).

The entry of drug-resistant pathogens in the gut alters the gut microbiome and the community structure by shifting resistant genes to other pathogens in the gut. The opportunistic pathogens which have resistant genes move from animal to human and vice versa by different methods but the most common methods are direct interaction and vector transmission (Parmar et al. 2018). The World Economic Forum identified in its 2013 Global Risks reports that antibacterial resistance to many antibiotics is one of the major public health issues. Antibiotics used in humans and animals are released in unmetabolized forms due to incomplete metabolism. These unmetabolized antibiotics contaminate drinking water and sewage and are excreted in animal feces. The high level of these residues in the environment creates antibiotic-resistant genes by changing the genetic makeup of the bacteria. As a result, produces many antibiotic-resistant bacteria (Parmar et al. 2017).

5. MECHANISM OF DEVELOPMENT OF BACTERIAL RESISTANCE

There are five mechanisms of the development of bacterial resistance: 1) little amount of antibiotics enter into the bacterium due to a change in the permeability of the bacterial cell wall; 2) change in the target site of antibiotics; 3) inactivation of antimicrobial enzymes; 4) change the pathways of those enzymes which are targeted by antimicrobials and 5) remove the antimicrobials out of bacterium (Fig. 1) (Davies 1997; Levy 1994; Salyers et al. 1997). These five mechanisms have been shown in Figure 1. The antimicrobials used in the veterinary field are inactivated by one of these mechanisms. For instance, beta-lactam resistance is developed due to the presence of beta-lactamase, which cleaves the ring of beta-lactam antibiotics (Bush et al. 1995). The resistance of fluoroquinolones antibiotics are developed due to bacterial mutation in the A subunits of the DNA Gyrase enzyme and this mutation cause active efflux and decreased its accumulation (Everett et al. 1996, Piddock 1995; Gonzalez et al. 1989).

There are mainly two forms of antibiotic resistance natural and acquired antibiotic resistance (Reygaert 2018). In acquired resistance, bacteria change their genetic material by conjugation, translation, transposition, and mutation in their chromosomal DNA (Lerminiaux and Cameron 2019: Culyba 2015). There are two ways to inactivate antibiotics:1) chemical alteration of the drugs and 2) destroying the drugs (Blair 2015). Bacteria produce enzymes that are attached to the chemical groups of different drugs that prevent the attachment of drugs to their target spot in the cell wall. Chemical group transfer is one of the most effective methods of drug inactivation for example adenyl, acetyl, and phosphoryl chemical groups (Lin et al. 2015). One of the best examples of drugs is aminoglycosides. Through phosphorylation and adenylation, aminoglycosides are t argeted by altering the hydroxyl and amino

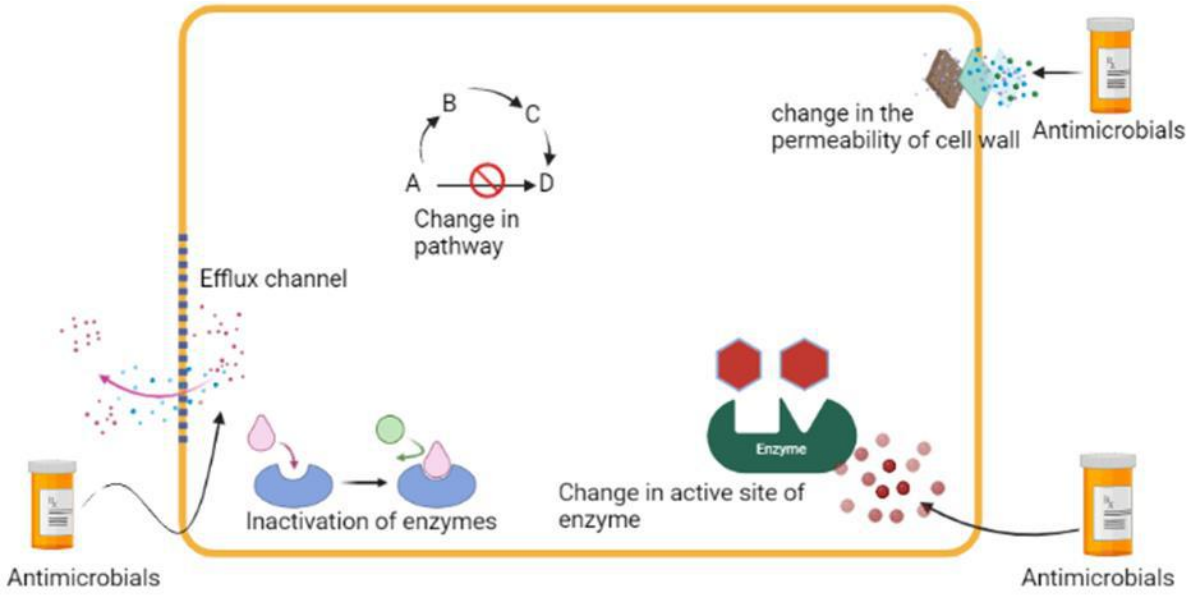

Fig. 1: Mechanisams of antimicrobial resistance

group of it with an aminoglycoside modifying enzyme (AME) and making it inactive (Munita and Arias 2016). The common mechanism of bacterial resistance is the modification of the antibiotics target. The mechanism of resistance towards the beta-lactam drugs is altering the arrangement of the target and changes the amount of penicillin-binding proteins (PBPs). Change in the number of PBPs affects the amount of drugs to attached the target (Bush and Bradford 2016). The other example of target modification against lincosamides, macrolides, and streptomycin is through the erythromycin ribosome methylase (erm) gene family which changes the drug-binding site and methylates the 16S RNA ribosome (Peterson and Kaur 2018).

6. CURRENT STATUS OF CHEMICAL ANTIBIOTICS AGAINST BACTERIAL ZOONOSIS

For treatment purposes, different antibiotics are widely used against different zoonotic bacterial pathogens.

6.1. *PASTEURELLA*

Pasteurella species are gram-negative, anaerobic coccobacillus, which is part of the natural flora in the upper respiratory tract of dogs and cats (Freshwater A 2008; Dolieslagar et al. 2011). *Pasteurella* infection can be transferred to humans through direct or indirect contact such as bites, scratches, or licks (Oehler et al. 2009). A study in Germany shows that *Pasteurella* shows resistance to some antibiotics like tetracycline (11.5% -19.2%), and trimethoprim-sulfamethoxazole (4% -10%) (Kaspar et al. 2007). For the treatment of *Pasteurella*, the first line of antibiotics is Penicillin and potentiated beta-lactams (Roy et al. 2007; Perez Garcia et al. 2009). *Pasteurella* infection can be treated with second and third-generation cephalosporins, macrolides, fluoroquinolones, and cotrimoxazole (Lloret et al. 2013).

6.2. *SALMONELLA*

Salmonella species are anaerobic, gram-negative bacilli found in mammals' large intestines. Investigators recorded resistance patterns in antibiotics like ciprofloxacin (100%), chloramphenicol (91%), ceftriaxone

(91%), and tetracycline (86%) (Adzitey et al. 2020; Casaux et al. 2019). Salmonella spp. could be treated by macrolides, beta-lactams, and fluoroquinolones (Leonard et al. 2011).

6.3. *BRUCELLA*

Brucella is the most widespread bacterial disease which has a very high zoonotic potential. It can be transferred through direct and indirect contact. It is transmitted by the consumption of unpasteurized milk (Saleem et al. 2010; Lucero et al. 2010). The treatment protocol includes a combination therapy of doxycycline plus streptomycin or rifampin for 6 weeks (Pappas et al. 2005).

6.4. *CAMPYLOBACTER*

Campylobacter species are gram-negative bacteria that cause campylobacter enteritis. Campylobacter can be commonly found in the gastrointestinal tract and transmitted directly and indirectly (Janda et al. 2006; Hermans et al. 2012). *Campylobacter* species are resistant to antibiotics like erythromycin, ciprofloxacin, and tetracycline (Harrow et al. 2004). *Campylobacter* can be treated by fluoroquinolones, macrolides, or aminoglycosides successfully (Ternhag et al. 2007).

6.5. *COXIELLA BURNETII*

Coxiella burnetii is an intracellular obligate gram-negative bacteria that causes Q fever in humans. It is mainly transmitted to humans from animals through aerosol or by direct contact (MAURIN et al. 1999). *Coxiella burnetii* can be treated with fluoroquinolones and doxycycline successfully (Patel et al. 2011).

6.6. *LEPTOSPIRA*

Leptospira is aerobic zoonotic bacteria that cause leptospirosis in humans. It can be transferred to humans through environmental sources like soil, urine, and water from infected animals (Moore et al. 2006). *Leptospira* is resistant to antibiotics like gentamycin, kanamycin, Streptomycin, and spectinomycin (Poggi et al. 2010). Many antibiotics like cefotaxime, ceftriaxone, penicillin, amoxicillin, doxycycline, and ampicillin are used for the treatment of leptospirosis (Kobayashi 2001)

6.7. *BORDETELLA BRONCHISEPTICA*

Bordetella bronchiseptica is gram-negative bacteria commonly residing in the upper respiratory tract of cats and dogs and can be transferred to humans via aerosol transmission. It causes kennel cough in humans (Woolfrey and Moody 1991; Ner et al. 2003). *Bordetella bronchiseptica* is resistant to drugs like macrolides and cephalosporins and can be treated by fluoroquinolones and trimethoprim/sulfamethoxazole (Egberink et al. 2009).

So, the zoonotic diseases can be cured with the help of antibiotics. Many antibiotics are widely used in the treatment of bacterial zoonotic diseases such as Penicillin, tetracyclines, macrolides, fluoroquinolones, beta-lactam, cephalosporins, ampicillin, amoxicillin, ceftriaxone, doxycycline, etc (Ghasemzadeh and Namazi 2015).

7. ALTERNATIVE TREATMENT APPROACHES

Antibiotic resistance is increasing day by day and is leading to cause serious problems in the treatment of diseases. So, there is a search for other methods for the treatment of diseases. Some of these methods have been mentioned below:

8. PHYTOCHEMICALS

Bacteria get resistant to excessive use of antibiotics, so need alternative compounds to cope with bacteria. Plant Therapy is the oldest effective experimental treatment used instead of antibiotics (Shin B and Park W 2017). Synthetic medicines are costly and cause toxicity due which causes damage to the intestines while herbal antibacterial compounds are less toxic, least expensive, and environmentally friendly (Newman and Cragg 2012). Phenolic and terpenoids are commonly used phytochemicals (Russel and Duthie 2011). Palmarosa oil extracted from the *Cymbopogon martini* plant has a very good antimicrobial activity against S aureus and E. coli (Lodhia et al. 2009). Carvacrol and Thymol are widely used again pathogens like E. coli, Listeria monocytogenes, and vibrio cholerae (Magi et al. 2015; Hyldgaard et al. 2012). Eugenol and isoeugenol have a synergistic effect with some antibiotics like tetracycline, ampicillin, noro-ofloxacin, rifampicin, and vancomycin (Langeveld et al. 2014).

9. NANO-PARTICLES

Nanotechnology has come up with a bounteous solution for the issue of bacterial antibiotic resistance. Nanoparticles bind to the bacterial surface and rupture the cell wall of the bacteria and cause cell death (Wang et al. 2017). Nanoparticles whose size is <20 nm can penetrate the cell wall and destruct the organelles which leads to cell death (Arakha et al. 2015). Flavonoid caps are naturally present on biogenic nanoparticles which inhibit enzymatic activity and stop the synthesis of nucleic acid (Fayaz et al. 2010). Nanoparticles give damage the cell membrane by generating reactive oxygen species (Li and Webster 2018). The application of nanoparticles is used in the eradication of Methicillin-Resistant Staphylococcus aureus infection (Li et al. 2022; Mohamed et al. 2022). Various nanoparticles like gold, silver, zinc oxide, silica, and bismuth have killing effects on Methicillin-Resistant Staphylococcus aureus (Nunez et al. 2009; Hemeg 2017; Gwon et al. 2021; Kadiyala et al. 2018; Ahmad et al. 2022).

10. PHAGE THERAPY

The most commonly found zoonotic bacterial pathogens related to poultry are Salmonella spp., and E. coli (Wernicki et al. 2017). Resistivity has been shown to antibiotics by these pathogens has been stated in the report by European Food Safety Authority (EFSA) (EFSA 2018). As an alternative approach lytic bacteriophage technique is used to cope with diseases (Fernández et al. 2018). Bacteriophages were discovered by Twort and d'Herelle in UK and France in the 20th Century (Duckworth 1976). Phage therapy has been used to treat Salmonella infection in chickens (El-Gohary et al. 2014).

11. SANITARY PROPHYLAXIS

Sanitary prophylaxis is a method of slaughtering or destroying infected or contaminated animals. This method is proven very efficient in the eradication of bovine tuberculosis, *brucella bovis, and brucella melitensis* in many parts of the world (Blancou et al. 2005).

12. VACCINATION

Due to the increase in antibiotic resistance in the veterinary field, attention has been to edible vaccines for the treatment of many bacterial zoonotic diseases (Sack et al. 2015). Anthrax an emerging bacterial zoonotic disease is controlled by an injectable vaccine obtained from culture filtrate (Koya et al. 2005).

Yersinia pestis a bacterial zoonotic pathogen is controlled by live attenuated and killed vaccines with certain risks (Sinclair et al. 2008). *Tuberculosis* a zoonotic pathogen can be controlled by BCG vaccine, plant-based vaccine, and transgenic modified carrot (Permyakova et al. 2015). *Listeria* is an infectious zoonotic disease that is effectively controlled with the help of a plant-based vaccine (Ohya et al. 2005). There are various limitations to the vaccine, including several booster doses, and temperature maintenance and it's not easy to carry (Shahid and Daniell 2016).

13. CONCLUSION

Zoonotic diseases are transmitted from animals to humans and vice versa. But as a whole everyone is at the risk of disease development from others. Many bacteria have zoonotic significance. The treatment of these infections is possible by antibiotics, but with time most bacteria develop resistance against the antibiotics due to some reasons like lavish use of antibiotics in humans as well as animals and the presence of antibiotics in animals and animals by-products at the sub-therapeutic level that results in an increase in resistance in bacteria.

Nowadays non-antibiotic approaches are widely used on the human and veterinary side to treat bacterial zoonotic diseases. Excessive use of antibiotics without proper knowledge and consultancy causes antibiotic resistance. Due to antibiotic resistance, alternative treatments are used to treat bacterial zoonotic diseases which include phytochemicals, phage therapy, sanitary prophylaxis, and vaccines. But these treatment measures also have some limitations like vaccines also need booster doses, phytochemicals do not act on all bacteria, and phage therapy is limited to some bacteria only. So, we need much more study and research on digging new methods for the treatment of bacterial infections and there is a need for extensive studies on the present alternative methods to overcome the limitations of these methods

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Viruses of Zoonotic Potential

07

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ABSTRACT

Zoonotic infections of humans from animal reservoirs can result in severe disease in individuals and, in rare cases, lead to pandemic outbreaks. Vast spectrums of new and re-emerging infectious diseases, nearly 75% of which are zoonoses, have become a serious hazard to human health. Zika virus, influenza virus, coronavirus, filovirus, and Rabies virus are examples of zoonotic viruses transmitted from animals to humans. Human diseases are often transmitted by animals through direct contact or vector-mediated transmission. Natural reservoirs are the habitat in which infectious disease pathogens live, matures, and multiply. Several bat species Wild ducks, farmed poultry, swine, horses, and dogs have been identified as zoonotic viruses' reservoirs. Microbial adaption, human habitat, climate change and agriculture intensification are different factors play a vital role in the emergence of zoonotic diseases. Zoonoses pose a severe health risk to the global society. Surveillance is essential for the prevention and control of zoonotic illnesses. To avoid viral infection is to utilize vaccinations with enhanced safety profiles and efficacy, which serve as the foundation for contemporary generation vaccines. Animal vaccinations limit disease transmission in companion animals, secure safe food supply by maintaining healthy livestock herds, and act as a significant hurdle to the transfer of several zoonotic illnesses to humans. To promote human health, manage disease effectively, and reduce mortality and morbidity in humans and animals, it aids in adjusting control strategies against new and reemerging diseases. Research concentrating on a certain health strategy must be prioritised in order to discover crucial interventions phases in disease transmission due to the connection of humans, animals, and the environment. Strong multi-sectoral collaboration among medical professionals, veterinarians, environmental health personnel, and agricultural staff is required.

Keywords: Zoonosis, Animal-human interface, livestock farming, zoonotic viruses.

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1. INTRODUCTION

Zoonotic diseases are defined as infections that may be transferred between vertebrate humans and animals, with either the person or the animal as the receiver, via food-borne infections, direct contact, or intermediate vectors such as mosquitos and ticks (Christou 2011). Vast spectrums of new and re-emerging infectious diseases, nearly 75% of which are zoonoses, have become a serious hazard to human health. Zika virus, influenza virus, coronavirus, filovirus, and Rabies virus are examples of zoonotic viruses transmitted from animals to humans (Dong and Soong 2021). Only around 25% of these infections arise in domestic animal species, with the remainder originating in wildlife animals (Tomori and Oluwayelu 2023). Because RNA viruses can emerge and spread quickly, they pose a particularly high zoonotic risk. The most reliable sign of interspecies transmission and infection in humans, according to a statistical analysis of 146 cattle viruses, is a virus's propensity for cytoplasmic reproduction. (without nuclear entry) (Pulliam and Dushoff 2009). Combining the Greek words "zoon" (animal) and "nosos" (disease), "zoonoses" is a disease. The World Health Organisation defines zoonosis as any disease or infection that can spread spontaneously from vertebrate animals to humans or from humans to animals. Zoonoses are a major public health risk that can potentially result in mortality (Rahman et al. 2020). The reservoir might be the origin of the agent's transmission to a susceptible host. The target population is exposed to an infectious illness from the natural reservoir, which is a population of organisms or a particular habitat where the illness that is transmissible lives and reproduces naturally or on which the pathogen depends heavily. Typically, a pathogen lives inside an actual host of a particular kind (human or animal), sometimes without generating illness in the reservoir or it can exist in an environment that is not part of the organism, such as contaminated air or water (Peters 2003).

Human-harming zoonoses may originate in either household pets or wildlife; the latter, as hunters, ambitious tourists camping in the woods, and cave explorers have demonstrated, is becoming a more significant reservoir for human disease. In their nonhuman vertebrate hosts, these viruses typically cause little or no obvious sickness. Some zoonotic viruses have extremely narrow host ranges, whereas others may infect a broad variety of vertebrates. Human infection can range from undetectable to deadly. Both new and ancient viral zoonoses play a critical role in developing and reemerging virus diseases (Reed 2018). The human health burden and livelihood effect of zoonotic illness are larger in underdeveloped nations than in industrialized countries, but due to poor diagnosis and underreporting, the influence of zoonotic disease on overall human disease burden is not well characterized (Jones et al. 2013).

2. ZOONOTIC VIRUSES AND THEIR TRANSMISSION

Some notable zoonotic viruses and their routes of transmission are discussed below;

2.1. CORONAVIRUS

Coronaviruses are a part of the Nidovirales order and the Coronaviridae family. They are separated into the genera coronavirus α, β, γ, and δ coronavirus. Their hosts mainly, humans, bovines, avians,

porcine, etc. suffer from infections like diarrhea, pneumonia, kidney failure, and enteric indications (Satarker and Nampoothiri 2020). The 2019 novel coronavirus (2019-nCoV), also referred to as the SARS-CoV-2, originated in Wuhan, Hubei Province, China, and is currently spreading quickly throughout the world. Under an electron microscope, coronaviruses, which have spike-like protrusions on their surface which give them the look of a crown, appear to be enclosed positive sense RNA viruses. The incident was reported to China on December 31st, 2019, and the WHO was informed. On January 1st, the Huanan sea market for food was shut down. On January 7th, the virus was determined to be a coronavirus with >95% homology to a bat coronavirus and >70% resemblance to the SARS-CoV (Bhatt et al. 2021).

2.2. INFLUENZA VIRUS

Influenza viruses (IVs) are Orthomyxoviridae family members that possess segmented, single-stranded RNA genomes that are oriented in the -ve direction. Based on genetic and antigenic variations, IVs are classified into three types: A, B, and C. They infect mammals as well as birds (Nuwarda et al. 2021). IVs pose a constant and serious worldwide hazard to humans and many animal species. Influenza is a highly infectious, acute respiratory illness with worldwide implications that affects people of all ages and can reoccur. Because ducks are the natural reservoir for the disease's etiological agent—the influenza virus—and many other animal species can be affected, the virus cannot be eliminated. As a result, the sickness will continue to resurface regularly (Abramo et al. 2012).

2.3. FILOVIRUSES

Filoviruses are non-segmented negative-stranded RNA viruses of the order Mononegavirales that differ genetically, morphologically, physiochemically, and physiologically from other members of the order Mononegavirales (Languon and Quaye 2019). These are the zoonotic viruses that infect human beings. Filoviruses are thought to be transferred from animals to humans via interaction with reservoir fruit bats (Mekibib and Ariën 2016).

2.4. RABIES VIRUS

Rabies is a neglected zoonotic illness produced by negative-strand RNA viruses of the Lyssavirus genus. Rabies viruses circulate in a wide range of animal reservoir hosts within this genus, are found globally, and are virtually invariably lethal in non-vaccinated humans (Nahata et al. 2021).

2.5. ZIKA VIRUS

The arthropod-borne Zika virus (ZIKV) belongs to the Flavivirus genus and Flaviviridae family of viruses. Many animal species serve as arbovirus reservoirs. ZIKV is often spread by the bite of an infected mosquito (Kuno 2016).

3. VIRAL RESERVOIR AND AMPLIFYING HOSTS

There is extensive pathogen transfer from animals to humans in zoonotic illnesses. Human illnesses are often transmitted by animals through direct contact or vector-mediated transmission. The involvement of animals in the transmission, amplification, and zoonotic overflow of causative agents of developing zoonoses is depicted in Fig. 1.

Table 1: Transmission route of zoonotic viruses

Zoonotic Viruses	Route of transmission
Coronavirus	Multiple modes of transmission including, direct transmission by physical contact with an infected patient, airborne transmission and indirect transmission through contaminated objects (Dhand and Li 2020)
Filo virus	Human-to-human transmission through direct contact with an infected person, their body secretions (sweat, breast milk), blood and excretions (stool, vomit, semen, urine) (Mekibib and Ariën 2016)
Influenza virus	Transmission through direct contact with an infected person, contaminated hands, aerosol droplets, and indirect transmission via fomites (Asadi et al. 2020)
Rabies virus	Virus transmitted through direct contact between infected saliva and broken skin, or via bite, or ingestion of infected animals (Fisher et al. 2019)
Zika virus	Vector-borne transmission, arthropods transmit the virus from one vertebrate to another, horizontal transmission of infectious saliva during blood feeding, and vertical transmission from mother to child, Via bone marrow and sexually transmitted (Kuno 2016)

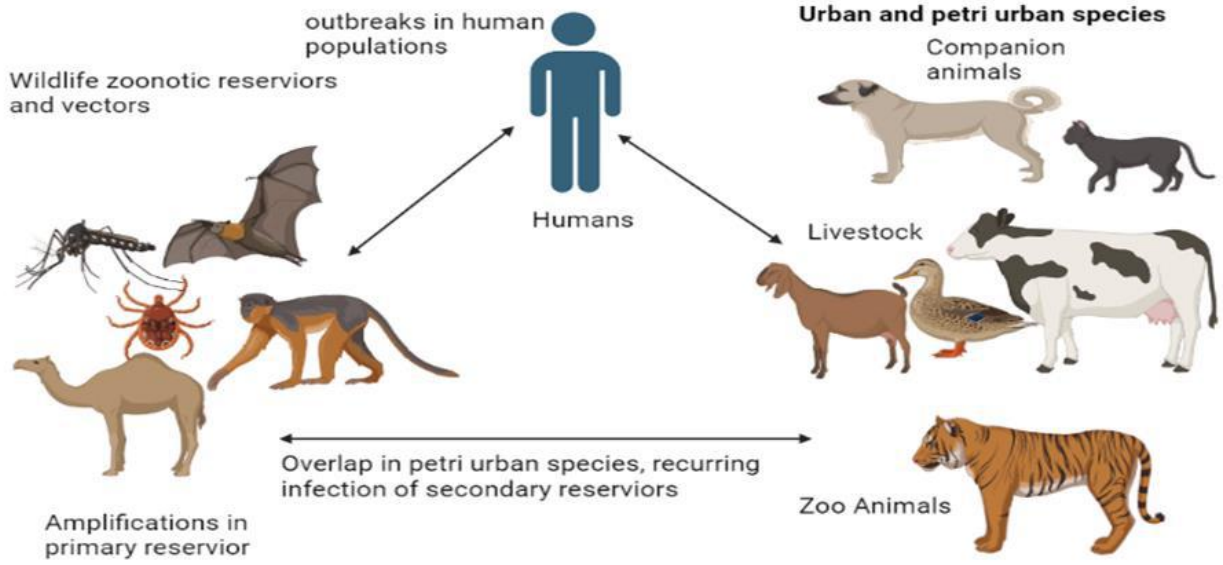

Fig. 1: Represent pathogen transmission between human, wildlife and urban or peri-urban species

Natural reservoirs are the habitat in which infectious disease pathogens live, matures, and multiply. They include humans, animals, and the environment (both alive and dead). Many pathogens live in animals and sometimes jump species to infect humans. Animal reservoirs are made up of pathogen-infected wild and domesticated animals. Animals have been implicated in the spread of zoonotic viral infections to humans. Several bat species have been identified as zoonotic virus reservoirs, including rabies and other lyssaviruses. Domestic dogs are the most common reservoirs, accounting for more than 99% of all human rabies deaths (Tomori and Oluwayelu 2023). Wild ducks, farmed poultry, swine, horses, dogs, and bats are reservoir hosts for influenza virus. Coronavirus is found in a variety of wild and domestic animals (dogs, cats, bats, pangolins, and so on). There have also been reports that palm civet cats (SARS) and dromedary camels (MERS) served as intermediate hosts for the Coronavirus (Singla et al. 2020). According to research, female Aedes mosquitoes are the main vectors for ZIKV transmission. Where non-human primates are absent, humans act as important amplification hosts, and transmission occurs mostly in urban and sylvan settings. The latter serves as the amplification host in a sylvatic cycle. As hematophagous arthropods,

mosquitoes pick up the virus during a blood meal and carry it about for the rest of their lives without getting sick. They convey it to the following amplification host, or their target, during the subsequent blood meal (Gutiérrez-Bugallo et al. 2019). Zika virus was first identified from, ducks, goats, rhesus monkeys, horses, cows, carabaos, bats, domestic sheep, and rodents. Filoviruses are thought to be spread from animals to humans via reservoir fruit bats, intermediate hosts such as great apes, duikers, pigs, or monkeys, and infected individuals who come into touch with bat saliva or feces (Kuno 2016).

4. ZOONOTIC VIRUSES AT THE HUMAN-ANIMAL INTERFACE

Epidemics mostly brought on by infectious diseases spread by animals, particularly wildlife, have long plagued humans. Everyone agrees that the human-animal interface—direct or indirect interactions between humans and animals and their bodily fluids—is necessary for effective cross-species transmission. Fresh food markets where animals that are alive are bought and killed, usually for food or medicine. According to reports, the ongoing COVID-19 outbreak began at the Huanan seafood wholesale market in Wuhan. The availability of live wild animals like snakes, small mammals, and birds at this seafood market increased the risk of zoonotic disease transmission from wildlife to humans (Peters, 2003). In some parts of the world, primarily in tropical regions where livestock is underdeveloped, hunting for wildlife and consuming are still common. This meat is often referred to as "bushmeat," especially in Africa. Wildlife is a key source of protein and/or revenue in these contexts through the selling of meat, large-game tourism, and exchanging items for medicine (Alves and Alves 2011), and it is also valued for traditional hunting and ritual occasions (Walters and Touladjan 2014). In this perspective, any action that involves the manipulation of wildlife species creates an human-animal interface that allows pathogens to spread (Wolfe et al. 2005). Hunters (mostly males) and anybody handling dead animals for cooking or trade (mostly females) are exposed to possible infections found in animal remains and bodily fluids. Bush meat eating has also been linked to the formation of Ebola virus illness, which has resulted in multiple outbreaks in Central Africa over the previous 5 decades, as well as the big epidemic in West Africa from 2013 to 2016, which killed over 11,300 people. Fruit bats were discovered to be a reservoir species, with direct or indirect spillover to humans occurring via an intermediary animal species (Magouras et al. 2020). The worldwide increase in animal-human interfaces and the mixing of diverse kinds of animals in human-compact marketplaces enabled the establishment of new viral infections such as avian influenza H5N1, A/H7N9, SARS, and the present COVID-19 epidemic (Singla et al. 2020). The excessive involvement of Human activities in varied ecosystems has increased the possibility of human-animal encounters. This increases the transfer of infectious and contagious illnesses from animals to people, and subsequently among humans. In most situations, animals serve as reservoirs for viral species, contributing significantly to viral outbreaks. Birds also serve as a reservoir for many viruses and spread infections as they migrate over large areas every year (Mohsin et al. 2021).

5. FACTORS INFLUENCING ZOONOTIC EMERGENCE

There are the following factors play a vital role in the emergence of zoonotic diseases as mentioned in Fig. 2. These are as,

6. CLIMATE CHANGE AND HUMAN HABITAT

Species distributions can fluctuate as a result of large-scale environmental change (e.g., landscape modification and climate change), favoring species responsible for illness initiation and transmission. Temperature and humidity have been demonstrated to be substantially linked with mosquito populations.

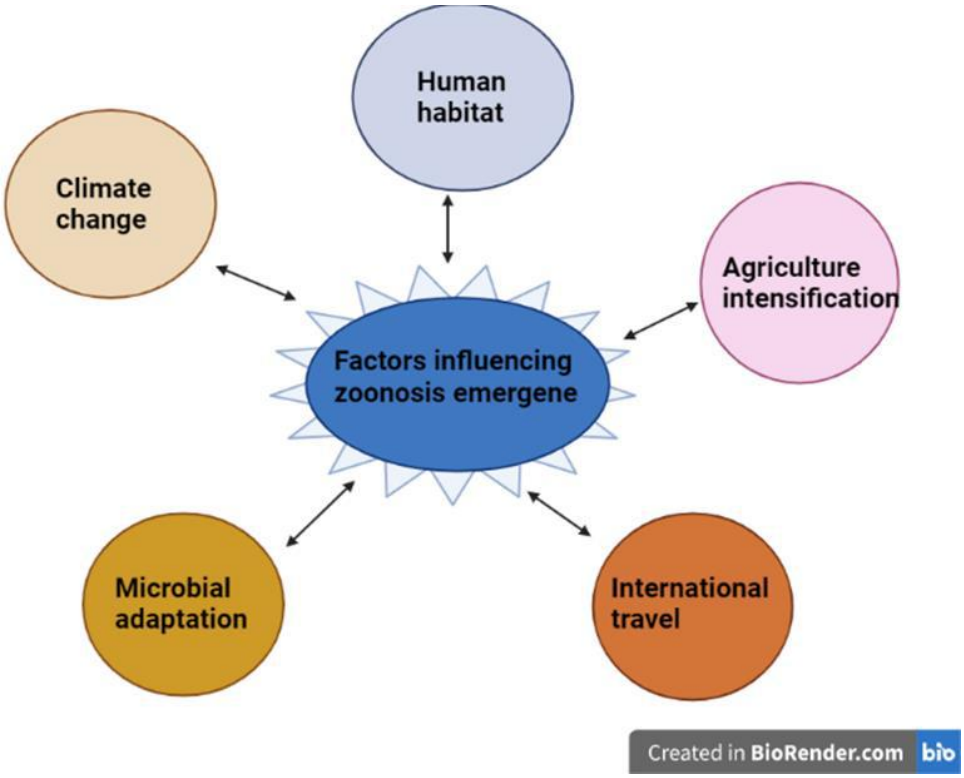

Fig. 2: Represent factors influencing zoonotic emergence

While regular rainfall increases the number of outside bodies of water in which mosquitoes may spawn, dryness causes additional Buildings that store water in populated areas to increase the number of breeding sites that are viable (Xu et al. 2017). Climate has a big influence on vector-borne and water-borne infections. Since vectors of arthropods are most active in high temperatures and lack of water during droughts results in poor sanitation, climate change is predicted to accelerate the spread of illnesses transmitted by vectors and diarrheal diseases in Southeast Asia (Birhan et al. 2015).

Ecotone transition zones between adjacent biological systems are developing as a result of human settlements and agriculture encroaching on natural ecosystems. In these areas, species assemblages from various environments mix. This opens new avenues for disease spread, genetic diversity, and adaptability. The current appearance of bat-associated viruses in Menangle virus, Australian bat lyssavirus, Australia and Hendra virus is linked to habitat degradation caused by deforestation and agricultural growth. Changes in the size, structure of bat colonies, and location as well as feeding in periurban fruit trees, have resulted in increased interaction with livestock and people, raising the risk of disease spillover (Field 2009). Pathogen spillover can be exacerbated by biodiversity loss. Vectors achieve larger disease prevalence in low-diversity populations because they feed more often on main reservoirs. Water management actions may enhance the density of mosquito breeding places (Gottwalt 2013).

7. AGRICULTURE INTENSIFICATION

As the human population grows, agricultural systems will become more dependent on providing food and other resources. The danger of consumers contracting food-borne illnesses increases with rapid growth in meat consumption, particularly from chickens and pigs (Gilbert et al. 2015). Because industrial food animal production systems establish varied wildlife-livestock-human interactions, they raise the likelihood of zoonotic development as agriculture develops (Hassell et al. 2017). In these industrial systems, a high

number of animals are kept in close physical contact in a limited space, where infections may readily be transferred. Workers on large-scale animal farms and nearby people are particularly vulnerable to harmful bacteria and viruses (White and Razgour 2020).

8. INTERNATIONAL TRAVEL

Increased international travel, particularly without sufficient vaccination and other preventive measures, leads to increased illness among travelers, who then bring the infection back home with them when they return (Fauci 2005). In addition to human migration, increasing animal and livestock trade across borders is concerning. In trading centers, for instance, humans and dozens of different species can be combined prior to there are transported to other sectors, sold on a local level, or even released and sent back into the wild (Birhan et al. 2015).

9. MICROBIAL ADAPTATION

The significance of healthcare system variables as influences, especially about the emergence of newly resistant strains, should not be understated. These factors, in addition to climatic conditions, globalization, global mobility, and trade of environmental and demographic factors, can drive the growth of new illnesses and increase the occurrence, prevalence, or geographic scope of existing ones. Microbes are particularly adept at adapting and changing in the face of selection pressures for survival and replication. In animals and humans, microbes become resistant to antimicrobials used for the treatment of infection (Michael et al. 2014).

10. IMPORTANCE OF SURVEILLANCE SYSTEM AND ONE HEALTH APPROACH

Zoonoses pose a severe health risk to the global society. Surveillance is essential for the prevention and control of zoonotic illnesses. It can detect early illness, sick people and animals, reservoirs, vectors, and endemic areas like "hotspots" (Van der Giessen et al. 2010). To promote human health, manage disease effectively, and reduce mortality and morbidity in humans and animals, it aids in adjusting control strategies against new and reemerging diseases. Pathogen monitoring for the detection and identification of pathogens.

- By monitoring immunological responses, serological surveillance can be utilised to detect diseases in either human or animal blood.
- Syndrome surveillance, which uses analysis of data based on symptoms to identify potential illnesses. The existence of infections cannot be detected by this type of surveillance.
- Risk surveillance to identify risk variables that contribute to disease transmission. This control approach cannot be utilised to identify the clinical characteristics and prevalence of many illnesses (Rahman et al. 2020).

To prevent and control infectious diseases such as zoonotic diseases, international organizations and researchers devised the "One Health Concept" and defined the interaction between humans, animals, and the environment. This paradigm was established to appropriately address global health concerns (Kelly et al. 2017). Microorganisms can be passed from people to animals via contaminated food and direct touch. Ecosystem loss, foodborne illness brought on by consuming animal products, vegetables, tainted water, and fruits, and environmental degradation are all factors and environmental pollution are all relevant issues that cannot be controlled or eliminated by a single sector alone. Because they share an ecosystem, animals, and humans are afflicted by many of the same pathogens (Fig. 3). As a result, One Health's strategy across the animal-human-environment sectors is essential to successfully address these concerns. To promote human and animal health, The One Health approach is used to coordinate disease surveillance, handle

and avoid zoonotic disease outbreaks, and enhance food security and safety. By promoting vigorous cooperation across key sectors, the One Health concept improves the disease monitoring system, the data exchange method with every stakeholder, diagnostic laboratory systems, and the system to speed up reaction and detection of zoonoses (Erkyihun and Alemayehu 2022).

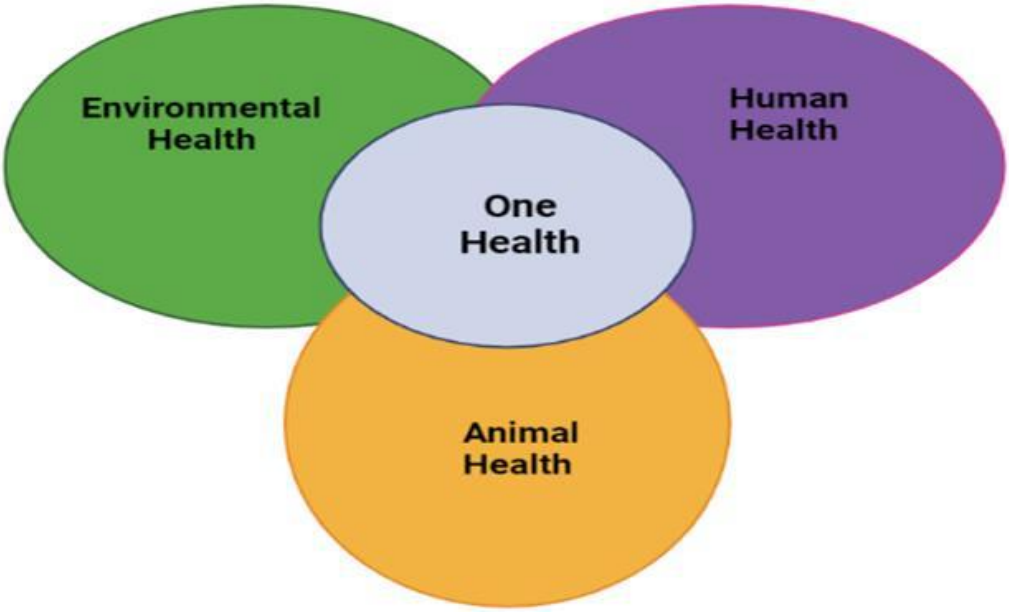

Fig. 3: Elaborate One Health Concept

Emerging illnesses and their fast or subtle spread have troubled societies throughout history. Current generations have suffered the costs of HIV/AIDS, SARS, and MERS, which have resulted in the loss of lives and livelihoods, as well as significant economic consequences. The recent appearance and spread of the ZIKV and COVID-19 show the world is so ill-prepared to respond and manage quickly shifting disease dynamicsThe overwhelming majority of emerging infectious diseases, or EIDs, are zoonotic, which means they are brought on by pathogens that are transmitted from animals to people. These diseases kill 10 of thousands of people each year, and the economic costs of a single epidemic can run into the tens of billions of dollars (Shaheen 2022).

Human, animal, and ecological well-being are inextricably linked, and early detection and response to emerging pathogens require an integrated, cooperative, cross-sectoral, multidisciplinary strategy at the regional, local, and global levels. Recent examples of zoonosis include the H1N1 pandemic, influenza H5N1 and H7N9 avian influenza, ZIKV, and EVD (Heymann and Dixon 2013). PREDICT's monitoring system was created in response to the need for a more comprehensive, proactive strategy for preventing pandemics, in which diseases are identified before they start or become out of control among people (Morse et al. 2012). Building an integrated monitoring system that includes humans, animals, and the environment can provide more comprehensive ways to prevent disease spread at the source (Shaheen 2022). PREDICT, which was first adopted in more than 20 countries, increased illness detection and response through 5 major strategies:

1. Developing or improving zoonotic viral detection capability
2. Enhancing diagnostic laboratory capabilities and illness outbreak response capabilities
3. Identifying high-risk human-animal interfaces
4. Improving prediction models for disease onset and dissemination
5. Employing communication and information management systems to create a more incorporated, worldwide approach to sharing zoonotic virus monitoring data (Kelly et al. 2017).

11. CHALLENGES TO CONTROL VIRAL ZOONOSIS

Several obstacles to halting the spread of viral zoonosis have been identified. There aren't many regulations governing cross-sector collaboration, there isn't many medical equipment available (such as masks and goggles), and there aren't many lab facilities for illness assessment. Furthermore, many instances may have been asymptomatic, making it impossible to anticipate when the pandemic would peak and complicating case discovery. Poor information sharing, inadequate management of the animal, human, and environmental health sectors, competing priorities for zoonotic disease prevention and control strategies, a lack of government leadership and funding for One Health, a limited capacity of diagnostic laboratories to identify causal agents, and weak or nonexistent legislation implementing One Health continue to plague most nations (Lee and Brumme 2013). Most universities throughout the world are unable to offer One Health course curricula in veterinary, human, and another field (Fasina et al. 2021). The main challenges of One Health are assorted zoonotic diseases; increased animal-human-environment interaction as human and livestock populations grow exponentially, extremely intimate relationships between wild and domesticated animals that can lead to forest encroachment, quickly expanding urbanization, shifting agricultural practices, the globalization of trade in animal products, and climate change are all factors (Aliyi et al. 2015).

Recent zoonotic outbreak and lesson learned (COVID-19).

Because the COVID-19 pandemic exerts demands on society from all areas of life, both nationally and worldwide, it poses unusual ethical quandaries. Health practitioners must comply with judgements regarding how to assign finite resources, It might cause moral distress and hurt mental health. Everybody must contend with travel restrictions that have caused entire economies to collapse to smooth out the epidemic curve: recent zoonotic epidemics and their lessons. Here, we address some of the ethical and potential lessons quandaries.

This outbreak acts as a sharp reminder of the disparity among individuals who have access to medical care compared to those who cannot and could be forced into hardship as a result in countries without universal health care. Unfortunately, we live in a world where people can die because it is too expensive. It occurs often in sectors such as humanitarian help, road safety and the support of drug development (Hauer 2011). Every nation's healthcare budget will always include a budgetary cap on our attempts to save lives. The goal is for budget allocation to be transparent and inclusive of all stakeholders, governed by the ethical ideals of usefulness and equit (Hughes et al. 2005). Whatever tools are utilized, they must be basic and examined on a frequent basis as the pandemic progresses.

We must be aware that the COVID-19 epidemic will have an impact on mental health. Decisions on resource allocation produce disagreement and mixed feelings in both healthcare providers and the broader public. Ethical discomfort affects us all and must be respected and shared honestly. Those who are stigmatized as disease carriers will suffer psychologically. Chronic stress is caused by racism and prejudice. They are impediments to the realization of equality, a fundamental principle of human rights.

Quarantine and travel restrictions Loneliness, bewilderment, resentment, aggravation, boredom, and a persistent sense of inadequacy may come from recommended and approved steps to reduce transmission, such as school and employment closures (Brooks et al. 2020). Children are vulnerable simply because they lack power. Some of these issues may be mitigated by appeals to benevolence.

While our attention is on preserving lives, a severe health risk is posed by economic collapse. For individuals who are struggling financially, access to healthcare will be a major worry, especially given that the pandemic increases the dangers of less secure employment. Although many employers urge employees to work remotely, this is not always an option. A worldwide recession is approaching, and the pandemic will ultimately impact everyone's financial situation (Fernandes 2020).

Interventions are required to address the issue. We have an ethical responsibility to learn as much as possible as rapidly as possible in order to produce effective health policies, medications, and vaccinations. Researchers, clinicians, ethical committees, administrators, sponsors, and regulators all have a responsibility to confirm that this happens as soon as possible. Protocols can be devised to allow expedited ethics assessment without jeopardizing fundamental ethical concepts such as benevolence, respect for people, and fairness. One possibility is to enable the advance assessment of general research procedures, which can then be promptly changed and reviewed. International relationship can assist assure the feasibility of the research. International collaboration and data exchange are required to expedite clinical trials. We require licensing agreements that span foreign boundaries (Khoo and Lantos 2020).

12. VACCINATION

The rapid appearance of prominent zoonotic viruses in recent decades has become a major source of worry for global public health. Ninety-nine percent of infectious illnesses are caused by zoonotic viruses with a high potential for spread, infecting a vulnerable population with no herd immunity. The development and reemergence of viruses that continually change has considerably expanded the possibility of transmission and immune escape mechanisms in humans. As a result, the only way to avoid viral infection is to utilize vaccinations with enhanced safety profiles and efficacy, which serve as the foundation for contemporary generation vaccines. Animal vaccinations limit disease transmission in companion animals, secure safe food supply by maintaining healthy livestock herds, and act as a significant hurdle to the transfer of several zoonotic illnesses to humans (Gutiérrez et al. 2012). The idea of immunising both domestic and exotic animal species has been put out as a strategy for zoonotic disease animal vaccination programmes. Evolving new and better vaccinations to limit the spread of difficult or developing zoonotic diseases is an essential future research focus (Murphy 2008). The CDC Global Immunisation Strategic Framework in the United States provides guidelines for the CDC's activities over the next 10 years to progress the elimination, eradication and control of vaccine-preventable illnesses (Carpenter et al. 2022).

13. CONCLUSION

Animals are responsible for the majority of infectious illnesses in humans. These illnesses not only make animals sick, but they also jeopardise human health. Growing human-wild animal interaction, changing food patterns, the origin and resurgence of a number of zoonotic illnesses are influenced by factors such as climate change and environmentally harmful human activities. Research concentrating on a certain health strategy must be prioritised in order to discover crucial interventions phases in disease transmission due to the connection of humans, animals, and the environment. Strong multi-sectoral collaboration among medical professionals, veterinarians, environmental health personnel, and agricultural staff is required. To detect zoonoses early and effectively, In order to execute efficient control measures, monitoring must be conducted across all aspects of a single health plan.

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Rabies: A Preventable Zoonotic Disease

08

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ABSTRACT

Rabies is a highly zoonotic viral disease of central nervous system that is caused by genus lyssavirus of family rhabdoviridae .There are several species recognized in this genus all of them affect central nervous system and cause rabies like symptoms .It is characterized by acute progressive encephalomyelitis with case fatality rate of upto 100 %.It is basically transmitted from one animal to other animal through bite of rabid animal via saliva.Almost all mammals are prone to infection by rabies virus and primary reservoir of rabies include foxes ,raccoons ,skunks and dogs .Nervous signs of rabies are exhibited in two forms :furious form and paralytic form.Furious stage also called “mad dog syndrome is presented as nervousness. aggressive behavior and hyperexcitability .Paralytic stage include paralysis of masseter muscle and diaphragmatic muscle and ultimately death.The gold standard test for diagnosis of rabies is Flourescent Antibody Test (FAT)test which is recommended by WHO.Timely diagnosis of rabies is crucial for prompt administration of post exposure prophylaxis to prevent onset of clinical otherwise it has nearly 100% mortality rate .Prevention of rabies is key to lessen the risk of such global public health threat .Mass vaccination of dog , administration of pre exposure and post exposure and oral vaccination of wild animal reservoir is recommended for prevention Major focus is to implement preventative strategies to eliminate rabies globally beacuase it is incurable once clinical signs appear.

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1. INTRODUCTION

Rabies is a preventable zoonotic disease of mammals that is caused by lyssavirus and is characterized by acute progressive encephalomyelitis. According to reports by the World Organization for Animal Health, it is a global public health hazard that is responsible for mortalities of 59,000 people annually with case fatality rate of100% (WHO Expert Consultation on Rabies 2018). It is primarily transmitted to humans by the bite of a rabies infected animal that introduces virus-laden saliva into the host. Its primary reservoir includes dogs, foxes, raccoons, skunks, and bats (Barecha et al. 2017). Dogs serve as important reservoir of rabies and more than 99% of human rabies are caused by dogs (Fitzpatrick et al. 2014). Therefore, combating lethal zoonosis at its animal source is necessary for disease control and elimination. The disease is prevalent worldwide except in Antarctica; most cases are reported in underdeveloped countries of Africa and Asia, with thousands of mortalities reported annually (Wandeler 2012). Clinical signs of rabies are manifested in two forms: classic furious form and paralytic rabies that resembles Guillain-Barré syndrome (Vaish et al. 2011). After exposure to rabies, immediate post-exposure prophylaxis must be followed which includes wound management, rabies immunoglobulin administration, and rabies vaccination course that can prevent the appearance of clinical signs. (Sparrow et al. 2019). It has no pathognomonic clinical signs or gross lesions that can distinguish it from other nervous disorders. The most commonly recommended and gold standard test for rabies diagnosis is the direct fluorescent antibody test. Although it is a preventable disease but it is fatal once clinical signs appear. (Ahmed et al. 2022). An integrated approach consisting of pre-exposure vaccination, control of stray animals, minimizing contact with wildlife, post-exposure prophylaxis, responsible pet ownership, and public awareness rules and regulations regarding animal movements can help control rabies.

2. ETIOLOGY

Rabies is a viral disease caused by the rabies virus of the genus Lyssavirus. It is a single-stranded negative-sense RNA virus that belongs to the genus *Lyssavirus*, family *Rhabdoviridae* and order *Mononegavirales*. (Nigg and Walker 2009). 14 species of genus lyssavirus have been recognized which are categorized based on their genomic sequencing; they are the Rabies virus, Mokola virus, Lagos bat virus, Australian bat lyssavirus, Duvenhage virus, European bat lyssavirus type 1, European bat lyssavirus type 2, Khujand virus, Aravan virus, Irkut virus, West Caucasian bat virus, Bokeloh bat lyssavirus, Shimoni bat virus and Ikoma Lyssavirus (Cifuentes et al. 2017). All these species are genetically related, highly neurotropic, affect the nervous system, and are collectively called rabies-related lyssavirus (Wunner 2007). The majority of these viruses are found in bats, researchers have proved that lyssavirus originated and spilled over from order Chiroptera to Carnivora which led to the emergence of rabies in mammals (Badrane and Tordo 2001).

It is a bullet-shaped virus with a negative sense, single-stranded RNA genome. Rhabdovirus is 180nm in length and 75nm in width. Its structural components include a helical ribonucleoprotein core and an envelope that surrounds the core (Garg and Garg 2014). Its genome encodes five viral proteins that are: matrix protein, nucleoprotein that encapsulates viral RNA phosphoprotein which is required for transcription, the glycoprotein which is a membrane-bound moiety that mediates viral attachment and fusion at cell surfaces. (Zan et al. 2016). In addition, it induces the production of viral neutralizing antibodies and polymerase, which is required for RNA synthesis (Rupprecht et al. 2002). These viruses become inactive outside the host and are quickly deactivated by sunlight, drying and heat Within the host cell rabies virus has a high affinity for nerve cells and replicates also within muscle cells (Nigg and Walker 2009).

3. TRANSMISSION

Since all mammals are vulnerable to rabies this virus is readily transmitted between mammals, whether they are of the same or different species. Most commonly this virus is transmitted by the bite of a rabies infected animal that introduces the virus into the host by saliva (Corstjens et al. 2016). Less often, this virus can also enter the host by abrasion in the skin or mucus membrane. Aerosol transmission of rabies virus has also been reported under laboratory conditions. It has been documented that rabies virus has been transmitted from human to human by organ transplantation. (Lu et al. 2021).

Mammals of order Carnivora and Chiroptera serve as primary vectors of rabies. (Kotait et al. 2019). Whereas, In underdeveloped countries, dog bites are responsible for the majority of cases. Cats are also efficient vectors of disease transmission; however, it appears that neither domesticated nor wild cats act as reservoir hosts. (Rupprecht et al. 2002). In different parts of globe particularly in developed countries, rabies is predominantly transmitted by wildlife, particularly bats. There are two epidemiological cycles for rabies: the urban rabies cycle and the sylvatic rabies cycle (Devleesschauwer et al. 2016). In urban rabies, dogs are the primary reservoir of viruses that transmit disease. In underdeveloped countries of Asia, Africa, and Central America urban rabies cycle predominates where the population of unvaccinated and free-roaming stray dogs is still under control (Barecha et el. 2017).

In developed countries of America and Europe, rabies is transmitted mainly due to contact with wildlife like bats raccoons, foxes and skunks (Nayak et al. 2022). Control of stray animal populations and mass vaccination of dogs have nearly eliminated the urban cycle of rabies transmission. The majority of the cases are caused by contact with wildlife reservoirs of the rabies virus.

The reservoirs of rabies are most important in maintaining the transmission cycle of this disease as shown in Fig. 1. Reservoirs are responsible for the long-term existence, persistence, and transmission of the virus. Canines are considered source for the majority of cases of human rabies in Africa, Asia, and Central America (Ceballos et al. 2014). In more developed countries of the United States and America, bats serve as the primary vector for the transmission of rabies (Finnegan et al. 2002).

4. PATHOGENESIS

Rabies virus is a highly neurotropic virus that infects the central nervous system of the host by traveling within peripheral nerves and ultimately producing fatal encephalitis in the host. The main pathological features of rabies are neuro-invasiveness and neurotropism (Dietzschold et al. 2008). Rabies virus cause dysfunction of the central nervous system unlike other diseases of nervous system that cause marked inflammation and necrosis of the CNS. This feature of rabies is particularly attributed to its ability to avoid the immune system of the host by evading innate and adaptive immune responses and preventing alteration in the permeability of blood-brain barrier that ultimately favors viral propagation in the brain. (Hemachudha et al. 2013). After the entrance of the virus into the host tissue, virus is deposited and remain in the local tissue of muscle for an average of 3 to 6 weeks following preliminary replication in the cytoplasm of the epithelial site (Isloor et al. 2020). Replication of the virus in muscle is very slow that's why the incubation period of the virus is quite prolonged that may extend up to 7 years and immune response is negligible (Hemachudha et al. 2013). Viral infection is initiated after viral attachment to host cell receptors. Viral replication in muscle is facilitated by its binding to nicotinic acetylcholine receptors at the postsynaptic muscle membrane. (Isloor et al. 2020). After replication in striated muscle, it travels to the axons of the motor neuron through the neuromuscular junction. Rabies virus travels towards CNS through retrograde axonal transport at speed of 12-100mm/day (Kelly and Strick 2000). The entry of the virus in neuron is facilitated by its attachment to neural cell adhesion molecules and p75 neurotropic

receptors (Lian et al. 2022). Main mechanism involved in the invasion of CNS is transneuronal spread of virus in brain. At this stage viral infection of the brain leads to an inflammatory response from the host that causes encephalitis by attracting cytokines and chemokines that further attract leukocytes crossing blood-brain barrier. However, rabies induces mild inflammation while producing major neuronal dysfunction supporting the fact that nervous dysfunction is responsible for rabies rather than neuronal degeneration due to the inhibition of synthesis of nerve transmitters in the brain (Jackson 2011).
There is the centrifugal spread of the virus from central nervous system to peripheral nervous system and then highly innervated areas like salivary glands as described in Fig. 2. This virus is secreted from salivary gland into saliva and ultimately infect other animals. (Embregts et al. 2022).

5. CLINICAL SIGNS

Clinical signs and symptoms of rabies progress in five stages: incubation period, prodromal stage, acute neurological phase, coma, and death. (Hemachudha et al. 2013). The incubation period of rabies is highly variable ranging from a few days to several years but the average duration is 1 to 2 months. (Nigg et al. 2009). The incubation period of rabies depends upon various factors including the site of viral infiltration and immunity of the host but the amount of virus inoculated is the primary factor determining the length of the incubation period (Müller and Freuling 2020). It is reported that closer to the inoculation site to the

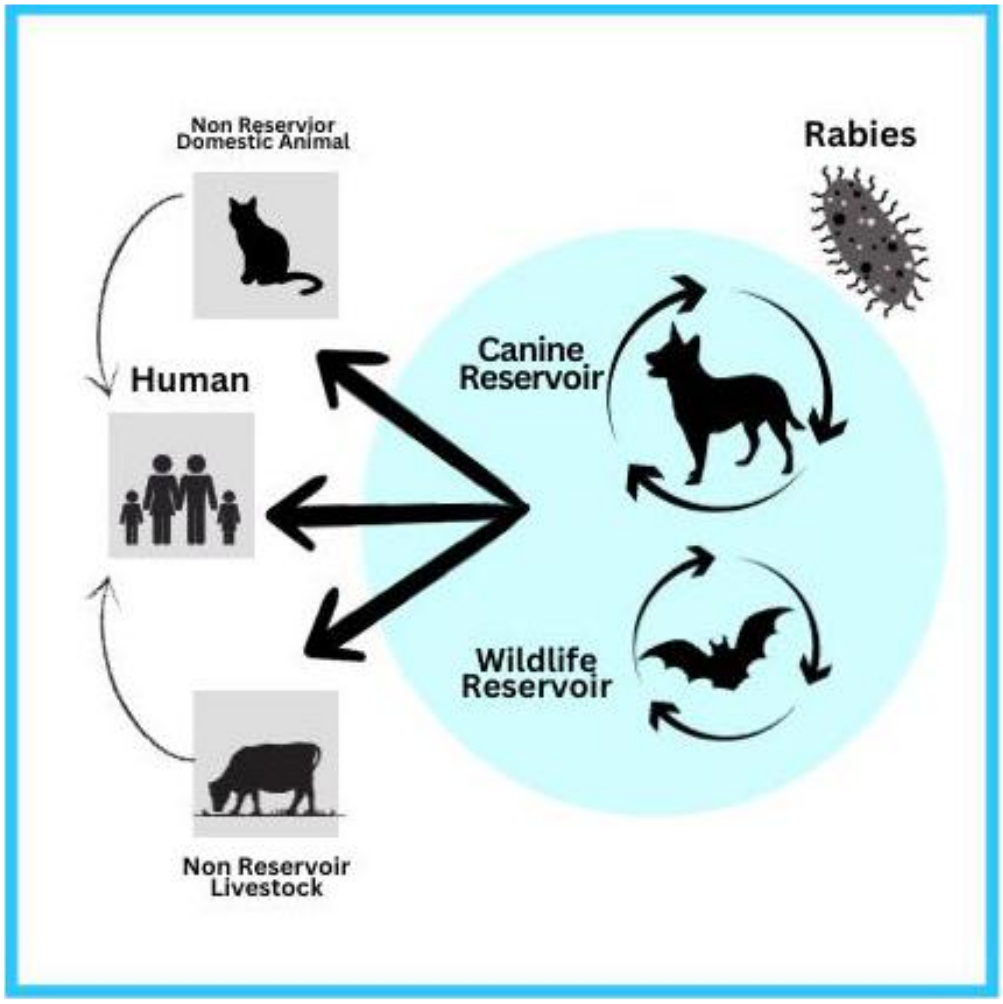

Fig. 1: The transmission cycle of rabies.

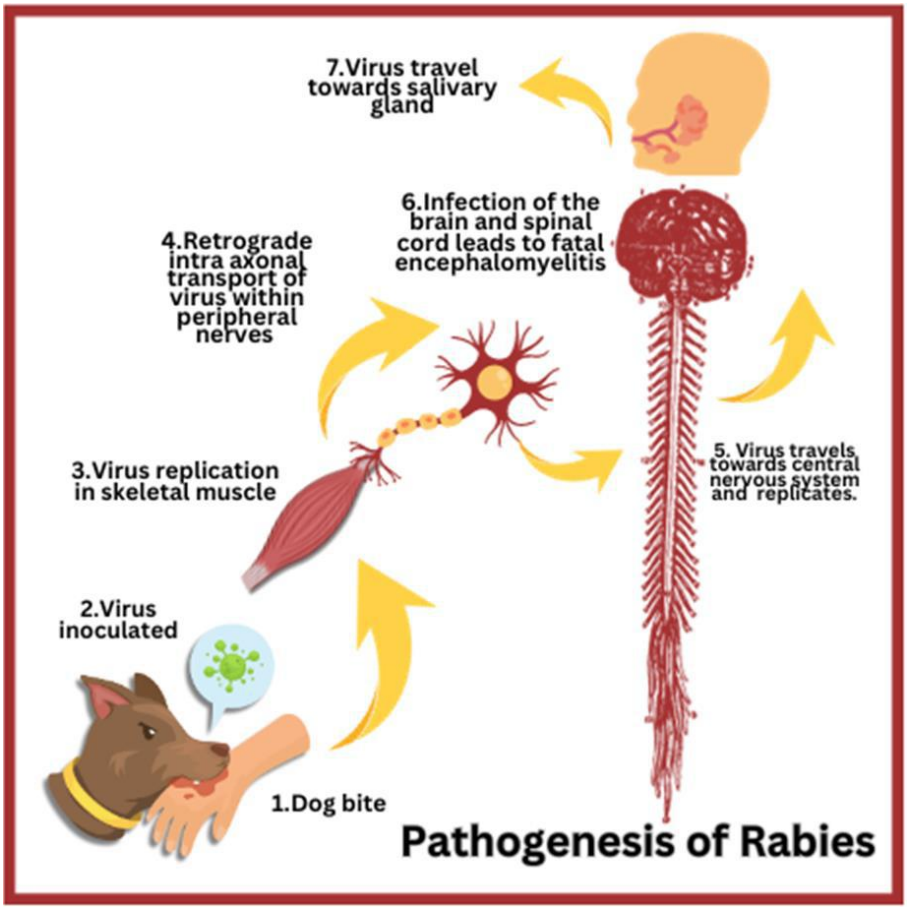

Fig. 2: Pathogenesis of rabies.

central nervous system or highly innervated areas, the incubation period decreases. The incubation period of rabies also decreases with an increase in viral inoculum titer in the host. (Nayak et al. 2022) The immunity of host which primarily depends on vaccination status is a major factor contributing to development of progressive encephalomyelitis in the host.

Initial clinical features of rabies exhibit nonspecific symptoms in the prodromal stage. This stage is initiated 2 to 10 days after exposure (Hankins and Rosekrans 2004). Prodromal stage is characterized by fever, anorexia, and lethargy which progresses to an acute neurological phase both in humans and animals.

Acute neurological phase of rabies is presented in two forms: furious form and paralytic form. Furious form of rabies exhibit severe aggression, hyperexcitability, nystagmus, and hallucinations in humans. In addition to these symptoms in animals, they roam extensively, chew foreign objects, and lose fear of people and this form is rabies is called “mad dog syndrome” (Praveen et al. 2015).

The paralytic form is presented by ataxia, hypersalivation dropped jaw in animals due to paralysis of masseter muscles. This stage further progresses to limb paralysis and ultimately paralysis of the diaphragmatic muscle which causes death. (Rupprecht et al.2002).

The end stage of this disease before death is coma, it is associated with multiorgan failure, myocarditis, cardiac arrhythmias, and death. (Alexander et al. 2022).

6. DIAGNOSIS

Conventionally, rabies was diagnosed on the basis of the history of animal bites accompanied by progressive behavioral changes and laboratory diagnosis which included nonspecific histological evidence

of brain inflammation and detection of eosinophilic intracytoplasmic inclusions bodies known as Negri bodies by seller's staining in neuronal cells (Singh et al. 2017). However, the limitation of this conventional approach is that the presence of acute nervous sign and progressive behavioral change coupled with a history of animal bite cannot be used as foundation for confirmatory diagnosis. Because there are many nervous diseases in which animals exhibit similar signs and in some cases, rabies may be transferred by non-bite route or bite may go unnoticed as in 78% of cases of bat rabies in the United States where a history of animal exposure is not reported. (Willoughby et al. 2015).

Although the presence of eosinophilic intracytoplasmic inclusion bodies is a pathognomonic lesion for rabies these characteristic inclusion bodies may be absent in neurons and often difficult to recognize (Kurup et al.2023).It has very low sensitivity and can only be performed on fresh brain specimens. It is no longer recommended for diagnosis of rabies. (Mani and Madhusudana 2013).

The most widely used and standard diagnostic test for the detection of rabies is the fluorescent antibody test (FAT) of fresh brain samples or preserved brain samples. The sensitivity and specificity of this test is about 99 % (Duong et al. 2016). The organ of choice for the detection of rabies antigen in brain tissue because it is present in neural tissue as opposed to other viruses which are present in the blood (Fooks et al. 2017). Medulla oblongata, thalamus, and pons are those parts of brain that are considered desirable samples for this diagnostic technique (Woldehiwet 2005). The direct fluorescent antibody test is based on the finding that animals infected by rabies virus have rabies virus proteins present in their brain tissue. This test uses fluorescently labeled anti-rabies antibodies and these fluorescently labeled antibodies will illuminate under a fluorescence microscope upon interaction with an antigen that is present in a suspected rabies sample. The labeled antibody will bind to antigen when it is incubated with questionable brain tissue samples for rabies. Unbound antibodies can be removed by washing and antigen-antibody interaction can be visualized as fluorescent green areas using a fluorescence microscope which indicates presence of rabies antigen in the brain sample (Centre for Disease Control). The accuracy of this test is determined by quality of brain tissue, a fresh brain sample is preferable although formalin-fixed brain sample can also be used but the accuracy of test is reduced, it requires high-quality anti-rabies diagnostic conjugates, a fluorescence microscope, and an experienced laboratory technician to yield accurate results. (Wadhwa et al. 2017).

7. IMMUNOCHEMICAL TEST

This test is very similar to the direct fluorescent antibody test. In this test rabies antibody is conjugated to an enzyme such as peroxidase instead of fluorescent isothocyaniate. This conjugated antibody directly measures rabies antigen with the same sensitivity as the fluorescent antibody test. (Shankar 2009).

8. RAPID RABIES ENZYME IMMUNODIAGNOSIS (RREID)

Rapid rabies enzyme immunodiagnosis is a convenient and simple diagnostic technique for the detection of rabies antigens. This test is economical and user-friendly as compared to FAT with the same sensitivity and specificity. It is a specific ELISA technique for rabies that uses monoclonal antibodies that capture rabies nucleoprotein antigen from brain smears. This antigen-antibody interaction is detected by the development of color by streptavidin peroxidase amino-ethyl carbazole and counter-staining with hematoxylin. (Madhusudana et al. 2012.)

9. DOT ELISA

A dot ELISA is also available which can detect the presence of rabies antigen. It is a simple, rapid, and economic test. In addition to postmortem diagnosis which requires a brain specimen as a sample this test

can also be used for antemortem diagnosis utilizing saliva and serum as samples. This test does not require highly skilled laboratory personnel and allows rapid confirmation without compromising sensitivity and specificity at a very early stage of disease when clinical signs are not definitive. All these qualities of dot ELISA make it a good choice not only for diagnostic purposes but also for epidemiological surveys under field conditions. (Singathia et al. 2012). The principle of this test is based upon detection of viral antigen by enzyme immunoassay using an agent blotted on nitrocellulose membrane. (Madhusudana et al. 2004).

10. PAN LYSSAVIRUS REAL TIME PCR

Pan Lyssavirus Real Time PCR offers various advantages over other methods because it enables the detection and differentiation of different species that belong to the genus lyssavirus and cause rabies-like symptoms. Furthermore, these assays offer real-time data and are closed-tube systems that reduce the danger of contamination during setup. (Marston et al. 2019).
This assay has been used by many laboratories that enable rapid and sensitive identification of rabies both in animals and humans. It is beneficial for the detection of viruses in organs with a low viral load like saliva, and eyewash (Wadhwa et al. 2017). It is the best method for early and rapid diagnosis of rabies, for timely provision of post-exposure prophylaxis, and for control of disease.

11. PREVENTION

Once clinical signs appear, it is incurable therefore the primary focus is prevention of disease to avoid the fatal outcome of this disease. The prevention of rabies requires an integrated strategy involving the cooperation of experts in the fields of human, animal, and environmental health as well as a global, strategic, and targeted approach at local, national, and international levels. (Acharya et al.2020.)

12. PRE EXPOSURE IMMUNIZATION

Modern cell culture vaccines can be used for pre-exposure and post-exposure prophylaxis. Veterinarians, lab personnel healthcare workers, and people traveling to endemic areas are more prone to be exposed to rabies must be vaccinated. The use of pre-exposure immunization is very important in areas where rabies is endemic. (Hankins and Rosekrans 2004).
After administration of 1st dose of rabies booster dose is mandatory at day 7, 21 and 28 to maintain a protective antibody titer against rabies (Manning et al. 2008).

13. MASS VACCINATION OF DOGS

In addition to immunizing humans, it is really important to vaccinate dogs as a vast number of cases are caused by dog bites in underdeveloped countries where the urban cycle of rabies is prevalent. According to the World Organization for Animal Health (OIE) and World Health Organization (WHO) vaccine coverage of 70% or more dog population can dramatically reduce the incidence of rabies (Franka et al. 2013). This will ultimately reduce human exposure.Therefore, Investment in canine vaccination, particularly mass vaccination, is beneficial in the long term with higher cost-efficient results **(**Lechenne et al. 2017). Hence, mass immunization of canines is one of the fundamental methods for controlling rabies in both human and animal populations. To maximize the effectiveness of this strategy proper recording, confinement, and mandatory vaccination of stray and domesticated dogs is required. Follow-up booster shots of the vaccine should also be administered to achieve a persistent level of protective antibody titer against the

rabies virus (Acharya et al. 2020). In addition to dogs, cats must also be vaccinated because they effectively transmit rabies to humans although they are not reservoirs.

14. WILDLIFE VACCINATION

In certain states of America and Europe where the sylvatic cycle of rabies is prevalent and rabies is particularly transmitted by wildlife reservoirs, oral vaccination programs for wildlife must be followed to break the sylvatic cycle of transmission. In Europe and Canada, the use of oral vaccines in foxes has successfully controlled fox rabies. This intervention has successfully eliminated the artic fox rabies variant from Canada (Nel and Markotter 2007).US was also declared free of canine rabies in 2007 by eliminating rabies in coyotes through an oral vaccination program (Elmore et al. 2017) For managing the disease, particularly in terrestrial wildlife reservoirs and in populations of free-roaming or feral dogs where parenteral vaccination is not feasible, oral rabies vaccination represents a socially acceptable approach that can be implemented in a wide geographic region (Slate et al. 2009). In short proper vaccination strategies are the foundation for the prevention, control, and elimination of rabies.

15. POST -EXPOSURE PROPHYLAXIS

Post-exposure prophylaxis is a concerted approach to decrease the patient's probability of developing clinical rabies after exposure to the virus (Nigg and Walker 2009). Although there is no treatment for clinical rabies, this disease can be prevented through prompt provision of adequate post-exposure prophylaxis (PEP) (Kessels et al. 2019). Research has shown that proper administration of rabies immunoglobulin along with vaccination after exposure to rabies is 100 % successful in preventing rabies (Kroger et al. 2015.) The long incubation period of the disease offers an advantage to implement this approach successfully. Post-exposure prophylaxis is followed after an animal has been exposed to rabies. Post-exposure prophylaxis regimen consists of washing and flushing the wound, a dose of human rabies immunoglobulin administered intradermally around the wound, rabies immunization administered on the day of exposure then a booster dose of vaccine is administered (Sreenivasan et al. 2019) The recommended dose for human rabies immunoglobulin is 20 IU /kg body weight and for equine rabies immunoglobulin is 40 IU/kg by WHO (Scholand et al. 2022). The fundamental objective of post-exposure prophylaxis is to neutralize or inactivate inoculated virus in the wound before it can invade the nervous system of the patient and initiate acute neurological disease. Therefore, a health care worker must make a quick decision whether to initiate post-exposure prophylaxis based on careful evaluation of risk (Tenzin et al. 2011). Before starting post exposure prophylaxis, it is really important to asses individual critically and determine whether patients should receive this treatment or not based on category of exposures as defined by WHO because resources for contemporary human post exposure prophylaxis are limited in many underdeveloped countries. Exposure to Category II and Category III should immediately receive post-exposure prophylaxis as individuals placed under these two categories of exposure are those who have skin abrasion, laceration, or a major bite from a dog or any other reservoir. WHO category I exposures include contact with a potentially rabid animal, or involve licks on intact skin and do not require intervention (Rupprecht et al. 2002) as presented in Table 1.

Furthermore, animals to which humans were exposed should be observed for at least 10 days by trained health care professionals for the development of any abnormal behavior. If the suspected animal does not develop any sign or symptom related to rabies, then there is no requirement for post-exposure prophylaxis only wound management is needed. (WHO Guide for Rabies Pre and Post Exposure Prophylaxis in Humans Updated 2014). The immune status and behavior of the suspected animal is also a major factor to consider the administration of post -exposure prophylaxis. If the animal is immunized or

Table 1: Represents the requirement of post-exposure prophylaxis according to the category of exposure. (WHO pre- and post-exposure prophylaxis in humans updated 2014).

Category	Description	Type of exposure	Requirement of post-exposure prophylaxis
Category I	Contact with animal or animal lick, skin is intact	No exposure	Not Recommended
Category II	Animal bite, skin is not intact, small skin abrasion	Minor exposure	Recommended
Category III	Major bite	Severe exposure	Recommended

does not exhibit any unusual behavior, then the use of post-exposure is not recommended (Grill 2009). When an animal has been identified as rabies-positive retrospective case assessment should be implied and contact tracing is required to trace potential contacts to timely administer post-exposure prophylaxis. The 1st step of post-exposure-prophylaxis is the management of the wound. The wound should be thoroughly washed at least for 15 min to clear the virus from wound and decrease the risk of bacterial infection. Use of povidone-iodine solution and 20% alcohol or virucidal agent has been reported to reduce viral transmission from wounds (Hankins and Rosekrans 2004).

Human rabies immunoglobulin provides passive immunity against rabies virus by directly neutralizing rabies virus. It should be administered intradermally around the wound immediately after confirmation of exposure. There are two types of rabies immunoglobulin: human rabies immunoglobulin and equine rabies immunoglobulin both are derived from the plasma of humans and equine respectively who have been hyper-immunized by purified cell culture based vaccine against rabies and have very high titer of rabies antibodies against the virus (Haradanhalli et al. 2022).

It is only recommended to use immunoglobulin up to 7 days of vaccine administration because after that time active immunity against rabies has started to activate and the use of immunoglobulin will cause interference of passive immunity with active immunity. If the patient has no history of pre-exposure vaccination then rabies vaccination and immunoglobulin should be administered on day 0 followed by a booster dose of vaccination on days 3,7 and 14. For immunocompromised persons, it is preferable to administer the last dose of vaccination on day 28 rather than day 14 (Center for Disease Control). Patients who have already received either pre-exposure or post-exposure rabies prophylaxis should be administered only two rabies vaccine boosters upon exposure given on Days 0 and 3. Administration of rabies immunoglobulin is prohibited in such patients. This will boost the production of antibodies and cause an anamestic response (Kessels et al. 2019).

16. ONE HEALTH APPROACH FOR PREVENTION

Since rabies is a zoonotic disease, efforts to control rabies must be multidimensional involving veterinary health professionals, human health care workers, and environmentalists. One health program is based on the foundation that the health of humans is associated with the health of animals and our shared ecosystem (Acharya et al. 2020). One health approach emphasizes outbreak management and control of rabies in both humans and animals, preventing animal-to-human dissemination of rabies, it also reduces the cost of post-exposure prophylaxis. Mass immunization of dogs, and control of stray dog population with animal birth control methods like orchiectomy in male dog and ovariohysterectomy in bitch has been implemented in many countries (Acharya et al. 2020.)

Moreover, community awareness and education also play an integral role in the prevention and control of rabies (Barroga et al. 2018). Educating the public about how lethal is rabies for humans, livestock and their companion animals about the importance of vaccination and timely reporting of disease can effectively help in the control of rabies.

In order to efficiently control rabies, surveillance mechanisms must be in place that allow for early case discovery and reporting. Rabies control and eradication depend heavily on an effective surveillance system. Early case detection and reporting made possible by efficient surveillance systems is essential for prompt action and allows for well-informed judgments and decisions regarding when and where to step up control activities. Following the implementation of interventions, monitoring is necessary to gather information on their effectiveness and cost in order to ensure their long-term sustainability. (Townsend et al. 2013).

17. CONCLUSION

To put it briefly, prevention is the only way to avoid the devastating effects of this neglected zoonotic illness that is extremely pathogenic, and lethal, and causes over 1.8 million DALYs (Disability-adjusted life years) every year (Regea 2017). It not only represents a threat to humans but also to companion animals and livestock. As mentioned above, efforts are needed on multiple levels to prevent this disease, including mass vaccination of domestic dogs, which has significantly decreased the burden of rabies in developed countries, oral rabies vaccination of wildlife in the form of bait, reducing contact with wildlife, public education about prevention, prompt reporting of rabies, an efficient surveillance system, and adequate post-exposure and pre-exposure vaccination.

About 95% of human mortalities from rabies are reported from Asian and African countries. (Ling et al. 2023). Several factors are responsible for the heavy burden of rabies in these continents. The majority of countries in these continents lack the infrastructure and resources to implement widespread vaccination programs. Furthermore, there is a significant population of free-roaming stray dogs population that exacerbates the incidence of rabies. In certain areas of Africa, there is a proximity of human and wildlife reservoirs that increase the chances of rabies. Lack of awareness among the public, underreporting, and limited access to healthcare facilities like lack of timely provision of pre-exposure and post-exposure prophylaxis have contributed to this problem. Keeping in view these problems efforts are being made by many organizations to help control this major public health threat. Prospects regarding rabies control is a joint effort by the World Health Organization, World Organization of Animal Health, Food, and Agriculture Organization, and the Global Alliance for Rabies Control whose goal is to end dog-mediated rabies in humans by 2030 (Nel et al. 2017). These organizations are working together to end rabies by 2030. This is only possible if proper prevention strategies are followed to control rabies as discussed above.

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Rabies Neglected Modes of Transmission in Pakistan

09

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ABSTRACT

Rabies is a contagious but preventable disease. While canine rabies remains the predominant mode of transmission in Pakistan, there are other under-recognized reservoirs and routes of exposure to rabies that pose a significant public health threat. This chapter delves into these neglected routes of rabies transmission, urging a comprehensive approach to rabies control and prevention. Bat-transmitted rabies, mongoose-transmitted rabies, and rabies transmitted through wildlife to human beings are also significant contributors to this disease. Fruit bats have wide-ranging foraging patterns that emerge as potential sources of fruit-borne transmission incidents. Interactions with wildlife are also a cherished aspect of Pakistani culture and warrant scrutiny. Transmission of rabies through professional activities also causes transmission to health care professionals and veterinarians. Ritual activities such as dog fights also spread this disease; fighting dogs also spread this disease ultimately to human beings. Rodents that are present in almost every region and contaminate every household in Pakistan also transmit this disease to human beings. Bites or scratches from seemingly docile or playful animals such as foxes, jackals, mongooses, etc. can spread the rabies virus. Public education initiatives emphasizing responsible wildlife interactions and prompt post-exposure prophylaxis are crucial in the prevention of rabies transmission. Ignoring these non-canine transmission pathways hinders effective rabies control. This chapter advocates for a multifaceted approach encompassing expanded surveillance of diverse animal reservoirs, targeted interventions tailored to specific transmission routes, and heightened public awareness about neglected vectors. Only through such holistic approaches can Pakistan effectively combat the multifaceted threat of rabies.

Keywords: Rabies, Modes of Transmission, Bat-Transmitted Rabies, Public Health, Wild Life.

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1. INTRODUCTION

Rabies is a highly contagious viral disease affecting mammals' central nervous system. It is caused by the highly contagious rabies virus (Baer 1988; Kaplan 1977). The rabies virus (RV) is a single-stranded RNA virus that belongs to the Rhabdoviridae family of viruses (Wunner and Conzelmann 2013). Dogs are the most frequent source of rabies infection in humans globally (Dutta 2014). The disease is usually transmitted through the bite and scratch of an infected animal to healthy animals and human beings (Hankins and Rosekrans 2004). There are other ways to transmit rabies, but they are neglected and have a significant role in disease epidemiology (Singh et al., 2017). These neglected ways should be considered for effective disease control (Constantine 1962).

For control and prevention strategies to be successful, it is essential to understand modes of rabies transmission (Catherine 2011). Public health authorities and researchers can design focused measures to lower the incidence of rabies and reduce the danger of outbreaks by investigating both the primary and neglected modes of transmission (Afshar 1979).

In this chapter, we'll look at various ways the rabies virus is transmitted, particularly the rare and undervalued methods (Rupprecht et al., 2002). We seek to raise awareness and add to the overall understanding of rabies transmission dynamics by shedding light on these neglected modes of transmission (WHO 2018). This information may be advantageous in formulating thorough strategies to prevent and treat this deadly disease (Crowcroft and Thampi 2015).

2. NEGLECTED MODES OF RABIES TRANSMISSION

2.1. TRANSMISSION THROUGH MONGOOSES

While animal bites and scratches are the main ways of spreading rabies, other overlooked zoonotic transmission mechanisms must be considered (Davis et al., 2007). Some cases of mongoose-borne rabies are recognized in some areas as a potential source of human infection. In this article, we'll talk about how mongooses spread rabies (Everard and Everard 1988).

Small carnivores such as mongooses are known for their agility and predation (Everard and Everard 1992). Mongooses are found in nearly all countries worldwide but frequently in African and Asian territories and some islands (Nel et al., 2005). Mongooses are not generally considered reservoir hosts for rabies, but in some Asian and African regions where they coexist alongside rabies-carrying animals, reports of rabies transmission from mongooses to humans have been observed (Tierkel et al., 1952).

Uncertainty surrounds the precise transfer mode from mongooses to people (Van Zyl et al., 2010). However, similar to other rabies transmission means, it is speculated to occur through the transfer of saliva (Berentsen et al., 2015). Rabies infection can occur due to bites, scratches, or open wounds exposed to mongoose saliva (Krebs et al., 2003).

Mongoose-to-human rabies transmission is regarded as a neglected zoonotic mode due to its comparatively low frequency when compared to cases from other sources (Nellis and Everard 1983). However, in places like Pakistan, India, and the Caribbean, where mongoose populations are numerous, and rabies is endemic, it is vital to consider these ignored transmission pathways for successful rabies control (Seetahal et al., 2018).

3. TRANSMISSION THROUGH RODENTS

Rabies transmission from rodents to humans rarely occurs, but some cases have been reported (Fitzpatrick et al., 2014). Rodents are not considered reservoirs of the rabies virus, but they can become infected and transfer the virus to humans if they are bitten by a rabid animal (Eidson et al., 2005). There have been many incidents where rodents transmitted the rabies virus to humans through bites, scratches, or exposure to their saliva (Jackson 2002). Such instances are relatively infrequent, and rodents are not typically a significant source of human rabies infections (Winkler 2017). Nonetheless, caution should be exercised when handling or encountering wild or stray rodents, especially if they display unusual or aggressive behavior (Mørk and Prestrud 2004).

5. TRANSMISSION THROUGH OTHER WILDLIFE

In addition to common carnivores, other wildlife species may also play a role in the transmission of rabies (Macdonald 1980). Animals such as raccoons, skunks, and bats are known reservoirs of the rabies virus. Bites and scratches from infected wildlife are the primary modes of transmission (Winkler and Bögel 1992). Raccoons and skunks can transmit rabies to humans, particularly in areas where these species are endemic (Sterner and Smith, 2006). Bats, in particular, are important vectors of rabies and can transmit the virus through bites or, in rare cases, even through direct contact with mucous membranes or broken skin (Tinline 1988). It is essential to exercise caution and avoid handling wildlife, especially if they appear sick, disoriented, or exhibit aggressive behavior (Rupprecht et al., 1995). Vaccination of domestic animals, particularly against bat-associated strains of rabies, is essential for preventing transmission from wildlife to pets and humans (Acharya et al., 2022).

6. TRANSMISSION THROUGH DOMESTICATED ANIMALS

Pets' mainly unvaccinated dogs and cats, can easily get infected by the rabies virus and transmit it to their owners and other animals (Have et al., 2008). It has been documented that domestic cats who wander outside their houses unvaccinated are more likely to acquire the rabies virus than cats who have had vaccinations (Wyatt 2007). In case studies, it has been seen that cats missing from home for several days showed stress signs and later started showing signs of rabies (Beran and Frith 1988). The primary transmission route is scratching or biting by infected animals (Crozet et al., 2020). If one of these unvaccinated pet animals gets bitten by an infected animal, they can get infected with the virus and spread it to humans (Chang et al., 2002). To stop the spread of rabies and protect both animal and human health, it is essential to have well-trained pets and to immunize domesticated animals regularly (Beeler and Ehnert 2020).

7. TRANSMISSION THROUGH ENVIRONMENTAL EXPOSURE

Transmission of the rabies virus can occur occasionally after environmental exposure (Dürr and Ward 2015). Transmission may occur when individuals come in contact with objects or surfaces exposed to

infected animals (Setyowati and Machmud 2018). There is a slight chance of a person's mucous membranes or an open wound coming into contact with contaminated surfaces (Rupprecht et al., 2008). Environmental exposure contributes to only a fraction of human rabies cases and is not a significant cause of transmission (Layan et al., 2021). However, it is essential to maintain excellent hygiene and steer clear of potentially infectious objects or surfaces, especially in areas where rabies is prevalent (Dhand and Ward 2012).

8. TRANSMISSION THROUGH UNCOMMON OCCUPATIONAL EXPOSURES

Certain occupations that involve close contact with animals or animal tissues may expose workers to rabies (Parize et al., 2021). Veterinarians, animal control workers, researchers, and laboratory workers may be more likely to be exposed if they handle rabies-infected animals or work with the rabies virus in the laboratory (Rupprecht et al., 2006). Incidental needle stick wounds or scratches from infected animals can prompt transmission (World Health Organization 2018). To reduce the occupational risk of rabies transmission, adhere to proper safety protocols, such as wearing personal protective equipment and getting vaccinated (Kessels et al., 2017; Tarrant et al., 2020).

9. CROSS-SPECIES TRANSMISSION

Rabies is a disease that primarily affects mammals; however, occurrences of cross-species transmission have been reported (Wallace et al., 2014). In rare cases, rabies infection can be transmitted from one species to another, possibly prompting human diseases (Gordon et al., 2004). Cross-species transmission can occur through bites, scratches, an open wound, or the brain tissue of an infected animal (Borucki et al., 2013). The transmission of rabies to humans from non-reservoir species, such as non-human primates or marine mammals, is an example of cross-species transmission (Bonnaud et al., 2019; Mollentze et al., 2020). Albeit such occurrences are inconsistent, observation and checking of creature populations are fundamental to distinguishing potential cross-species transmission occasions and carrying out suitable preventive measures (Holmes et al., 2002; Singer and Smith 2012).

10. CONTROVERSIAL OR DEBATED ROUTES OF TRANSMISSION

In rabies research, several transmission routes are still debatable or controversial (Thomas et al., 1990). These include transmission methods that are either not fully understood or have not been thoroughly investigated (Banyard et al., 2019). A few instances predict that infection might spread through infected animals' tears, sweat, or urine, although the evidence for these theories is scant or ambiguous (Fallon Jr and Schmalzried 2008). Current scientific knowledge does not believe these controversial modes of transmission are significant contributors to human rabies cases (Rupprecht et al., 2017). Continuous research is crucial to analyze and explain these transmission routes to guarantee a thorough understanding of rabies transmission routes (Derbin and Flamand 1985).

11. VERTICAL TRANSMISSION

Vertical transmission refers to the transmission of a pathogen from an infected mother to her offspring during pregnancy, childbirth, or breastfeeding (Aguèmon et al., 2016). In rabies, vertical transmission is considered a rare and unusual transmission mode (Iehl et al., 2008). While it is theoretically possible for

a pregnant animal infected with rabies to transmit the virus to her fetus or newborn, documented cases of vertical transmission in mammals, including humans, are extremely rare (Nidia Aréchiga-Ceballos et al., 2019; Swamy and Heine 2015). Vertical transmission of rabies is not a significant concern in the overall epidemiology of the disease, and the primary modes of transmission remain bites and scratches from infected animals (Aréchiga-Ceballos et al., 2019; Warrell and Warrell 1988).

12. TRANSMISSION THROUGH NON-BITE EXPOSURE

Rabies commonly spreads through bites and scratches: there are reports of very few cases in which the virus was not spread through saliva from one infected animal to another (Winkler et al., 1972). Non-biting openings incorporate cases where the infection enters the body through mucous films (like the eyes, nose, or mouth) or broken skin that comes into contact with infected animals, discharges, like urine, tears, or respiratory drops (Barnard et al., 1982; Di Quinzio and McCarthy 2008). Despite this, it is unusual that non-biting openings result in the spread of the rabies virus, and these cases are regarded as outstanding and extraordinary modes of transmission (Balachandran and Charlton 1994). The most crucial and pervasive ways of rabies transmission are bites and scratch wounds (Balsamo et al., 2009).

13. BLOODBORNE TRANSMISSION

Bloodborne transmission refers to transmitting rabies through contact with infected blood (Dean et al., 1963). Although the rabies virus is found in the blood of infected animals, it is rarely transmitted to other animals via blood contact (Horta et al., 2022). The virus is primarily concentrated in the nervous tissue and saliva of infected animals, making bites and scratches the main modes of transmission (Lodmell et al., 2006). However, in rare cases of organ transplantation from an infected donor or accidental exposure to infected blood in laboratory settings, there is a theoretical risk of bloodborne transmission (Wang and Jin 2009). Strict safety protocols and proper screening of potential organ donors are in place to mitigate this risk (Roine et al., 1988).

14. TRANSMISSION THROUGH CONTACT WITH INFECTED ANIMAL WASTE

Contact with infected animals' wastes, like urine, feces, or bedding material sullied with the infection, is not considered the principal mode of rabies transmission (Wright et al., 2021). The virus is fundamentally present in infected animals' sensory tissue and saliva, and the fixation on side effects is ordinarily low (Gilcreas 1966). In this way, the risk of contracting rabies through contact with contaminated animal waste is negligible (Maurer and Guber 2001). When handling or cleaning areas contaminated with animal waste, however, it is still essential to maintain good hygiene, including washing one's hands thoroughly, to lessen the likelihood of contracting additional infections (Goor 1949; Strauch and Ballarini 1994).

15. ANIMAL-TO-ANIMAL TRANSMISSION

While rabies primarily affects mammals, the virus can be transmitted between animals (Bano et al., 2017). Animal-to-animal transmission can occur through bites, scratches, or close contact with an infected animal's saliva or neural tissue (Niezgoda et al., 2003). Animal-to-animal transmission is standard in wildlife populations and can contribute to the maintenance and spread of rabies within animal species (Barecha et al., 2017). However, the direct transmission of rabies between animals without subsequent transmission to humans is not considered a neglected mode of zoonotic

transmission (National Association of State Public Health Veterinarians. Compendium of Animal Rabies Prevention and Control 2005). This heading focuses primarily on neglected transmission modes related to human infection (Brown et al., 2011).

16. TRANSMISSION THROUGH ENVIRONMENTAL RESERVOIRS

Environmental reservoirs describe environments or places where the rabies virus can survive, even without nearby animal hosts (Scheffer et al., 2014). The virus spreads mainly through direct contact with infected animals, but if specific conditions are met, environmental reservoirs can also infect humans (Escobar et al., 2015). For instance, the virus can survive in bat colonies, where infected bats' saliva, urine, or guano may contact humans (Wandeler et al., 1993). The chance of human infection from environmental reservoirs is often low, and the main focus of rabies control initiatives is on direct animal-to-human transmission (Vercauteren et al., 2012).

17. TRANSMISSION THROUGH EXPOSURE TO BAT GUANO

Bat guano feces can contaminate the rabies virus, particularly in areas where bats are identified as reservoirs of infection (Dimkić et al., 2021). Although bat guano has a low risk of transmission, it can be transmitted through handling and coming into contact with feces (Li et al., 2010). It occurs more often in congested areas like caves or attics (Robertson et al., 2011). It is essential to take precautionary measures and maintain hygiene to reduce the risk of contamination (CDC 1998).

18. INTRAUTERINE TRANSMISSION

Intrauterine transmission is the spread of the rabies virus from mother to fetus via the placenta (Qu et al., 2016). Even though rabies is rare to transmit through the intrauterine route, a few cases reported and described raise the possibility (Scheidegger 1953). However, the specific mechanisms and transmission perspective are still unknown (Otrzanowska-poplewska 1969). In the general epidemiology of the disease, intrauterine transmission is not regarded as a significant mechanism of rabies transmission but as a neglected one (Roszkowski et al., 1972).

19. AEROSOL TRANSMISSION

The possibility of rabies transmission through virus-laden respiratory droplets is called aerosol transmission (Winkler et al., 1973). Although bites and scratches are the primary routes of rabies transmission from one host to another, only a few studies and reports suggest the possibility of aerosol transmission in some cases, such as laboratories or highly controlled environments (Davis et al., 2007; Messenger et al., 2002). In any case, it is essential to note that aerosol transmission of rabies is not a typical or deeply grounded method of transmission, and further research is required to comprehend its importance (Adedeji et al., 2010; Held et al., 1967).

20. TRANSMISSION VIA INSECTS

Insects are considered vectors of various contagious diseases, but their role in rabies transmission is negligible compared to other modes of transmission (Shope 1982). Insects are not well known to reproduce or transmit the rabies virus to dogs, cats, or other warm-blooded animals (Pinto et al., 1994).

While bugs might precisely transmit the infection as they come into contact with contaminated spit and consequently bite another person or animal, there is no proof to suggest that this method of transmission is critical to the general transmission elements of rabies (Badrane and Tordo 2001). Rabies spreads most frequently through bites from infected mammals and about negligible through insects (Nel and Markotter 2007).

21. TRANSMISSION THROUGH ORGAN TRANSPLANTS

Although organ transplantation is perceived as a likely course of transmission, rabies transmission through this course is phenomenal (Nel and Rupprecht 2007). The transmission of the rabies virus from a rabies-infected donor's organ to a recipient has been observed in a few cases (Dietzschold and Koprowski 2004). To decrease the risk of infections from infected donors, strict screening processes, including point-by-point clinical history evaluations and serological testing, are set up (Bronnert et al., 2007; Srinivasan et al., 2005). Even though there is a low risk of transmission with organ transplants, careful donor selection and rigorous pre-transplant evaluation protocols are essential (Burton et al., 2005; Nigg and Walker 2009).

22. TRANSMISSION THROUGH COUNTERATTACK OF JACKALS

If the jackal is infected with the virus, there is a risk of rabies transmission when hunting dogs come into contact with jackals and engage in fights or counterattacks (Swanepoel et al., 1993). During hunting, if a jackal bites a hunting dog, the penetration of the jackal's saliva could transmit a virus to the dog through the bloodstream (Loveridge et al., 2001). The rabies virus attacks the nervous system and spreads to the brain via nerve fibers (Zulu et al., 2009). When the infection arrives at the brain, it starts to reproduce quickly, prompting the trademark side effects of rabies (McKenzie 1993).

The transmission of rabies through bite relies upon different variables, including the viral burden of the mucus of the infected animal, the abrasiveness and severity of the scratch, and the location of the bite (Barnard 1979; Cumming 1982). Higher risks are associated with bites to the head, neck, and limbs, which have an abundant blood supply (Blancou 1988; Hikufe et al., 2019).

It is critical to note that rabies in a jackal cannot be resolved outwardly, as an infected animal may not indicate the illness clearly (Benedictis et al., 2022). Infected animals might seem disturbed, confused, or behave strangely, yet they can transmit the infection during the asymptomatic stage (Atuman et al., 2014; Smith et al., 1993).

Following the previously mentioned preventative measures, such as vaccinating hunting dogs against rabies, is essential to preventing rabies transmission in such circumstances (Briggs 2012). Vaccination helps protect dogs in the event of potential exposure and significantly lowers the risk of infection (Brown et al., 2016; Rupprecht et al., 2016).

23. TRANSMISSION THROUGH RITUAL DOGS FIGHT

During a fight between two dogs, if one dog is affected by the rabies virus, it can transmit it to the other (Athingo et al., 2020). This can happen through bites and scratches that one dog gives to another dog (Broban et al., 2018).

At the point when two canines take part in a battle, their chomps can cause stabbings, gashes, or other wounds that permit the infection to enter the circulatory system (Kanda et al., 2022; Rattanavipapong et al., 2019). If the infected dog's saliva contains the rabies infection, the infection can be transmitted into

the infected dog's body through these injuries (Lembo 2012). The virus can then reach and replicate in the central nervous system of other dogs, including the brain, where it causes the onset of rabies symptoms once it has entered the body through the peripheral nerves (Wunner and Briggs 2010).
It is noteworthy that not all dog fights result in the transmission of rabies (Lapiz et al., 2012). The presence of rabies in one of the canines included is a pivotal element (Fahrion et al., 2016). In regions with effective vaccination programs, rabies is relatively rare in domestic dogs (Coetzer et al., 2018). Nonetheless, in areas where rabies is more common or where immunization rates are low, the risk of transmission increases (Pemberton et al., 2007).

24. RABIES AND PUBLIC HEALTH

Rabies is a significant public health concern because it is highly contagious and spreads rapidly (Hampson et al., 2015; Knobel et al., 2005). The primary concern is in African and Asian countries where vaccines are not readily available (Iqbal et al., 2023). We can reduce the risk of rabies transmission through prevention and control ((Baer 2017)). This can be achieved by increasing the vaccination rate (Taylor and Nel 2015). Causalities from rabies post-bite exposure can be reduced through proper wound management and prophylactic treatment (Parviz et al., 2004; Shankaraiah et al., 2015).

25. IMPORTANCE OF RABIES PREVENTION AND CONTROL

Rabies can only be controlled through prevention and precautionary measures (Coleman et al., 2004). As we know, rabies is a viral disease with a high mortality rate, and there is no known treatment for this deadly disease; therefore, it can only be prevented through vaccination (Taylor and Nel 2015). Pet vaccination is critical to reducing the spread of rabies (Durr et al., 2009). Live rabies vaccines can be used in this regard because they have been observed to be effective in preventing rabies (WHO 2018). We can also reduce prevention by prohibiting pets' exposure to wild animals (Morters et al., 2015).
Dogs are the most prominent source of rabies spreading to humans all across Pakistan ((Seimenis 2008)). In this regard, ensuring vaccination of the maximum canine population can help reduce disease spread in communities (Singh et al., 2017). This is hard to achieve in Pakistan because it is costly, so developing a cheaper and more effective vaccine is needed to fight this disease ((Kumarapeli and Awerbuch-Friedlander 2009)). Therefore, it is essential to vaccinate animals in high-epidemic areas (Barecha et al., 2017; Knobel et al., 2013).
On exposure to rabies, quick and timely vaccination before the onset of neurological signs can prevent the disease (Wandeler et al., 1988). As the first line of treatment, proper wound cleaning and post-exposure prophylaxis treatment can be done as first aid to prevent disease development in infected individuals (Hampson et al., 2008; Tarantola et al., 2019).
In short, implementing preventive measures and vaccinating animals can help reduce the spread and control of rabies (Briggs 2012; Manning et al., 2008).

26. EDUCATION AND AWARENESS PROGRAMS FOR PUBLIC HEALTH

Education and awareness programs are some of the most effective tools for public health (Balaram et al., 2016; Hasanov et al., 2018). Rabies can be significantly prevented by spreading awareness among individuals and communities (Acharya et al., 2020; Meslin and Briggs 2013). There is a crucial need to educate people in rural areas because there are many reports of children's deaths due to rabies in Pakistan (Ahmed et al., 2020). We can have seminars or community awareness programs in these areas

to prevent the disease (Khan et al., 2019). Educating people in rural areas can save several precious lives (Prakash et al., 2013; Muthunuwan et al., 2017). Educating people about vaccinating their pets can be very helpful in the control of this disease (Ahmad, Naeem et al., 2021); Dodet et al., 2008)). Arranging workshops about first aid wound management and prophylactic treatment ((Parviz et al., 2004; Farooqi and Hayat 2009). This can help reduce post-bite control for patients and reduce deaths in endemic areas (Garg and Garg 2014; Rupprecht et al., 2022). In short, raising awareness among the community can significantly help prevent and control this disease ((Weyer and Blumberg 2007)).

Pre-exposure Vaccination				
Animals	Age of Vaccination	Second Dose	Booster Dose	Amount of Vaccine
Dogs	3 months	21 Days	Annually	1 ml
Cats	3 months	21 Days	Annually	1 ml
Ferrets	3 months	21 Days	Annually	1 ml
Ruminants	3 months	21 days	Annually	2 ml

Post Exposure Vaccination			
Animals	Quarantine	Vaccinated	Un vaccinated
Dogs	96 hrs	Quarantine 3 months	Euthanize
Cats	96 hrs	Quarantine 3 months	Euthanize
Ferrets	96 hrs	Quarantine 6 months	Euthanize
Ruminants	96 hrs	Quarantine 6 months	Euthanize

27. CONCLUSION

Rabies is a highly contagious disease transmitted mainly through bites and scratches, but there are several other ways of transmission. These ways should be considered for maintaining public health. Taking preventive measures to reduce spreading through these modes of transmission can help eradicate this disease from the world.

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BATS: Originators of Most of the Zoonotic Pathogens

10

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ABSTRACT

Bats are an important host of various viruses. Bats have a role as reservoir hosts for various types of viruses and they can transmit these viruses to humans and other animals via their secretions and excretions. Immunological changes are induced in bats after flight. Such phenomenon may play a part in the origination of endemic infections, having significant manifestations of zoonosis. Spillover is when bat pathogens cross-species transmission into other species. Bats are also capable of causing airborne diseases through bugs that feed on bat blood or stool. Viruses from Bats can enter the host cell by attaching itself to cell receptors, thereby infecting it with viruses or viral DNA. viral genome replication is done through the making of negative strain RNA which forms the basis of creating new virus genomes. A virus replicates its genomic RNA by interacting with the 5' and 3' termini of its genome. Upon completion of the replication process by the viral proteins, they subsequently release newly synthesized virions that can then go on to infect neighboring cells before spreading through the entire host's body system. It is important to understand how viruses can jump from animals to mankind to facilitate targeted surveillance, detecting emerging diseases in good time, and designing relevant vaccines and treatment methods. In brief, this chapter discusses the importance of bats in virus transmissions, how the immune system responds to bat flight, and how coronaviruses multiply in host cells. These mechanisms are central in diagnosing, treating, and preventing bat-borne zoonotic diseases.

Keywords: Bats, Zoonosis, Viral infections, Cross-species transmission, Immune response. Anthropogenic land-use change.

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1. INTRODUCTION

Humans are not the only creation living on this planet rather this world is full of different kinds of creatures other than humans such as animals, plants, birds, insects, and microbes. All these creations live and interact with each other to survive. These interactions can be advantageous, and species get benefits from each other in a healthy interaction. Sometimes these interactions can be hazardous because one species can carry some pathogens which transmit different diseases to the other species. Humans interact with different animals to feed in order to get protein and other nutrients needed for their growth and survival (Rosenberg 2015).

Bats have been known to be the rational originators of most zoonotic microorganisms (pathogens). Their fascinating physiology has an immediate impact. They are known to be the primary warm-blooded animals that can fly, and have a high metabolic rate, which grants them to convey a lot of energy. Moreover, they have a unique safe system that licenses them to get through diseases that would be lethal to various animals. Likewise, bats are known to be the transporters of different befoulment, including the Ebola sickness, Mar-burg infection, Nipah illness and Hendra tainting. These diseases are known to cause difficult ailments in individuals and various animals (Brook and Dobson 2015). The legitimization for why bats are carriers of these diseases is that they have a unique resistant system that licenses them to persevere through the contaminations without turning out to be sick. This suggests that they can convey the contaminations for a long time without showing any secondary effects. The close relationship of bats with individuals and various animals has similarly added to the spread of these diseases (Phan and Nguyen 2020). Bats are known to roost in caves, trees, and designs, which are a concept close to human settlements. This plans that there is a high chance of contact between individuals and bats, which can provoke the transmission of these contaminations. The use of bat meat and bat guano as a fertilizer has moreover been associated with the transmission of these contaminations (Guth and Mollentzn 2022). In specific social orders, bat meat is seen as a delicacy, and it is eaten rough or cooked. This can incite the transmission of the contaminations from the bat to human. The use of bat guano as fertilizer (compost) has moreover been associated with the transmission of contaminations. It is rich in enhancements, and used as manure in numerous districts of the planet. Regardless, the guano can be corrupted with contaminations, which can provoke the transmission of the diseases to individuals and various animals. Bats are known to spread contaminations of zoophytic imaginable in more than one manner. One way is through direct contact with individuals or animals (Hayman and Bowen 2013).

Bats can convey diseases in their spit, urine, and manure, which can be imparted to individuals or animals through bites, scratches, or contact with dirty surfaces. Another way that bats can spread diseases is through eating bat meat. As Bats are eaten as food in specific social orders, and the meat can be contaminated with diseases. This can similarly provoke the transmission of contaminates, as the guano can be corrupted with the diseases (Schneeberger and Voigt 2016). Bats can also spread contaminates through the air. A few contaminants can be shed in bat droppings and urine, which can dry and become airborne. When the droppings or urine of bats are distributed, the disease can become airborne and accidentally taken in by individuals or animals. In this way, bats can spread contaminants through bugs that feed on bat blood or stool. A couple of bugs, similar to mosquitoes and ticks, can profit from bats and subsequently eat individuals or animals, spreading the diseases meanwhile (Schneeberger and Voigt 2016).

2. ZOONOTIC DISEASES

When transferred naturally from animals to people and vice versa, several microorganisms that cause illnesses can infect both vertebrate animals and humans. (Rahman et al. 2020). The natural transmission of infectious diseases from animals to humans due to different pathogens is called zoonosis (Wang and

Crameri 2014), and the term "zoonotic pathogens" refers to pathogens that primarily spread illness when they come into contact with people (Cross et al. 2019).

Zoonotic diseases spread by bats are not new because several viruses have previously caused various outbreaks. Yet, due to limited outbreaks, these diseases were not identified as zoonotic, and a pathogen may remain unnoticed if it does not result in a large-scale disease outbreak (Wang and Crameri 2004).

Infectious organisms including viruses, bacteria, parasites, fungi, prions (Wang and Crameri, 2004), protozoa, and many other pathogens are responsible for different zoonotic diseases (Rahman et al. 2020). More than half of infectious diseases in humans are transferred from animals and this number is continuously increasing due to multiple reasons like different human activities (Cross et al. 2019). Anthrax, TB, plague, yellow fever, and influenza are just a few illnesses that have been transmitted to people through domestic animals, poultry, and cattle during the past ten years. Zoonotic diseases could have detrimental impacts on people's health and the economy, and the upward trend in their frequency is expected to continue (Wang and Crameri 2004). Zoonoses have a substantial negative influence on the environment, industry, and the economy at large. (White and Razgour 2020).

3. HUMAN ACTIVITIES AND ZOONOSIS

Human activities are involved in the sharp rise of zoonotic diseases from wildlife species due to different activities like the destruction of animal habitats and agricultural changes etc. (Wang and Crameri 2004). In the same way, a wide range of geological and biological causes, including changing the climate, industrialization, animal movement, commerce, tourism, and vector biology, have had a substantial influence on the development, recurrence, spread, and pattern of zoonoses (Rahman et al. 2020). The spread of these disorders and the danger of transmission have been exacerbated by recent land-use changes (LUC), such as deforestation and agricultural expansion, which are the aspects that are expected to expand in future owing to human population growth and rising resource demand (White and Razgour 2020).

4. OUTBREAK OF ZOONOSIS

Since more than 75% of new illnesses are zoonotic in nature, zoonotic diseases are no longer rising, rather they are now posing a severe threat to the entire planet (Field 2009). When diseases from a vector species infect its host species, zoonosis develops (Brierley et al. 2016). Bats are the second most species-rich order of animal, with more than 1,200 species spread throughout the world. After it was discovered that bats in Australia were the natural reservoir of Henda virus, there has been a huge rise in researcher’s interest in bats by considering it as the reservoir of numerous important known and undiscovered zoonotic viruses. Since bats are so diverse, zoonotic infections can spread easily among them. Their capacity to fly helps them to disseminate these infections over a huge geographical area (Wang and Crameri 2014). As a result, both scientists and general public have become more interested in the origin of zoonotic viruses from bats (Voigt and Kingston 2015). Previously the outbreaks of zoonotic diseases have often been attributed to bats. Since bats are hosts of more than 200 zoonotic viruses, many of which are RNA-based and have considerable genetic variety, these viruses are able to significantly adapt to shifting environmental conditions. (Allocati et al. 2016).

5. GENOMIC VERIFICATION

To generate a strong hypothesis regarding bats as a source of different zoonotic diseases (specifically coronavirus), genomic studies were made which supported that bats are likely to be the natural host of

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and *MERS*-like viruses in Asia and South Africa. The discovery of a little polymerase chain reaction (PCR) fragment in the Egyptian tomb bat (Taphozous perforates) in Saudi Arabia, provided more evidence in favor of this notion. In addition to the above-mentioned bat zoonotic viruses, several other previously unidentified viruses have been found in the past two decades. Other viruses with a history of zoonotic transmission, include the Menangle virus in Australia and the related Tioman and Melaka viruses in Malaysia. In addition to these, there are other related bat reoviruses as well. Large numbers of bat viruses, including lyssaviruses, parainfluenza viruses, hantaviruses, hepaciviruses, and pegiviruses, have also been linked to recognized human illnesses. Several additional paramyxoviruses, coronaviruses, astroviruses, adenoviruses, and herpesviruses are also documented (Wang and Crameri 2014). These viruses mostly reside inside the bats and then transferred to different organisms where they cause different zoonotic diseases (Hayman 2016).

6. CLASSIFICATION OF ZOONOSIS

Zoonotic diseases are classified into many different types depending upon the conditions in which these diseases spread into different species, such as direct zoonosis and reverse zoonosis (Rahman et al. 2020).

7. DIRECT ZOONOSIS

Humans can get infections from animals either directly or indirectly. Diseases spread by direct zoonoses are those that transfer from animals to humans directly through the environment or other means of transmission. A well-known illustration of direct zoonoses is the virus known as avian influenza, which travels from animals to people through droplets or fungal spores. Additionally, rabies which is one of the deadliest zoonotic illnesses, transmitted when infected animals can bite people and directly transmit viruses to them (Rahman et al. 2020).

8. REVERSE ZOONOSIS

Animals typically infect humans with zoonotic diseases. However, some stories claimed that humans can infect animals as well. Such conditions are referred as reverse zoonoses. Examples of such pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA), *Campylobacter* spp, and influenza A virus (Rahman et al. 2020).

9. CLASSIFICATION BASED ON ETIOLOGY

Based on etiology, zoonoses are classified into:

i. Bacterial zoonoses (such as Anthrax, Tuberculosis, Lyme disease, and Plague)
ii. Viral zoonoses (such as rabies, Ebola, and Avian Influenza)
iii. Parasitic zoonoses (such as Trichinosis, Malaria, and Echinococcosis),
iv. Fungal zoonoses (such as Ringworm)
v. Rickettsia zoonoses (such as Q-fever),
vi. Chlamydial zoonoses (such as Psittacosis),
vii. Mycoplasma zoonoses (Mycoplasma pneumoniae infection),
viii. Protozoal zoonoses (Toxoplasmosis) (Rahman et al. 2020).

10. ZOONOTIC DISEASES CAUSED BY BATS

Many individual bats are captured repeatedly over time as part of a standard method in bat-borne disease research, and their samples are taken (such as blood, urine, feces, or saliva) and examined for the presence of viruses using PCR or serology (Giles et al. 2021). Research has proved that there are many zoonotic pathogens that make bats as their host and then transmit different diseases to humans and other animals (Giles et al. 2021).

A well-known and well-established virus in the family Rhabdoviridae is rabies virus (RABV), which is still one of the most significant zoonotic infections linked to bats (Voigt and Kingston 2015). This bat-associated virus belongs to the genus Lyssavirus, one of the six negative-sense RNA virus genera that make up the Rhabdoviridae family. At least 14 distinct species of the Lyssavirus genus are found in bats, which are believed to be the viruses' original hosts. The first recorded instance of the rabies virus (RABV) occurred in 1911, and it was bat-to-human transmission (Allocati et al. 2016).

Hendra virus disease is another example of a zoonotic disease transmitted by bats. Bats are the reservoir hosts for Henipa viruses, according to viral isolation from pteropodid bats and experimental genomic analyses of virus (Voigt and Kingston 2015) and it is most likely spread by eating food, drinking pasture water, or drinking feed that has been contaminated by the feces, saliva, or urine of sick bats (Allocati et al. 2016). This virus also affects horses, who serve as its intermediate hosts and produces a deadly illness in them. This virus caused the Hendra virus (HeV) illness in Australia in 1994, 20 horses and 2 individuals experienced problems in just two weeks, which led experts and high-ranking officials to launch a thorough investigation. Despite the presence of numerous novel zoonotic viruses in the human population, including the extremely dangerous Hendra virus and its close sibling Nipah virus (NiV), their ability to spread to non-reservoir species is only moderately effective (Wang and Crameri 2014).

In 1999, researchers in Malaysia found the second henipaviruses, Nipah virus (NiV), in pigs and encephalitic pig workers (Voigt and Kingston 2015). It is an encapsulated, single-stranded, negatively skewed, non-segmented RNA virus with helical symmetry. The virus circulates between fruit bats, pigs, and humans as well as between pigs to pigs and man. Fruit bats serve as a natural reservoir for Nipah infections (Singh et al. 2019). The Henipavirus genus is the most noteworthy group of Paramyxoviridae viruses found in bats (Voigt and Kingston 2015). Menangle virus (genus Pararubulavirus*)* is the fourth zoonotic virus in the family Paramyxoviridae transmitted by bats (Van Brussel and Holmes 2022).

Coronaviruses were initially discovered in animals of the genus Miniopterus, although their zoonotic potential is unknown (Voigt and Kingston 2015). The family Coronaviridae and order Nidovirales both contain single-stranded positive-sense RNA viruses with genomes between 16 and 31 kb, (Hernández-Aguilar et al. 2021). Coronavirus has different strains, including severe acute respiratory syndrome, Middle East Respiratory Syndrome, and Coronavirus. Additionally, it has been proposed that coronaviruses are borne by bats, and genetic research has supported this theory (Hu et al. 2015). Coronavirus is the most recent global zoonotic pandemic which disturbed the whole world and damaged the world economy. The primary host of the coronavirus is bats, and these bats transferred this virus to humans and caused a global pandemic (Hu et al. 2015).

A well-known filovirus, Ebola virus, is responsible for severe hemorrhagic fever in humans, high fatality rates, and fast transmission across the communities in Africa (Voigt and Kingston 2015). Negative-strand RNA viruses with no segments are known as filoviruses. These viruses are filamentous, enclosed particles of varying lengths (Filo, from the Latin filum meaning thread). The filovirus genomes generally measure 19 kb in size (Olival and Hayman 2014). Another study has connected filoviruses to the ecology of bats. Anti-EBOV antibodies and EBOV RNA were found in various fruit bat species; and it was discovered that the Ebola virus disease is spread from bats to people through direct contact or through bat feces (Fiorillo et al. 2018).

11. BIOCHEMICAL PATHWAY OF VIRUS TRANSMISSION

The only mammals capable of power-driven flight are Bats, which makes Bats able to migrate across a wider area than other land mammals (Durai et al. 2015). It is important to note that Mammals belong to the second largest category, including bats, which are found all over the world. The phylogenetic study divided bats into two significant suborders, the Yinpterochiroptera, including five Rhinolophoidea (micro-bat) families and one Pteropodidae (mega-bat) and the Yangochiroptera, which had a total of thirteen (micro-bat) families (Durai et al. 2015). Also, the capacity of bats to migrate has importance in disease transmission, and it is suggested that flying provides a selective pressure for cohabitation with viruses. This theory is supported by the fact that a few extremely dangerous human illnesses have been associated with bats. Bat filoviruses (Marburg virus, mental virus, and ebola virus), henipa viruses (hendra virus and nipah virus), lyssaviruses (rabies virus) and CoVs (SADS-CoV, SARS -CoV, and MERS -CoV), among others that have been thoroughly described, represent a danger to human health (Durai et al. 2015). A thorough examination of the interactions between mammalian hosts and viruses revealed that Bats are substantially more likely than other mammalian orders to contain animal disease viruses. Because the hosts cells' translational and transcriptional patterns, cytoskeleton, cell cycle, and apoptotic pathways change as a result of infection with several corona viruses (CoVs). For the same reason inflammation, stress and altered immunological responses, and altered pathways of coagulation may also be brought on by CoV infection. The balance between the genes that are up-and down-regulated may be the key to understanding how these viruses induce disease. Unquestionably by putting part of viral proteins in the nucleus of the host cell, Corona Virus (CoV) may be able to regulate the cell machinery during the cytoplasmic replication of its genome in a microenvironment protected by a membrane. Both cap-dependent and cap-independent processes are used by CoVs to start the translation (Isakbaeva et al. 2004). When a negative strand of sub-genomic mRNA is extended during CoV transcription, discontinuous RNA synthesis (template switching) takes place. The RNA chaperone activity of CoV proteins may aid in the initiation of template switching. Proteins from both cells and viruses are needed for transcription and replication (Isakbaeva et al. 2004).

A better understanding of the biochemical pathway of virus transmission, replication and possible outcomes of viral infection, have been described by the most recent virus outbreak in the world i.e., Corona Virus transmission. The coronavirus (CoV) causes significant morphological and metabolic alterations in infected cells. Virus enters a host cell by attaching to its receptors present on the surface of cell, and made some conformational changes in the vial protein. Non-enveloped viruses enter through penetration and enveloped virus enter by fusing with cell membrane or by endocytosis. This process is completed by injecting viral DNA into the host cell. Once DNA is in the host cell it will start multiplying. In the same way recognition of the 5’ and 3’ ends of the RNA genome by cellular and viral proteins may be necessary for CoV transcription and replication. Like positive-strand RNA viruses, in CoV genome replication is also carried out by the production of negative-strand RNA, it serves as a template for the production of new viral genomes (Isakbaeva et al. 2004). According to mapping experiments using MHV (Major Histocompatibility Virus) defective-interfering (DI) RNAs, replication of DI RNA requires 470 nucleotides from the 5’ end and 436 nucleotides from the 3’ end. Additionally, positive-strand synthesis requires both ends of the genome, whereas the synthesis of the negative-strand needs the final fifty-five nucleotides from the 3’ end and the poly(A) tail. Hence, the replication signal at the 3’ end of the genome interacts with replication signals at the 5’ end to exert the influence on the synthesis of RNA since it is the final area of the genome that the viral polymerase reaches during the synthesis of positive-strand RNA. This knowledge has led to the hypothesis that during RNA replication, the genome's 5’ and 3’ ends interact (Wiersinga and Rhodes 2020). Normally when viral proteins replication process in a host cell is completed, it releases its newly synthesized molecules called

virions to start infection in extracellular adjacent cells and slowly whole host body is infected and when most of the host's body cells get infected it starts showing symptoms through which one can try to identify the cause of illness (Wiersinga and Rhodes 2020). Fig. 1 shows the bat viral symphony and the replication in flight.

12. CROSS-SPECIES TRANSMISSION OF BAT PATHOGEN

Cross-species transmission, also known as interspecific transmission, host jump, or spillover the spread of a transmissible pathogens, such as by means of a virus, across masses that belong to different species.

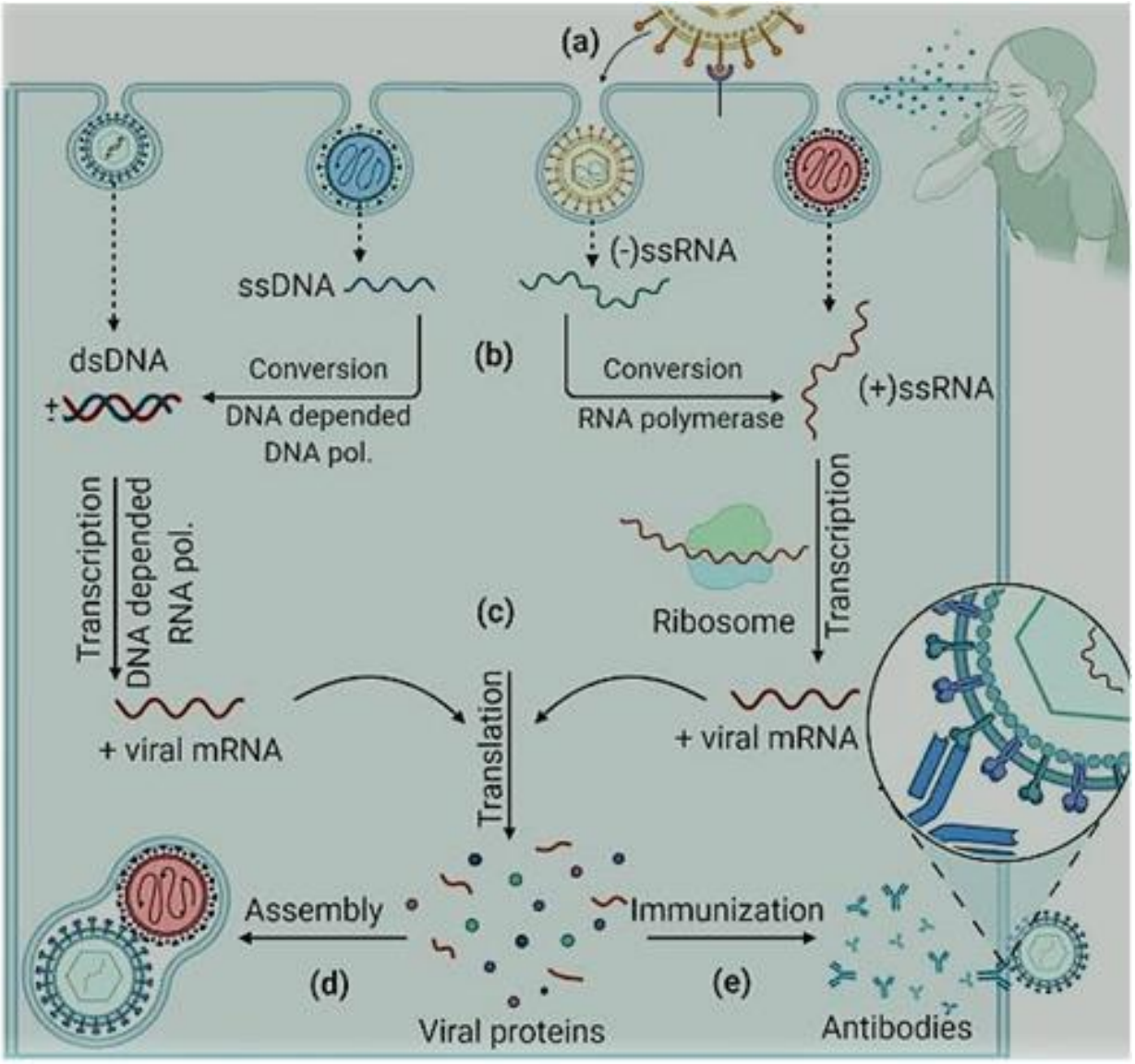

Fig. 1: Bat Viral Symphony: Replication in Flight

In fact, the bacterium may get indisposed in the new host once it has been introduced, or it may develop the capability to infect people of the same kind, permitting it to proliferate throughout the new

population. Although the peculiarities are typically focused on virology, cross-species spread can occur with bacteria or other types of viruses. Contact between the bacterium and the congregation and the operative infection of an underlying specific host, which may result in augmentation, are steps involved in transferring microorganisms to new multitudes equally. Contact between the bacteria and the host, as well as the primary infection of an underlying specific host, which may result in replication, are both processes in transferring microorganisms to other populations (Faria et al. 2013).

Clearly though stages involved in the transmission of microbes to new hosts include direct interaction between the virus and the host, effective contamination of original specific host, which may cause development of an epidemic, as well as microbe's variation within the first or original host, that may give the capability for effectively dispersion among populations of the new host as well as microbial diversity within the initial or original host, which may allow for effective dissemination among subsequent host populations (Allocati et al. 2016).

Because of the similarity of the hosts' immunologic defenses, the degree of evolutionary link across classes influences the likelihood that a microbe will be disseminated among them. The bulk of human zoonotic transmissions, for example, come from numerous warm-blooded animals., although some distantly related forms of microbes, such as plant diseases, may not be capable of contaminating humans in any way. Other factors that influence spread rates include topographical proximity and intraspecies behavior. Hence the risk of viral overflow is expected to rise as land use expands due to environmental changes and topographical challenges (Brierley et al. 2016).

When a disease that is typically present in bats is spread to another species, such as humans or other animals, it is referred to as the cross-species spread of bat infections. Ebola virus, SARS-CoV-2, and Nipah virus are a few bat-borne viruses that have been spread to people. To stop epidemics in the future and safeguard the public's health, it is crucial to research and comprehend these kinds of transmissions. Bats can carry various viruses and infections, making them a natural host for such pathogens. When bats and other animals come into close contact, bats may spread infections to other species, including humans. This happens because of their proximity. As human populations expand and encroach on bat habitats, the likelihood of human-bat interactions increase, there are more opportunities for bats and people to come into contact, which can result in the spread of viruses carried by bats (Brook and Dobson 2015).

Indeed, intermediate host is one of the important means in spreading viruses other than direct contact. In rare instances, the pathogen could be able to directly infect people or other animals without the aid of a host in between. Once the pathogen has been transferred to a new host, it could be able to adapt and reproduce there, which could result in sickness or illness (Chan et al. 2013).

Usually when a pathogen is transferred to a new host, it can adapt and multiply there, causing disease. Researching and understanding infectious diseases is critical for stopping future epidemics and protecting public health. By understanding how viruses jump from animals to humans, scientists can identify potential hotspots and high-risk species, allowing for targeted surveillance and early detection of emerging diseases. Additionally, studying these transmissions can help in the development of vaccines and treatments to mitigate the impact of future outbreaks. (Brook and Dobson 2015).

13. ECOLOGICAL AND PHYSIOLOGICAL PERSPECTIVE ON BATS AS RESERVOIR OF VIRUS

The Bats (Chiroptera), serving as ingrained reservoir hosts of different types of virus species, including scores of eminent zoonosis, have undergone a dramatic transformation to accommodate an extensive variety of viruses as their hosts. On the other hand, this flying mammal suggests the confluent attributes which can be concept to be the end result of powerful restraints on natural choice imposed by means of the demands of powered flight, which include scaled-down body length, intensified metabolic rate and

antioxidant potential, improved lifespan, and a few atypical immunological capabilities as compared to different non-flying mammals (Brook and Dobson 2015).

Because, bat, the only mammal adept at flying, hold significant importance in viral spillovers due to their ability to fly long distances, allowing the transmission of infamous viruses and their divergent forms among humans and other animals. The elevated body temperature and metabolic rate alongside flight expedite the stimulation of the immune system of bats on the basis of a biological clock. Thus, ultimately the descriptive factor for the evolution of viral infections in bats without the production of overt clinical signs of illness could be flight. During the flying activity, the physiological temperature of the bat's body rises above 40°C, inducing a febrile body response that stimulates interferon production, helper T-cell mobilization, agitation, participation in cytotoxic activities, and other immune responses. When any virus challenges a bat, the 15-16 folds proportional increase in its metabolic rate during flight may augment a fundamental price of soaring metabolic rate in order to activate an immune response (Calisher et al. 2006). Due to these recurrent properties, increased body temperature, and metabolism corroborate viruses to survive and resist the innate immune response inside the bat's body. Table 1 highlights the body temperature of various bat species during flight.

Table 1: Body temperature of various bat species during flight

Bat species	Body temperature during flight(°C)
Miniopterus sp.	41.1 ± 0.45
Myotis yumanensis	40.0-40.8
Carollia perspicillata	40.2 ± 0.8
Hypsignathus monstrosus	37.2-40.0
Eptesicus fuscus	41.3 ± 2.1
Mops condylurus	40.5 ± 1.1

Interestingly, Bats produce echolocation by sending forth high-frequency sound pulses and listening to the resulting echo. An aftermath of this echolocation activity is the diffusion of saliva, mucus, or oropharyngeal fluids in the environment, allowing the dispersion of viruses that replicate in the buccal cavity or airways of other vertebrates and mammals. Also, Hibernation is a period of extended deep sleep or dormancy that allows bats to survive the cold winter with less energy and food. So, Bats lower their body temperature and metabolic rate during hibernation from November to mid-May but may wake up briefly for foraging. Resultantly, this perspective leads to molecular co-adaptations in viruses, favoring the co-existence of viruses in their Bat hosts for a very long duration. As far as Bats habitats are concerned, roosts are sites for mating, hibernating, and rearing young; they promote social interactions and offer protection from adverse weather and predators. Living in closer proximity plays a significant role in increasing viral diversification. The co-roosting grounds may encompass the Bat species that don't usually come in physical contact with each other outside the roosts, encouraging the dissemination and sustenance of different viruses in different species and making possible the host-virus shift (Field et al. 2004).

Most importantly an anthropogenic environment of Bats refers to the human-modified habitats and landscapes that Bats encounter and use. These factors influence bat distribution, abundance, diversity, and physiology. Usually Bats live in a densely population manner, making it easy for viruses to spill over into other mammals. The mostly documented lifetime of bats is nearly three and a half folds longer than any non-flying placental mammal with a homogenous body size. For this reason, the longer life span of Bats and the possibility of developing persistent viral infections without showing overt signs helps the maintenance and transmission of viruses in other vertebrates. Meanwhile the intense oxidative stress at the mitochondrial respiratory chain level produced during flight and high-

performance DNA repair helps the Chiroptera to evade viral infections effectively (Calisher et al. 2006). Fig. 2 shows the flight-Induced oxidative stress and robust DNA repair which are the key to Chiroptera's viral resilience.

As a rule, the Bat's immune system tolerates viral invasion for several months without developing clinical signs. Species of Bats showing longer periods of immunity have more chances of being seropositive to viruses. While the evolution of flight in Bats produces a unique set of antiviral immune responses, controlling the virus propagation and limiting reckless inflammatory responses in its body. On the whole, an antiviral immune pathway known as the "STING-interferon pathway" is waived off in the bat's body, maintaining enough immunity against viral infections without triggering a heightened immune response (O'Shea et al. 2014).

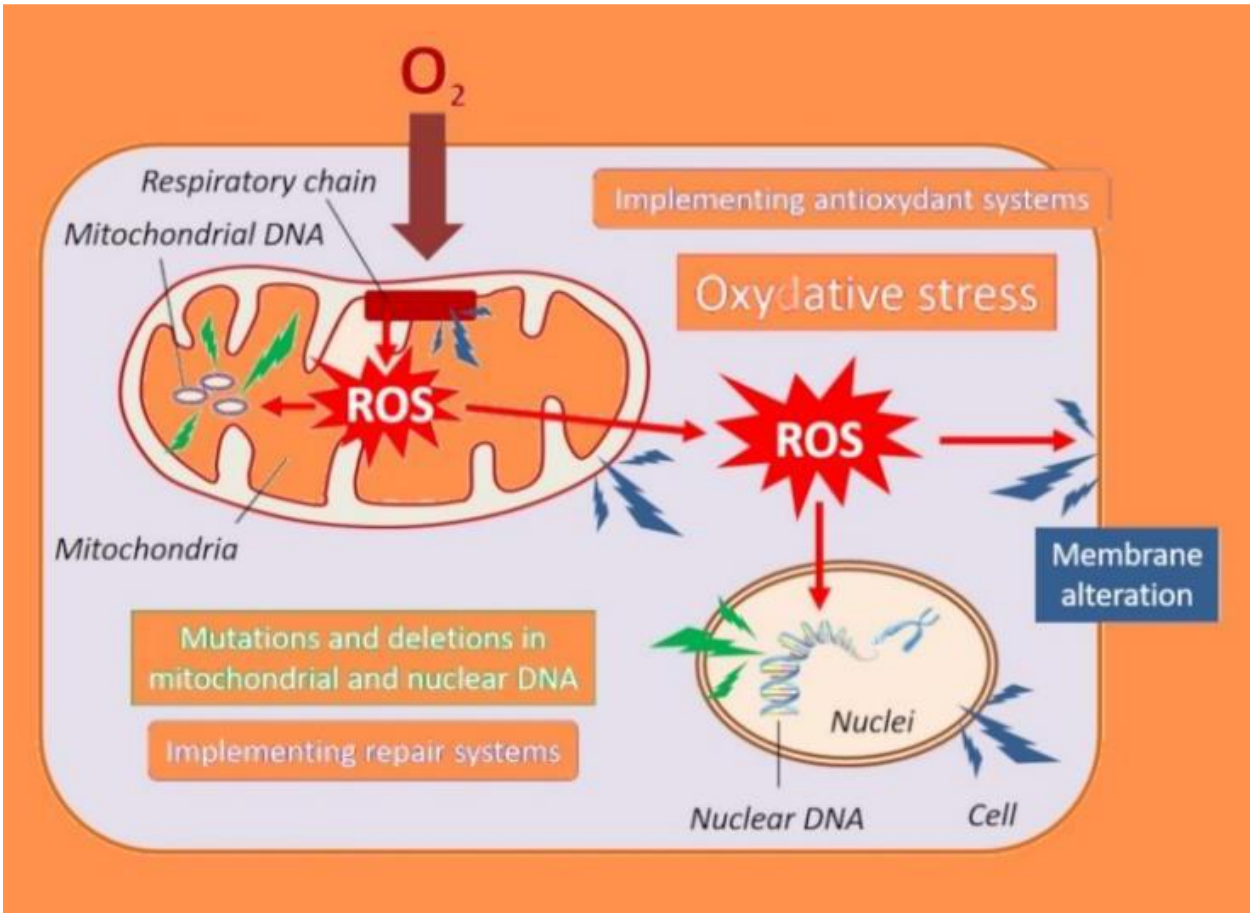

Fig. 2: Flight-Induced Oxidative Stress and Robust DNA Repair: The Key to Chiroptera's Viral Resilience

14. CONCLUSION

Bats are likely progenitors of the majority of zoonotic organisms. This is the result of their extraordinary physiology, behavior, and close relationship with humans and various creatures. As, bats are notorious vectors of zoonotic diseases that carry pandemics such as SARS, MERS, and the novel coronavirus. These pandemics have changed the global pattern of disease spread. Meanwhile the use of bat meat and the use of bat guano as excrement (feces) have also been implicated in the transmission of these infections.

Provided that, every possible precaution should be taken to prevent the transmission of these contaminations to humans and animals. Furthermore, it is also very important to take measures to prevent the spread of these infections to both humans and other organisms.

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Pathogenesis of Lyssa Virus

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ABSTRACT

Lyssa viruses, belonging to the family Rhabdoviridae, are notorious for causing rabies, a fatal zoonotic disease affecting various mammalian species, including humans. This review delves into the taxonomy, evolutionary relationships, and phylogenetic analysis of lyssa viruses, emphasizing the importance of accurate classification for effective disease management. The lyssa virus genus, within the Rhabdoviridae family, consists of species and genotypes designated by the International Committee on Taxonomy of Viruses (ICTV). Notable strains include Rabies lyssa virus (RABV), Lagos Bat lyssa virus (LBV), Mokola Virus (MOKV), Duvenhage Virus (DUVV), and European Bat Lyssa viruses (EBLV). Geographic distribution patterns reveal variations in prevalence across continents, with Africa hosting a multitude of lyssa virus species. Factors influencing distribution include bat species diversity, human-animal interactions, and vaccination coverage. Prevalence challenges arise from inadequate vaccination, limited post-exposure prophylaxis access, and socio-economic factors. The lyssa virus transmission routes encompass bites, licking, and even airborne infections, posing risks to both animals and humans. The pathogenesis unfolds through primary replication in local tissues, dissemination to the central nervous system, and neuroinvasion. Distinct clinical manifestations, including furious and paralytic rabies, result from the virus's spread within the central nervous system, causing varied neurological symptoms. The immune response involves both innate and adaptive components, with the lyssa virus employing immune evasion strategies, such as inhibiting the NF-kB pathway and interfering with type I interferon signaling. Diagnostic methods include serological assays, RT-qPCR, and histopathological examination. Prevention strategies focus on animal management and vaccination. Post-exposure prophylaxis, wound cleaning, and active vaccination with vaccines like Human Diploid Cell Rabies Vaccine (HDCV) are essential for treating potential lyssa virus exposure.

Keywords: Lyssa viruses, Rabies, Taxonomy, Geographic distribution, Immune response

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1. INTRODUCTION

Lyssa virus is basically a genus of the Rhabdoviridae family. Having single-stranded negative sense RNA, this virus infects mammals and provokes viral encephalomyelitis, which is commonly known as Rabies (Rudd and Davis 2016). The shape of the lyssa virus is like a bullet shape, and its size varies from 100 to 300nm (Lawaski et al. 2004). Mostly, the lyssa virus has five viral proteins: nucleoproteins are the first one, then polymerase, glycoprotein, matrix protein and phosphor protein. This virus has five serotypes:serotype 1, rabies; Lagos bat virus indicates serotype 2; Macula represents serotype 3, serotype four had been seen in Duvenhage and last serotype 5 found in the European bat Lassa virus (Bourhy et al. 1998). Being obligatory parasites, lyssa virus accomplished their life by controlling the biosynthetic machinery of the host cell (Rupprecht et al. 2011). The virion of lyssa virus consists of a central rib nucleoprotein complex (RNP), tightly coiled and with helical symmetry. RNP consists of a ribonucleic acid (RNA) genome. It is consisting of approximately 12,000 nucleotides, single-stranded, negative polarity that is closely associated with multiple copies of nucleoprotein (N protein) and polymerase (L protein) and its cofactor, phosphoprotein (P protein). A bullet-shaped lipoprotein envelope, derived from the host cell, surrounds the RNP during budding, and inside this envelope are many button tips, each of which is a glycoprotein (G protein) trimmer. The fifth viral protein, matrix protein (M protein), lies between the envelope and RNP. This can be built into the inner layer envelope, in the central axis of the RNP, or both as mentioned in the Fig. 1 (McColl et al. 2000).

Lyssa viruses, members of the family Rhabdoviridae, encompass a group of viruses known for their ability to cause rabies, a fatal zoonotic disease affecting numerous mammalian species, including humans, which remains a significant global public health concern. Accurate taxonomy and classification of lyssa viruses play a pivotal role in effective disease management and control. According to (Smith et al. 2019), understanding the taxonomic relationships within the Lyssa virus genus is crucial for studying the genetic diversity and evolutionary history of these viruses.

2. LYSSA VIRUS TAXONOMY

2.1. FAMILY RHABDOVIRIDAE

The lyssa viruses belong to the family Rhabdoviridae, which encompasses a diverse group of enveloped, single-stranded RNA viruses (Bourhyet al. 2005). The classification of lyssa viruses within this family is based on their structural and genetic characteristics, as highlighted by (Johnson et al. 2011).

2.3. GENUS LYSSA VIRUS

Within the family Rhabdoviridae, the genus Lyssa virus is comprised of viruses that primarily infect mammals, causing rabies. The classification of lyssa viruses into the genus was proposed by based on their shared antigenic properties and pathogenicity (Dietzscholdet al. 2003).

2.4. SPECIES AND GENOTYPES:

Lyssa viruses are categorized into different species and genotypes based on genetic and antigenic characteristics. The International Committee on Taxonomy of Viruses (*ICTV*) has designated several

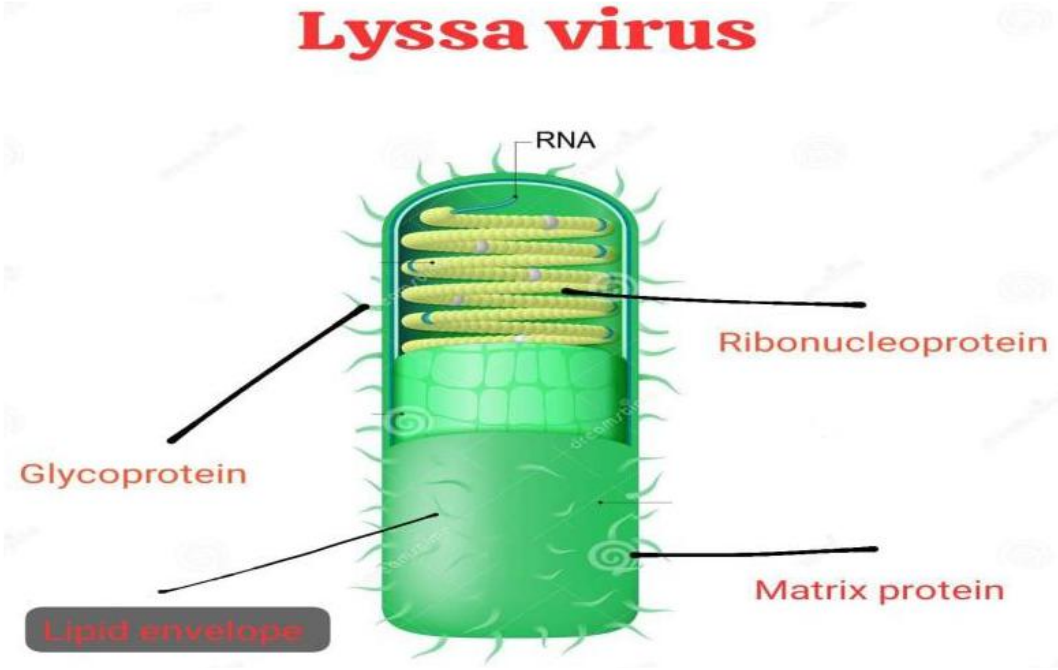

Fig. 1: Morphology of Lyssa virus

lyssa virus species and genotypes.Examples include the Rabies lyssa virus (RABV) species, which encompasses multiple genotypes such as the classical RABV, (Banyard 2017), and the Lagos bat lyssa virus (LBV) species (Markotteret al.2006).

2.5. EVOLUTIONARY RELATIONSHIPS AND PHYLOGENETIC ANALYSIS

2.5.1. MOLECULAR TECHNIQUES IN LYSSA VIRUS CLASSIFICATION

Advancements in molecular techniques have significantly contributed to the understandingof lyssa virus taxonomy. Molecular analyses, including whole-genome sequencing and phylogenetic reconstruction, have provided insights into the evolutionary relationships among lyssa viruses (Badraneet al. 2011).

2.6. PHYLOGENETIC STUDIES AND CLADE ANALYSIS:

Phylogenetic studies based on viral genomic sequences have helped elucidate the evolutionary relationships among lyssa viruses conducted a comprehensive phylogenetic analysis of lyssa viruses, identifying distinct clades and their relationships with different host species (Banyard et al. 2013).

3. TYPES AND STRAINS

Understanding the different types and strains of lyssa viruses is crucial for effectiveprevention, control, and management of associated diseases.

3.1. RABIES LYSSA VIRUS (RABV)

Rabies lyssa virus (RABV), the type species within the genus Lyssa virus, has a globaldistribution and various identified strains, including classical rabies virus (RABV). RABV is responsible for the majority of

human rabies cases worldwide, with transmission primarily occurring through the bite of infected animals, especially dogs and wildlife (Hemachudhaet al. 2002).

3.2. OTHER LYSSA VIRUS TYPES AND STRAINS

3.2.1. LAGOS BAT VIRUS (LBV)

Lagos Bat Virus (LBV) is associated with bats in Africa and has potential zoonotic implications. LBV was separated from multiple species of bat, including bats along with fruit straw-like color (*Eidolon helvum*) and the water mongoose (*Atilaxpaludinosus*), and has been linked to spread of rabies in humans, highlighting its importance in the region's public health (Markotteret al. 2006).

3.3. MOKOLA VIRUS (MOKV)

Mokola Virus (MOKV) is another lyssa virus found in Africa, primarily associated with bats. MOKV has been detected in both insectivorous and frugivorous bats, including the African straw-colored fruit bat and the banana pipistrelle bat. Although it has a more limited geographic distribution compared to RABV, it poses a significant risk to human and animal health in affected regions (Marston et al. 2012).

3.4. DUVENHAGE VIRUS (DUVV)

Duvenhage Virus (DUVV) is prevalent in insectivorous bats in Africa and is associated with human cases of rabies. DUVV was separated from multiple species of bat, containing the Egyptian slit-faced bat (Nycteristhebaica) and the Rufous mouse-eared bat (*Myotisbocagii*), and has been implicated in sporadic cases of rabies in humans, underscoring the need for surveillance and monitoring of this lyssa virus (Johnson et al. 2006).

3.5. EUROPEAN BAT LYSSA VIRUSES (EBLV)

European Bat Lyssa viruses (EBLV) consist of different strains found in bat species in Europe, posing potential risks to humans (Fooks et al. 2003). EBLV-1 and EBLV-2 are the two primary strains identified, with EBLV-1 related to serotine bats (*Eptesicusserotinus*) and EBLV-2 related to Daubenton's bats *(Myotisdaubentonii*) (Picard-Meyeret al. 2011). These strains have been responsible for a number of bat-associated rabies cases in Europe.

3.6. GEOGRAPHIC DISTRIBUTION AND HOST RANGE

3.6.1. LYSSA VIRUS DISTRIBUTION PATTERNS

Lyssa viruses exhibit varying geographic distribution patterns, which impact their prevalence and occurrence in different regions. This section explores the global distribution of lyssa viruses and associated factors. Streickeret al. (2013) conducted a study on the global distribution of bat-associated lyssa viruses, revealing regional differences in lyssa virus diversity and prevalence.

3.7. GLOBAL DISTRIBUTION OF LYSSA VIRUSES

Lyssa viruses have a worldwide distribution, with varying prevalence across continents,countries, and regions. Africa, known for its high prevalence of lyssa viruses, hosts several species, including Rabies

lyssa virus (RABV), Lagos Bat Virus (LBV), Mokola Virus (MOKV), and Duvenhage Virus (DUVV) (Marston et al.2012). In Asia, Rabies lyssa virus is the most common and widespread, with countries like India, Thailand, and China reporting a high number of human cases annually (Hu et al. 2013). Europe is of concern due to the presence of European Bat Lyssa viruses (EBLV) (McElhinneyet al. 2013), while North and South America have a significant burden of rabies cases, primarily transmitted by wildlife species (Freire de Carvalhoet al.2017).

3.8. FACTORS INFLUENCING DISTRIBUTION

Various factors influence the distribution of lyssa viruses. Bats, particularly insectivorous species, serve as important reservoirs for lyssa viruses, contributing to their prevalence in different regions (McElhinneyet al. 2013). Factors such as bat species diversity, human-animal interactions, and vaccination coverage can impact the transmission dynamics and regional prevalence of lyssa viruses (Hu et al.2013).

3.9. PREVALENCE AND CHALLENGES

The prevalence of lyssa viruses varies within regions due to local ecology, population density of reservoir hosts, and control measures implemented. Inadequate vaccination coverage, limited access to post-exposure prophylaxis, and inadequate surveillance systems contribute to the persistence of lyssa virus transmission. Socioeconomic factors, cultural practices and wildlife trade also play a role in the prevalence and challenges associated with lyssa viruses (Freire de Carvalhoet al. 2017).

3.10. TRANSMISSION OF LYSSA VIRUS

The biting of a rabid animal can transmit rabies and also by licking the rabid animal because saliva may also contain the lyssa virus. Corneal transmission from man to man is also seen. In modern days air born infection is also prevailing. In non-bitingtransmission category, the virus can be transmitted between laboratories workers. Rabies can also be transmitted by abrasion or open wounds that are exposed to the saliva or potentially hazardous material of a rabid animal (Dutta et al. 1992).

3.11. VIRAL REPLICATION:

3.11.1. THE REPLICATIVE CYCLE OF LYSSA VIRUS

The replication of the lyssa virus is just similar to that of other negative-stranded RNA viruses.

3.11.2. ATTACHMENT AND ENTRY INTO HOST CELL

The lyssa virus attaches to the host cell membrane via the G protein through the phenomenon of adsorption. After that, the lyssa virus creeps into the cytoplasm either by pinocytosis or fusion mechanism.

3.11.3. UNCOATING AND RELEASE OF VIRAL GENETIC MATERIAL

Uncoiling occurs within the cytoplasm, and genetic material is released, whereas the outer portion of the virus remains outside. After uncoating, the viral genome takes control of the host cell.

3.11.4. VIRAL GENOME REPLICATION

The core initiates the primary transcription of the five complementary monocistronic mRNAs by using virion RNA-dependent RNA polymerase. Each RNA is then translated to an individual protein.

3.11.5. EXPRESSION OF VIRAL PROTEINS

After viral proteins have been synthesized, replication of the genomic RNA continues with the synthesis of full-length, positive stranded RNA, which acts as a template for the production of progeny negative-stranded RNA.

3.11.6. ASSEMBLY AND MATURATION OF NEW VIRAL PARTICLES

After Renovo synthesis of viral genome and proteins, which can be post transcriptionally modified, viral proteins are packaged with newly synthesized viral genome into new visions that are ready to release from host cell. This process cans also refer to as maturation (Marston et al. 2018). All the steps have been shown in Fig. 2.

4. PATHOGENESIS OF LYSSA VIRUS IN THE HOST

4.1. PRIMARY REPLICATION IN LOCAL TISSUES

The virus first spreads from the bite site to the striated muscle spindle receptor of the wound, where it builds up and reproduces before spreading to the adjacent peripheral neurons. Peripheral nerve invasion typically occurs to three days after a local wound, while others believe the virus may remain at the invasion site for up to 2 weeks (Kuzmin and Tordo2012).

4.2. DISSEMINATION TO THE CENTRAL NERVOUS SYSTEM

At a rate of roughly 3 mm/h, the virus disseminates centripetally along the axonal plasma of the peripheral nerve. The virus multiplies after it enters the dorsal root ganglion before spreading to the spinal cord and the rest of the central nervous system, mainly infecting neurons in the brain and cerebellum (Murphy 1977)

4.3. NEURO INVASION AND SPREAD WITHIN CNS

The virus uses the endosomal transport system (endocytosis) to connect to surface cellular receptors and begin infection. The uncoating of virus particles and the release of helical RNP into the cytosol are caused by the low pH of the endosome, which also causes a process of membrane fusion. The P-L complex transcribes the viral genome in the following phase, resulting in the production of five positive-strand monocistronic mRNAs, followed by the translation of five viral proteins. Positive-strand replicative RNA (anti-genome), which serves as a template for creating a negative strand RNA genome, is created when the RNA polymerase activity shifts from transcription to replication. In order to create RNP, the produced viral RNA is subsequently packed with the N-P complex, and L. Then M joins the RNP complex to condense (Baloul and Lafon 2003). All the steps of pathogenesis are shown in the Fig. 3.

4.4. PATHOLOGICAL CHANGES IN THE BRAIN AND NERVOUS SYSTEM

Numerous variables, many of which are yet unknown, influence the clinical signs of rabies, which can take many different forms. However, the presentation of various clinical signs varies depending on

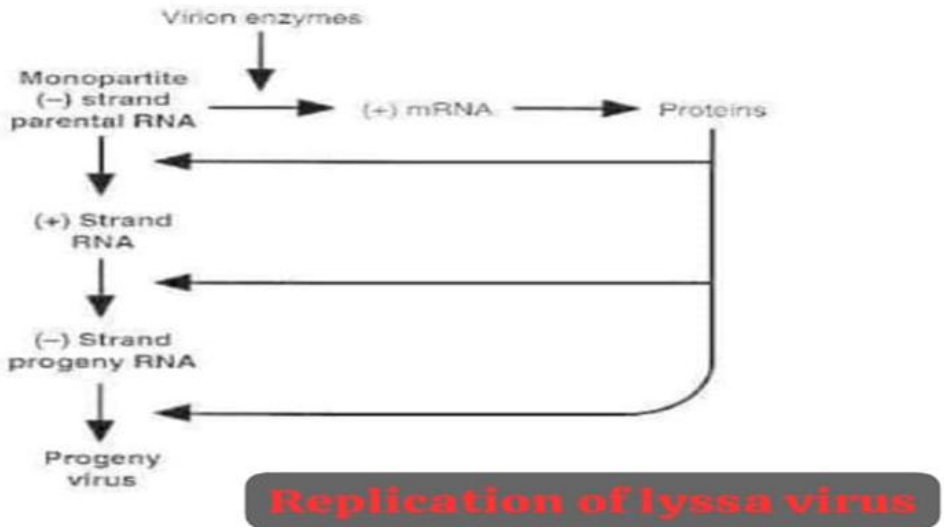

Fig. 2: Replication of lyssa virus

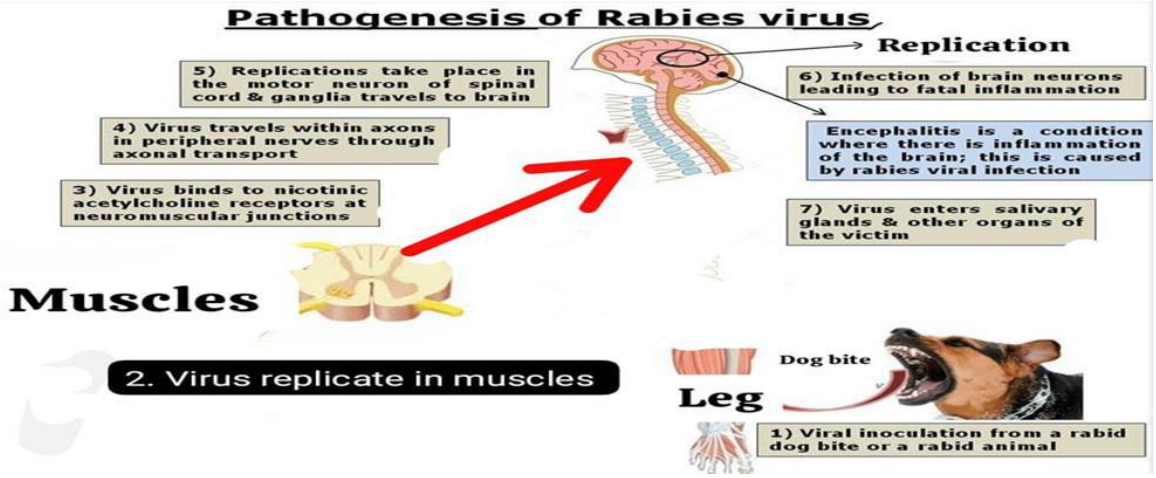

Fig. 3: Pathogenesis of lyssa virus.

depending on the lyssa virus species or RABV strain. For instance, dog strains of the RABV more typically exhibit classic hydrophobia and aerophobia, while bat strains more frequently exhibit tremors and involuntary jerking/twitching (myoclonus). Additionally, compared to dog rabies exposures, exposure to bat rabies was more likely to present with symptoms that were localized to the wound. Encephalitic (or classical or angry) and paralytic rabies, also called dump rabies, are the two types of rabies that can occur. In around80 % of patients encephalitic form of rabies is effective; of these, between 50 and 80% along with the typical signs of rabies, such as water phobia and fear of air. The remaining indications are specific like encephalitic illnesses, particularly in people of Africa, where dominant conditions like cerebral malaria can lead to rabies misdiagnosis. Unlike paralytic rabies, which is pronounced in the early days of illness, muscle weakness can be seen in the second form, encephalitic rabies often leads to severe coma, paralysis, and death, which may occur cause many organs get failed to work properly. Initially, it was believed that the symptoms of rabies were

brought on by widespread neuronal cell death; however, neuronal apoptosis is only induced by infections with strains with low pathogenicity. Instead, dysfunctional neuronal cells are assumed to be the cause of symptoms, which is in part brought on by increased NO synthesis by inducible nitric oxide synthase (NOS) in neurons and macrophages. Axonal swelling also occurs due to malfunctioning of mitochondria. This pathology is linked to the symptoms appearing, and it explains the symptoms of encephalitis (Hicks et al. 2013).

4.5. IMMUNE RESPONSE

4.5.1. INNATE IMMUNE RESPONSE

NF-kB transcription factors are involved in many cellular responses. Viral infections activate NF-κB that expresses antiviral cytokines. One of the members of NF-κB family named RelAp43 that expresses the genes involved in innate immune response. RelAp43 induces the expression of HIAP1, IRF1, and IFN-β. RelAp43 is also seen to be targeted by the matrix protein of lyssa virus (but not vaccine strains), which inhibits the NF-kB pathway, resulting a virulence factor (Luco et al. 2012).

To study the innate immune response within the brain to the lyssa virus, the mouse was subjected to infection. Transcript levels associated with innate response includingSTAT1, including IFN-c, tumors necrosis factor alpha, interleukin 6(IL-6), IL-1b, T-cell growth factor b and Toll-like receptors (TLRs), and the antiviral protein Mx1 were seen increased in the brains of mice (Koraka et al. 2018).

Type 1 IFNs were selected as the critical role in the development of the antiviral state chosen selected as a marker for the inflammatory response to viral infection in the CNSand Mx1 was selected as an IFN-inducible transcript with known antiviral properties for negative-strand RNA virus. Mice being inoculated were sacrificed, and their brains were removed to study disease. Transcripts of lyssa virus and host were analyzed by end-point PCR and quantitative PCR, respectively (Johnson et al. 2006). Amplifications were performed by a thermal cycler using an annealing temperature of 50 degree calcius(Johnson et al. 2006). It was observed that laboratory-adaptive viruses exhibit intensive inflammation and necrosis. Studies showed that the B2C variant stimulates gene expression of innate immunity (Wang et al. 2005).

5. ADAPTIVE IMMUNE RESPONSE

Investigations show that current rabies vaccines provide immunity against the lyssa virus classified within phyllogroup I. However, it does not give any Protection against phyllogroup II or any other variant. All these rabies vaccines comprise inactivated preparations of live attenuated classical rabies virus strains (Evans et al. 2012).

BALB/c mice were infected with lyssa virus through a peripheral route to study the responsiveness of T-cells (RTC). Two types of virus could be classified after the progression of infection.

1) Pathogenic virus
2) Non-pathogenic virus

The studies revealed that infection with pathogenic lyssa virus resulted in loss of RTC in subjected mice after antigen activation but not after polyclonal activation (Perrin et al. 1996).

5.1. CONTROL OF INFECTION BY ADAPTIVE IMMUNE RESPONSE

According to a study, mice infected with lyssaviruswere subjected to anti-lyssa virus human monoclonal antibody (mAb), F11, to demonstrate the efficacy of immunotherapy in subjected mice. The studies

revealed that even a single dose of F11 therapy can stimulate an adaptive response (T-cell dependent) that is highly effective against established CNS infection caused by virus(Huaman et al. 2022).

5.2. IMMUNE EVASION STRATEGIES EMPLOYED BY LYSSAVIRUS

Type I interferon are expressed as a host response to viral infection in humans, activating intracellular signaling (Wiltzer et al. 2012). Lyssa virus P protein plays an important role in the replication of the virus and immune evasion, which act as an antagonist of IFN 1 that targets signal transducers and activators of transcription (STATs). Phosphorylation of the C-terminal of tyrosine and cytokines activates STATs, which leads to the formation of hetero dimmers which accumulate within the nucleus. P protein directly binds to STAT 1 interacting C-terminal domain, hence binding strongly with tyrosine phosphorylated STAT hetero dimmers inhibiting the accumulation in the nucleus thus, affecting cytoplasm localization of complex. This inhibition mechanism appears to be critical in pathogenic RABV infection and progression. However, this detailed mechanism of inhibition of IFN production and pathogenicity of thelyssa virus cannot be completely understood (Harrison et al. 2020).

5.3. CLINICAL MANIFESTATIONS OF LYSSA VIRUS

These include headache, fatigue and fever. Then progresses to paralysis, convulsions and death within 1 to 2 weeks. Symptoms start from a few days to several years after contact with virus. In 1996, a 39-year-old female carried weakness of one arm followed by nervous symptoms, bulbar palsy and death within twenty-one days (kazachinskaia et al. 2022). In 1998, a female developed nervous illness, to which she ultimately succumbs. In 2018 a boy developed fever, anorexia, abdominal pain, distress, abnormal and aggressive behavior followed muscle spasms.

5.4. INCUBATION PERIOD AND INITIAL SYMPTOMS

According to WHO, the incubation period of lyssa virus is about 2 to 3 months but may vary from 1 week to 1 year depending upon the site of virus entry and viral load Initial symptoms like fever, pain, unexplained tingling, prickling and burning sensations (Poleshchuket al. 2023).

5.5. PROGRESSIVE NEUROLOGICAL SYMPTOMS OF LYSSA VIRUS

According to Charles E. Rupprecht, Neurological signs include nervousness, anorexia, irritability, ataxia, hyper excitability etc. There are two forms of rabies:

5.5.1. FURIOUS RABIES

Results in excited behavior, hydrophobia, aerophobia, ataxia, hyperactivity, etc. Death occurs in a few days because of cardio respiratory arrest (MSD Manual)

5.5.2. PARALYTIC RABIES

Presents about 20% in humans. This is less dramatic and usually longer than furious. Muscle becomes paralyzed. A coma develops, and death occurs (Hemachudha et al. 2005).

5.6. DIVERSE CLINICAL PRESENTATIONS IN DIFFERENT HOSTS

Bats are recognized as reservoir hosts which cross barriers to infect humans and other mammals. Bats are found everywhere in the world except Antarctica.New lyssa virus genome from the Lesser Mouse-eared bat (*Myotisblythi*), Kyrgyzstan They are emerging infectious Diseases. When bats are kept at low temperature, a virus with high titer is obtained associated with lyssa virus. Incarnivores' immune response is delayed until the centrifugal phase due to lymphocytic infiltration in infected tissues. Due to this, lymphocytic encephalitis is reported (Begeman et al. 1985).

5.7. DIAGNOSIS AND LABORATORY TECHNIQUES FOR LYSSA VIRUS

In rabies, lyssa virus diagnosis cannot be made during the incubation phase. As this is very common disease, now, physicians, doctors and patients less apart to diagnosis with laboratory techniques. The useful behavior of physicians for diagnosis is based on clinical signs and symptoms. After the appearance of clinical signs, mortality is 100%. The most challenging clinical signs are high protein concentration, abnormal cerebrospinal fluid, normal glucose level, and high T2 signaling (Dacheux et al. 2016).

5.8. SEROLOGICAL ASSAYS

5.8.1. DIRECT FLUORESCENT ANTIBODY TEST (DFAT)

This is a gold standard antibody test, highly sensitive and specific. For confirmation, a mouse inoculation test is performed. In this technique, the sample is collected from brain cells, i.e., cerebellum, brain stem cells and cortex sometime, skin biopsy is done. Take a slide and air dry it for 15-30 min at room temperature. Prepare positive control slides of rabies affected animal and negative control slides of the healthy animal. At the same time, prepare test slides as well. Hold it for 2 min; now, fix it with chilled acetone at -20°c for 30 min. Air dry it and incubate at 37°c for 30 minutes.Immerse the slide in PBS and air dry. Add mounting media as Fluoresce in isothiocyanate. Place the cover slip and observe under the fluorescent microscope at 400X. Lyssa virus antigen appears as fluorescent apple green intra cytoplasm inclusions for positive slides (European Union Reference Laboratory for Rabies 2021).

5.9. MOLECULAR METHODS FOR VIRUS DETECTION

5.9.1. RT-qPCR

To improve relevant specificity and sensitivity, a highly modified technique is real time reverse transcription PCR for Lyssa virus detection. The protocol is based on two types of reaction: (1) first reaction is probe based (TaqMan) real time reverse transcription PCR for rabies species as (Pan-RABRT-qPCR). (2) Second reaction uses a dye (SYBR GREEN) for other lyssa virus species (Pan-lyssa RT-qPCR).The collection sites for this test are brain tissues, saliva or CSF. In humans, lyssa virus detection (rabies), the best site is saliva as brain tissues or nerve cells sloughed off in CSF, which may give false positive PCR results. This method is more specific and less expensive than DFAT. (Biswal et al. 2007).

5.10. HISTOPATHOLOGICAL EXAMINATION OF LYSSA VIRUS

For immune histochemistry, sample is taken from hippocampus, mid-brain, thalamus etc. Tissues are first deparaffinised, fixed with 3% hydrogen peroxide, washed with water and exposed to buffer solution for 10

min and block solution for 7 min. Incubate for 30 min at 37°C. Stain the slide with Mayer's hematoxylin and cover it with cover slip for observation. The test sample contains intracytoplasmic inclusions as Negribodies' labelled, oval homogenous structure (Hooper et al. 1999).

5.11. PREVENTION & TREATMENT

Management and caring for animal is the central stone of any modern program for the prevention and control of rabies. However, with proportionally few exceptional cases, separating alone has not led to productive control of rabies (Nigg and Walker 2009).

5.12. CAN RABIES BE ELIMINATED?

Rabies, acute continuous encephalitis, is a former zoonosis. Society must recollect that despite the current identification of other important emerging infectious diseases, none surpass the case fatality rate of rabies. Given the clear significance of rabies in public health, agriculture and conservational biology, considerable international development must pursue amplified public consciousness, human rabies prevention, wildlife rabies control, and canine rabies cancellation with refreshed, concerted vigor (MacInnes et al. 2001).

5.13. PREVENTION IN MAN

Man is infected by the bite of a domestic rabid animal which put on him, or of violent wild animals (including bats) which inexcusably attack him. So, rabies in man can be prevented by keeping themselves safe from rabid animals by seeing the clinical signs of animals. Bats should be avoided from coming into the homes (Plotkin and Clark 1971).

5.14. TREATMENT

Rabies is the identically lethal viral encephalitis that causes 30,000 to 70,000 deaths worldwide per year.

5.15. PRE-EXPOSURE PROPHYLAXIS

Two more IM doses of vaccine must be given to the person having the possible rabies exposure; the preliminary dose should be administered straight away following the liability and the 2ndshould be administered three days later (Damanet et al. 2023).

5.16. POST-EXPOSURE TREATMENT

To reduce the chance of bacterial infection, the wound should be cleaned with water and soap considerably. A solution of Povidoneor ethyl alcohol 70% can also be used for this purpose to control the viral infection Behavioral abnormalities must be checked and noticed for at least ten days in the animal having the least risk of rabies. During these ten days observational period, at the first sign of rabies, treatment with RIG (Rabies Immune Globulins) and rabies vaccine should be done. 20IU/KG body weight is the dose criteria for RIG. Pain and soreness at the site of infection are some common side effects of the RIG. This RIG is used in passive vaccination.

5.16.1. ACTIVE VACCINATION

Almost two inactivated virus vaccines are available now.

1. Human diploid cell rabies vaccine (HDCV). Produced in human diploid cell culture.

Purified chick embryo cell vaccine (PCECV). Produced in chicken embryo cell culture (Jackson 2020).

5.17. CONCLUSION

The lyssa virus is one of the most prevailing fatal viruses spread by biting a rabid animal or human. So, public health departments should work with the government on local, national, and international level to eradicate this fatal condition. By understanding the transmission, pathogenesis of the Lyssa virus one can be able to make strategies to overcome its outbreaks, and treatments can be effective. By having enough knowledge about the pathogenesis of rabies from this chapter, research institute get huge benefits and can make remarkable achievements in devising the way for the permanent control and eradication of rabies. By having the proper knowledge of pathogenesis of the rabies, one can differentiate rabies from meningitis and encephalitis.The most prominent disease caused by the Lyssa virus is rabies, which is a neurological disease and thousands of deaths due to rabies are recorded per year. Louis Pasture was the first scientist to develop the vaccine against rabies. Simply by understanding the pathogenesis of rabies, we will be able to mitigate that havoc disease. With enough knowledge of the pathogenesis of lyssa fever, one can be able to know the chain of events that occurs during disease development and progression. By knowing the pathogenesis pattern veterinarian or researcher can find the perfect treatment and prophylaxis at the respective stage. Pathogenesis begins with the transmission, so by blocking the transmission routes and inhibiting or deactivating cell surface receptors (alpha - DG), the progressing of the rabid fever can be blocked.

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Emergence of CCHF Virus in Pakistan

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ABSTRACT

Crimean-Congo Hemorrhagic Fever (CCHF) is a zoonotic disease caused by a virus transmitted by ticks. In Pakistan, this illness has become a major concern due to various factors like changes in climate, tick population boom and transportation of carrier animals. CCHF outbreaks happen twice a year in Pakistan, mostly affecting areas that lack urbanization i.e., Baluchistan and Sindh. Pakistan is among the top countries with CCHF cases in Asia, and it has faced outbreaks since the 1960s.This disease presents significant challenges and widespread implications due to its potential to result in numerous fatalities and can be used as bioterrorism weapon. Challenges in controlling the disease include lack of awareness, poor hygiene standards, constrained diagnostic options and Inadequate disease monitoring and screening. Prevention of CCHF involves awareness among the people, use of protective gear, proper sanitation and monitoring of ticks regularly. Combining human, animal, and environmental health is crucial for stopping the disease. However, it's hard to coordinate everything, especially in places like Baluchistan where there aren't enough resources. To control CCHF from spreading enhanced inspection protocols, ticks control, and involvement of communities are important. This summary highlights the crucial necessity for joint endeavors focused on preventing, promptly detecting, and efficiently managing CCHF, ensuring the protection of public health and economic well-being.

Key words: zoonotic, amplifying host, ecchymosis, sporadic infections, surveillance.

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1. INTRODUCTION

The term CCHF stands for Crimean-Congo Hemorrhagic Fever. CCHF is found to be a tick-borne viral zoonotic disease caused by Crimean-Congo Hemorrhagic Fever Virus. It is said to be asymptomatic in domestic and wild animals and both of them act as reservoirs of the virus (Fanelli and Buonavoglia 2021). Every year, Eid-al-Adha (a significant Muslim Festival of Sacrifice), along with the Hajj, occurs in Mecca. In the last 10-15 years, Eid-al-Adha, which generally occurs in autumn-winter months, will shift to the summer months when the CCHF virus is more prevalent. So, a massive increase in the number of cases is reported (Leblebicioglu et al. 2015).

During World War II (1944-45), the first recognition of CCHF occurred among Soviet Union military personnel in the Crimea, leading to its initial designation as Crimean Hemorrhagic Fever. In 1969, it was discovered that the virus causing Crimean Hemorrhagic Fever was the same as the one responsible for a febrile illness in the Belgian Congo, which was known as the Congo virus. As a result, the two names were merged into one, giving rise to the current name of the virus: Crimean-Congo Hemorrhagic Fever Virus (Hussain et al. 2016).

CCHF virus is an RNA virus characterised by a single-stranded, negative-sense genome. Its genome is divided into three segments: small (S), medium (M), and large (L) (Papa et al. 2017). CCHF is caused by a virus known as CCHFV (Crimean-Congo Hemorrhagic Fever virus), which belongs to the Orthonairovirus genus within the Bunyaviridae family. The transmission of this virus occurs through various tick species belonging to the (Hyalomma) Ixodidae family. These ticks can remain attached to the primary host for a maximum of 26 days, and in the case of migratory birds, they may serve as potential carriers of the virus over long distances (De Liberato et al. 2018). The enzootic cycle of the CCHF virus relies on an intricate network involving ticks and host populations, suggesting that the disease may be more widespread than what we can see from the number of reported clinical cases (Vescio et al. 2012).

The amplifying hosts of CCHF are various mammal species that remain asymptomatic. Humans get infected by tick bites or by direct contact with animal blood and other body fluids (Fillâtre et al. 2019). CCHF poses a significant danger to humans as it is perpetuated within various tick species and can be transmitted to both wild and domestic animals in their natural habitats (Saijo 2018). Of significant concern for human exposure is the virus's ability to infect livestock without causing any apparent disease (Hawman and Feldmann 2023). Cases of nosocomial transmission are notable in highlighting the spread of the CCHF virus within healthcare settings (Leblebicioglu et al. 2016).

The disease usually has three phases: an incubation phase lasting 1 to 9 days, followed by hemorrhagic and hemorrhagic phases (in severe cases), and finally, the convalescence period. The hemorrhagic symptoms vary from small red or purple spots (petechiae) and nosebleeds (epistaxis) to widespread bruising (ecchymosis) and bleeding from different parts of the body (Papa et al. 2015). The symptoms of CCHF can vary from mild flu-like illness that resolves on its own to severe and life-threatening manifestations (Rehman et al. 2018). CCHF virus infection is characterised by fever and hemorrhage and is frequently accompanied by non-specific prodromal symptoms; these symptoms can include general malaise, fatigue, headache, muscle pain, and fever. These symptoms may precede the more specific manifestations of the disease, such as haemorrhage and organ dysfunction (Al-Abri et al. 2017). Severe CCHFV infection leads to the development of a condition which is distinguished by the presence of

petechiae, ecchymosis, epistaxis, gingival haemorrhage, and often gastrointestinal and cerebral haemorrhage (Zivcec et al. 2015).

In numerous countries, CCHFV has become a notable arboviral zoonotic disease, marked by the lack of specific antiviral therapies, a high mortality rate, and its capacity to spread through vectors (Dai et al. 2021). Due to the substantial genetic diversity observed among CCHFV strains, it is significantly essentialvital to focus on molecular protocols that can effectively detect all existing genetic lineages of the virus and in severe cases, there may be a delay or absence in the production of antibodies (Papa 2019). Due to the absence of an effective vaccination against the disease, disease prevention and treatment play a vital role. Consequently, immunotherapy is employed. Combining it with compensatory therapies such as blood and platelet replacement, water and electrolyte management, and Fresh Frozen Plasma (FFP) replacement, among other compensatory medicines, proves to be one of the most effective treatment approaches (Gholizadeh et al. 2022).

Although there is no treatment for CCHF and only anticipation is achieved through supportive therapy, it is observed that the use of proper PPE along with Ribavirin reduces CCHF virus infection among healthcare workers and also increases the chances of survival of infected person (Ergönül et al. 2018).

2. GLOBAL IMPACT OF CCHF

The epidemiology of Crimean-Congo Hemorrhagic Fever (CCHF) is being influenced by climatic and environmental changes, along with the growing global trade and mobility, leading to a risk for the continued transmission of the disease (Fanelli et al. 2022). Presently, Crimean-Congo Hemorrhagic Fever (CCHF) has been identified as endemic or potentially endemic in approximately 50 countries across Europe, Africa, and Asia. It leads to severe hemorrhagic syndrome and sporadic infections in humans (Nasirian 2019).

Evidence of Crimean-Congo Hemorrhagic Fever Virus (CCHFV) infection may have been documented as early as 1961 in Kenya, which was then known as British Kenya. Serological evidence of human CCHFV infection was initially obtained in the early 1980s (Temur et al. 2021). There was an outbreak in China in 1965, with an 80% case fatality rate (Ergönül 2006)

However, since the year 2000, the cases increased rapidly, and they have been reported in several countries, including Turkey, Iran, Pakistan, India, Greece, the Republic of Georgia, and some Balkan countries (Bente et al. 2013). From the year 2002 to 2004, it was declared that CCHF was endemic in Turkey with high mortality, and this outbreak was an alarming situation for all the countries near Turkey (Ozkurt et al. 2006). Furthermore, cases of CCHF imported from abroad were identified in France in 2004 and the United Kingdom (UK) in 2013 (Arteaga et al. 2020).

The frequency of CCHF outbreaks in Uganda is on the rise. Between 2013 and 2017, eight confirmed outbreaks were reported. Moreover, two additional outbreakattacks (not detailed in this manuscript) occurred in early 2018 (Mirembe et al. 2021). The affected regions of the world are represented in Fig. 1.

3. CCHF IN PAKISTAN

Over time, Pakistan has been grappling with the burden of both communicable and non-communicable diseases. Among these threats, CCHF is particularly concerning, exhibiting biannual peaks during March to May and August to October. Currently, cases of CCHF have been confirmed in all regions of Pakistan (Yousaf et al. 2018). Isolated cases of CCHF are documented in of the rural areas of Punjab, Azad Jammu Kashmir, and Khyber Pakhtunkhwa, as well as in neighbouring Afghanistan, where cattle herding is a common practice (Noreen et al. 2020).

Pakistan is classified as an endemic country for CCHF, ranking as the fourth highest in reported cases of CCHF infection in Asia, following Turkey, Russia, and Iran (Ince et al. 2014). The first isolation of the CCHF virus in Pakistan occurred during the 1960s, originating from ticks found in the Changa-Manga Forest located near Lahore (Saleem et al. 2016). In 1976, the first case of CCHF was reported in Pakistan at Rawalpindi General Hospital (Atif et al. 2017). As a consequence, the outbreak in the hospital gave rise to 11 additional cases, leading to the death of three individuals (Tabassum et al. 2023). During the period from 1976 to 2010, 14 outbreaks were reported in Pakistan (Qidwai 2016).

An outbreak was reported that from 1st January 2013 to the middle of June, and 16 cases of CCHF were outlined, and 6 of these died (ul Islam et al. 2014). In May 2017, an outbreak occurred in the Karak district of Khyber Pakhtunkhwa in which six individuals exhibited symptoms such as nausea, vomiting, and diarrhoea. Four out of six died within four days (Jamil et al. 2022). From January 2014 to May 2020, cases of CCHF rose in Pakistan, with approximately 356 instancespoints with a mortality rate of 25%. Among these patients, Baluchistan accounted for 38%, Punjab for 23%, Khyber Pakhtunkhwa for 19%, Sindh for 14%, and Islamabad for 6% (Ahmed et al. 2021). The data is represented in Fig. 2.

Pakistan has observed a higher incidence of CCHF virus since August 2016 (Wahid et al. 2019). In 2016, a surgeon and nurse who had been working at Bahawalpur Hospital lost their lives due to CCHF during their treatment at Agha Khan University Hospital (Ahmed et al. 2018). From January 2017 to December 2019, another outbreak of CCHF was recorded; a total of 244 patients displaying symptoms suggestive of CCHF were admitted to prominent hospitals in Rawalpindi. Among them, 45 patients (18.4%) tested positive for CCHF according to the diagnostic results (Ahmed et al. 2021).

A cross-sectional study was undertaken at Public Hospital Quetta from 2015 to 2020. Among the 480 suspected cases of CCHF, PCR was conducted on 73% of the cases. Of those, 52% were CCHF positive, with a Case Fatality Rate (CFR) of 25% (Saeed et al. 2021). It is observed that Baluchistan is most affected throughout the country on an annual basis. In 2021, 19 suspected cases were reported, of which 14 were confirmed positive and five resulted in fatalities. However, in 2022, there were a total of four confirmed cases in Punjab and Sindh (Tariq et al. 2023). The first case of CCHF in Peshawar was reported in mid-June 2022, and a total of 13 confirmed cases were reported from different regions of the country (Waris et al. 2022).

It is noted that CCHFV is endemic in two provinces of Pakistan, i.e. Baluchistan, which shares a border with Afghanistan and Iran, and Sindh, specifically Karachi. However, cases of the virus have also been reported in other provinces of the country (Umair et al. 2020).

4. FACTORS INFLUENCING THE EMERGENCE OF CCHF IN PAKISTAN

The reported emergence of CCHF is linked to climate change, environmental shifts, rising tick populations, increased presence of wild animals, the movement of domestic and trans-national animals, and the transportation of virus-carrying ticks through migratory birds (Leblebicioglu et al. 2016). Factors that are influencing the emergence of CCHF are:

5. ENVIRONMENTAL FACTORS

5.1. TICK-BORNE TRANSMISSION

Among environmental factors, ticks are the ones that may hold much more importance; ticks are the vectors for the CCHF virus and play a vital role in the spread of CCHF. In order to prevent CCHF, there should be strategies to control ticks during their peak periods (Iqbal et al. 2017).

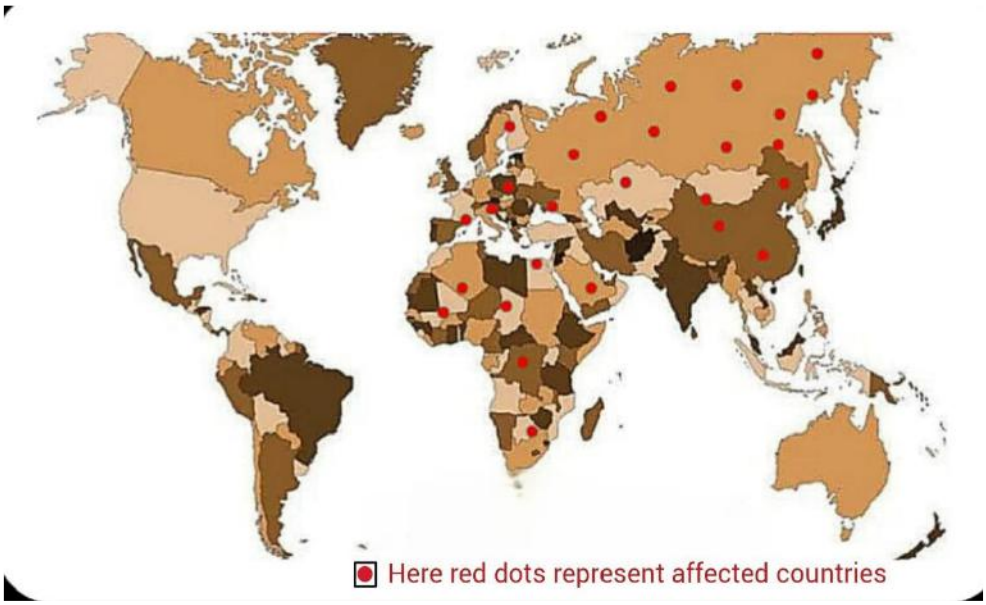

Fig. 1: Affected regions of the World.

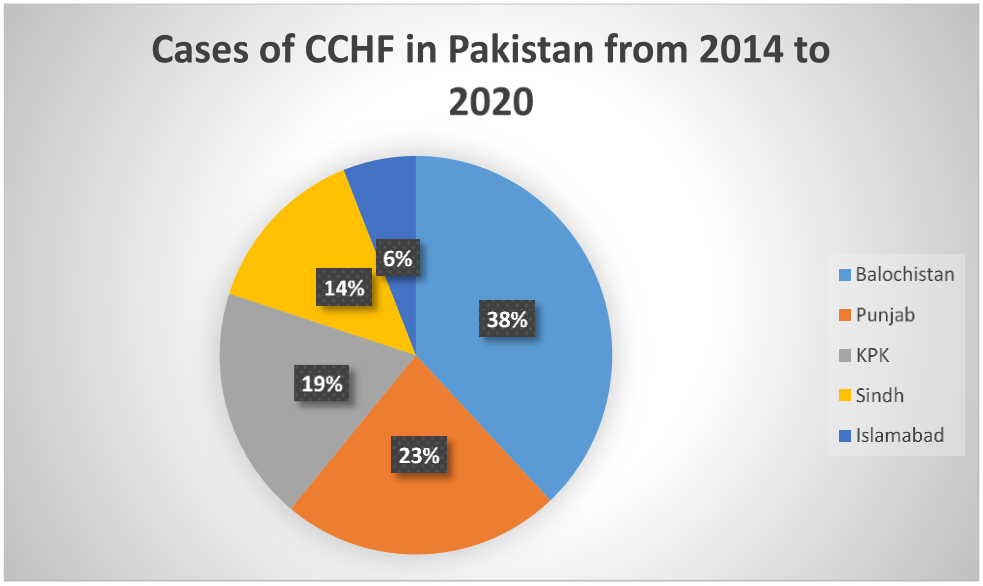

Fig. 2: Cases of CCHF in Pakistan from 2014 to 2020 (Self-designed figure; Data taken from Ahmed et al. 2021).

5.2. CLIMATE CHANGE

As far as the environment is concerned, the climate of the region matters. The escalating effects of climate change in Pakistan have led to a rise in CCHF incidence, attributed to intensified industrialisation, agricultural and occupational practices, and population density (Yasmeen et al. 2022). Ticks thrive in warm and arid environments, making an increase in temperature and a decrease in rainfall favourable conditions for their growth and reproduction (Hussain et al. 2016).

5.3. MIGRATION

Another critical factor which leads to a risk of transmitting the CCHF virus is migratory birds as they act as an amplifying host. They also spread tick species especially, especially hyalomma (Nili et al. 2020).

6. ANIMAL HUSBANDRY AND LIVESTOCK TRADE PRACTICES

6.1. LACK OF AWARENESS

Rural inhabitants exhibit a lower literacy rate and lack awareness about tick-borne illnesses. They inhabit their livestock without implementing any preventative measures and rely on both milk and meat for sustenance while also utilizing cattle dung for wound-healing purposes (Dashti 2012).

6.2. UNHYGIENIC CONDITIONS

Poor sanitation and unhygienic conditions play a pivotal role in facilitating the transmission of CCHF virus. In areas where proper sanitation practices are lacking, infected ticks and animals can easily contaminate water sources, leading to the virus's introduction to the human population. Addressing these issues through improved sanitation measures is crucial in preventing and controlling the outbreak of CCHF (Lea M 2023).

6.3. PASTURE CONTAMINATION

Factors like the grazing system and the age of the livestock can significantly affect the likelihood of disease occurrence. In the stable grazing system, only a small number of animals are affected by the CCHF virus, but this rate can increase up to 30% in the nomadic system (Ahmadkhani et al. 2018).

6.4. TRANSPORTATION

However, another major cause of propagation of the CCHF virus is the transportation of animals from rural to urban areas for business purposes, and it generates the potential to result in viral spillover, where viruses can be transmitted from animals to humans in urban settings (Mallhi et al. 2017). The swift advancement of transportation and the frequent global movement of people and goods have significantly accelerated the rapid spread of infectious agents across the world (Grout et al. 2017).

7. PUBLIC HEALTH IMPACT

CCHF virus poses a significant risk to public health and has been recorded as a potential bioterrorism threat. The community should remain vigilant concerning the possibility of importing CCHF cases from areas where the disease is enzootic (endemic) and the potential for human-to-human transmission, particularly in nosocomial situations (Suchal et al. 2018). The Centre for Disease Control and Prevention (CDC) has identified and categorized several viral agents as potential biological terrorism agents, including CCHF virus and considered them as weapons of mass destruction (Bronze et al. 2002).

As far as the public health impact of CCHF is concerned, there is an utmost requirement to conduct serological surveys on animals in regions identified as high-risk for CCHF occurrence (Fanelli et al. 2022). In the various areas of the country, the reporting quality of CCHF virus infection varies, leading to inconsistencies. Additionally, there is limited active surveillance of human CCHF virus infection, making it challenging to assess the extent and intensity of transmission accurately (Dreshaj et al. 2016).

Tick-borne viral diseases (TBVDs), specially CCHF virus in domestic livestock, present significant risks to global food security, national economies, and public health, as they have adverse impacts on farmer's income and act as a socio-economic factor in the emergence of CCHF virus (Oluwayelu et al. 2023). The main challenge faced by this endemic region is the insufficient coordination between the animal and

human sectors concerning disease control. Additionally, there is a scarcity of laboratory kits for diagnosing CCHF, especially at the district level. This can result in misdiagnosis or delayed treatment, leading to an increase in fatalities (Jafar et al. 2022).

8. PREVENTION AND CONTROL

Lack of consultancy, not caring about essential safety measures, and not having enough isolation rooms for sick people may contribute to nosocomial disease outbreaks. When people with a highly contagious disease are admitted to the hospital, it often generates anxiety, confusion, and fear among hospital staff, and this negligence lead to the spread of a disease (Smego et al. 2004). In order to prevent CCHF infection proper public awareness is needed; one should know how to avoid such risk factors that may lead to that febrile infection, i.e., farmers must use long sleeves and pants and reduce their work in ticks loaded environments (Hawman and Feldmann 2023).

Laboratory staff handling materials from suspected CCHF cases must adhere to good laboratory practices and maintain a high level of adequate biosafety precautions. This is necessary to mitigate the potential for sample-to-person or indirect transmission (Al-Abri et al. 2019). It is mandatory to use proper PPE, but it was observed that only PPE is not sufficientfor. This hazardous virus also getsenters the body through aerosol, and this PPE set does not protect the conjunctiva and upper respiratory tract against aerosols, which could contain the particles of sputum streaked with infected blood from the patient (Pshenichnaya and Nenadskaya 2015).

It is of utmost importance to raise public awareness about the modes of transmission and the symptoms to be vigilant about, as it plays a vital role in disease prevention. Implementing measures to restrict the entry of wild animals into human-inhabited areas has proven effective in reducing disease transmission and controlling infection cases (Greene et al. 2022). In order to lessen the risk of animal-to-human transmission, it is essential to implement quarantine measures while importing animals and ensure regular treatment with pesticides. Furthermore, maintaining hygienic conditions during slaughtering, whether in slaughterhouses or at home, is also crucial (Al-Rubaye et al. 2022).

For control of CCHF virus, active tick surveillance is required. To achieve this goal, it is essential to monitor the distribution, occurrence, and frequency of CCHF virus infection among the ticks in specific geographical areas. The use of pesticides should be encouraged in the habitats of ticks (Sah et al. 2022). At present, there is a lack of a surveillance system to report the condition, particularly in Baluchistan promptly. This surveillance is crucial for conducting risk assessments, disease mapping, and forecasting related to CCHF (Aziz et al. 2020). Both community leaders and technical experts should collaboratively raise awareness about disease prevention and control, ensuring the community receives sufficient knowledge. Employing a One Health approach is essential to effectively implement prevention and control strategies (Ayebare et al. 2023).

9. CONCLUSION

Crimean-Congo Hemorrhagic Fever (CCHF) is a significant tick-borne viral zoonotic disease with a rising incidence in Pakistan and global concern. The disease's enzootic cycle, involving ticks and host populations, indicates its likely broader prevalence beyond reported clinical cases. The emergence of CCHF in Pakistan is influenced by environmental changes, climate shifts, and increasing tick populations, along with human activities like animal husbandry and livestock trade. Preventing and controlling CCHF necessitates public awareness, strict quarantine measures for imported animals, and regular use of pesticides.

A comprehensive One Health approach is vital for disease prevention. Surveillance, serological surveys, and active tick monitoring can aid early detection and tracking. While specific antiviral therapies are lacking, advances in immunotherapy and proper use of PPE have shown promise in managing severe cases and protecting healthcare workers.

Socio-economic factors, such as livestock and agriculture impact, require attention in disease control strategies. In conclusion, a collaborative approach, investment in surveillance and research, and a focus on public awareness are essential in combatting CCHF's spread in Pakistan, safeguarding public health, and mitigating its impact on society and agriculture.

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Hanta Virus: An Emerging Threat for Public Health

13

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ABSTRACT

Hantavirus infection, a pervasive zoonosis exacerbated by global warming, intense rainfall, and flooding, poses a substantial public health threat, with an annual incidence of 150,000-200,000 cases globally. Influenced by climate change, the transmission dynamics of hantavirus are intricately linked to the population densities of its reservoir host, rodents, which constitute 42% of mammalian biodiversity. With 28 known hantaviruses causing severe diseases in humans, the infections range from renal dysfunction to pulmonary and cardiac syndromes, resulting in high mortality rates. The etiology involves enveloped RNA viruses belonging to the Bunyavirales order, with distinct genotypes and species identified. Human infections primarily occur through inhaling particles contaminated with rodent excreta or secretions. Epidemiologically, Hantavirus outbreaks have been documented globally, with varying prevalence and dominant strains. Pathogenesis involves the compromise of endothelial barrier integrity, leading to severe organ damage. The transmission, influenced by climate change, occurs through rodents as intermediate hosts, with a potential for limited person-to-person transmission. Clinical manifestations encompass Hemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Pulmonary Syndrome (HCPS), exhibiting diverse symptoms and severity. Managing severe cases relies on supportive care, with no specific antiviral treatment approved. Prevention involves rodent control measures, thorough cleaning, and protective measures during potential exposure. Vaccines against Hantavirus are essential for high-risk populations. Ongoing research explores antiviral agents, DNA-based vaccines, and immunotherapies as potential treatments. Comprehensive prevention and control strategies are imperative to mitigate the global impact of hantavirus infections.

Keywords: Hantavirus, Zoonosis, Climate Change, Hemorrhagic Fever, Rodent-borne Infections

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1. INTRODUCTION

Hantavirus infection is the most widespread zoonosis that is emerging partially due to global warming, intense rainfall, and increased severity of floods resulting in an annual incidence of about 150000-200000 cases (Sunil-Chandra et al. 2015). The mode of transmission and circulation of hantavirus can be influenced by climate change which can impact the population densities of the reservoir host i.e. rodents (Douglas et al. 2021). Rodents make up 42% of the total mammalian biodiversity in the world, consisting of 2,277 species that inhabit every continent except Antarctica. They serve as carriers for a diverse range of infectious agents (Milholland et al. 2018). People can get infected with hantaviruses by breathing in tiny particles of dust that have been contaminated by rodent droppings or urine (Mattar et al. 2015). The particles lead to various types of organ damage due to a temporary increase in pro-inflammatory cytokines, also known as a "cytokine storm" (Clement et al. 2019). Small mammals are the exclusive carriers of bunyaviruses, which are zoonotic agents capable of inducing Hemorrhagic Fever with Renal Syndrome (HFRS), Hantavirus Pulmonary Syndrome (HPS), or Hantavirus Cardiopulmonary syndrome (HCPS); both of which exhibit case fatality rate up to 50% (Witkowski et al. 2015). The exact cause of the disease is not well known, although it is believed that both interfere with blood vessels and strong responses from cytotoxic lymphocytes give rise to the development of the symptoms (Rasmuson et al. 2016). This condition frequently occurs when a person comes into contact with mouse feces or urine within 1 to 3 weeks after the start of symptoms (Moore and Griffen 2022). Hantavirus infections pose a high mortality rate. It is also worth noting that Hantavirus can be transmitted from person to person, underlining the significance of medical interventions for preventing and treating Hantavirus infections (Dheerasekara et al. 2020). Currently, there are more than 28 known hantaviruses that can cause various diseases in humans globally. These illnesses can range from renal dysfunction to fluid overload in the lungs and major bleeding conditions (Avšič-Županc et al. 2019).

2. ETIOLOGY

Hantaviruses, which are enveloped RNA viruses belonging to the Bunyavirales order, are responsible for a range of hemorrhagic fevers transmitted by rodents. Hemorrhagic fevers caused by various viral families within the Bunyavirales order; such as Phenuiviridae, Arenaviridae, Nairoviridae, and Hantaviridae, are characterized by their rodent-borne nature (Mocanu et al. 2023). The diameter of hantaviruses ranges from 80nm to 120nm (Avšič-Županc et al. 2019). The viral particles, which are enclosed in a spherical shape, feature a genome split into three pieces of negative-strand RNA. These segments are referred to as large (L), medium (M), and small (S) genome segments. The L segment encodes an L-protein, the M segment encodes a glycoprotein precursor called GPC, which consists of two envelope glycoproteins (Gn and Gc) and the S segment encodes a nucleocapsid protein (N) (Muthusinghe et al. 2021). A total of 76 strains and 70 isolates from nine rodent species, one bird species, blood samples of patients with HFRS, and sectional materials from deceased HFRS patients were isolated and identified. The identification process led to the discovery of new hantavirus species, namely Khabarovsk, Taimyr-Topografov, and Adler. Additionally, two new genotypes of the Dobrava/Belgrad virus, known as Kurkino and Sochi, were identified (Tkachenko et al. 2016). Hantaviruses like Sin Nombre (SNV) or Andes virus (ANDV) found in

America result in hantavirus cardiopulmonary syndrome. In Asia, Hantaan (HTNV) and Seoul virus (SEOV); and in Europe, Puumala virus (PUUV) and Dobrava-Belgrade virus (DOBV) are the prevailing hantaviruses responsible for causing hemorrhagic fever with renal syndrome (Klempa 2018). Old World hantaviruses such as Hantaan, Puumala, Seoul, and Dobrava result in hemorrhagic fever with renal syndrome (HFRS), which has a mortality rate ranging from 1% to 15%. This condition affects around 100,000 to 150,000 individuals annually. On the other hand, New World hantaviruses like Andes (ANDV) and Sin Nombre (SNV) viruses lead to hantavirus cardiopulmonary syndrome (HCPS), which has a higher case fatality rate of 40%. However, the number of cases for HCPS is relatively lower, with only a few hundred cases reported each year (Engdahl and Crowe Jr 2020). Hantaviruses can cause severe illnesses in people, with mortality rates up to 12% for HFRS and 60% for HPS in certain outbreaks (Jonsson et al. 2010). The reservoir hosts of HTNV, SEOV, PUUV, DOBV, SNV, and ANDV are striped field mouse (*Apodemus agrarius*), Rat (*Rattus*), bank voles (*Myodes galreolus*), field mouse (*Apodemus flaviollis*), Eastern deer mouse (*Peromyscus maniculatus*) and Long-tailed colilargo (*Oligoryzomys longicaudatus*) respectively (Koehler et al. 2022).
Hantavirus virions attach to host cells and enter through endocytosis. They release RNA nucleoprotein complexes into the cytoplasm through membrane fusion. Virus transcription and replication occur in the cytoplasm or at the endoplasmic reticulum–Golgi intermediate compartment (ERGIC). Capped primers for transcription are generated by the viral polymerase from cellular mRNA. Cellular endonucleases may also assist in primer formation. The viral mRNAs produce proteins such as N protein and glycoproteins on the ER membrane-bound ribosomes. The assembly site for Old World hantaviruses is the Golgi, while the plasma membrane for New World hantaviruses assembly. Spike-like projections on the viral envelope aid in virus assembly and cell entry. Finally, the virions are released from the cell through exocytosis (Muyangwa et al. 2015). The risk of human HFRS was six times higher in areas with severe selenium deficiency and two times higher in areas with moderate deficiency than in areas with enough selenium. Thus, Hantavirus infections in both humans and rodents were more common in areas with low selenium levels (Fang et al. 2015).

3. EPIDEMIOLOGY

The discovery of hantaviruses was prompted by two major outbreaks of disease that happened in the past century. The Korean War outbreak (1950-1953) affected over 3,000 United Nations troops, resulting in Korean hemorrhagic fever or hemorrhagic fever with renal syndrome (HFRS). Hantavirus pulmonary syndrome (HPS) or hantavirus cardiopulmonary syndrome (HCPS) was the name given to the second outbreak that occurred in 1993 in the Four Corners region of the United States. It was originally named Four Corners disease (Jonsson et al. 2010). An outbreak of acute pulmonary distress syndrome was reported in the southwestern United States in 1993 (Lundkvist and Plyusnin 2002). In Argentina, there were 29 confirmed cases of hantavirus pulmonary syndrome (HPS) in humans, which occurred in clusters in 1995. A hantavirus named Andes (AND) virus had been partly described from a lethal HPS case in southwestern El Bolson in 1995 before a severe outbreak occurred in the same area in the spring of 1996. The outbreak affected 18 people (Levis et al. 1998). In Germany, hantavirus infections reached a peak in 2012, with over 2,800 reported cases. The majority of these cases were concentrated in the federal state of Baden-Württemberg, which borders Switzerland. Among the reported cases, the most dominant variant was PUUV (and Vial 2014).
Active surveillance for hantavirus pulmonary syndrome (HPS) in Canada started in 1994 and became a reportable disease at the national level in January 2000. By 31 December 2014, there were 109 laboratory-confirmed cases of HPS documented in Canada, while the United States has identified over 600 cases. Notably, there was an increase in HPS cases in 2013 and 2014, with 13 and 10 cases respectively. HPS cases can occur throughout the year, but there is a distinct peak during the spring and

early summer, with more than 60% of cases reported between April and July (Drebot et al. 2015). Hantavirus pulmonary syndrome (HPS) cases in Brazil have been steadily increasing, accompanied by the emergence of new viral variants. Between October 2001 and December 2009, confirmed HPS cases rose from 134 to 1252, marking an over 800% increase in just eight years. While HPS can occur throughout the year, its highest frequency is observed during the winter and spring seasons. Young adult males, with an average age of 30, are primarily affected by HPS in Brazil (Pinto Junior et al. 2014). During the period 2009 to 2017, 533 cases of HPS have been confirmed in Argentina (Alonso et al.2019). From July 1997 to January 1998, a total of 25 cases of hantavirus pulmonary syndrome (HPS) associated with the Andes virus were identified during an outbreak in southern Chile (Toro et al. 1998). HFRS cases are prevalent across eastern Asia, specifically in China, Russia, and Korea. China is the source of approximately 90% of the global case reports. Presently, HFRS is endemic in 28 out of the 31 provinces in mainland China (Wu et al. 2015).

During the 1950s, outbreaks of HFRS occurred in the forest region of northern Inner Mongolia and the mountainous region of southern Shaanxi province. In the following decades, HFRS cases and epidemics emerged along the middle and lower valleys of the Yanze River and in the Sichuan Basin. Throughout the 1970s, HFRS spread further from these areas. The incidence and endemic areas of HFRS significantly increased from 1981 onwards, with the recognition of the Rattus-type of HFRS and major outbreaks along the middle valleys of the Yellow River. By 1986, 1257 counties in 25 provinces were identified as endemic areas of HFRS, with about half of them newly discovered between 1980 and 1986 (Song 1999). During the period of 2014-2015, the southwest region of Korea experienced a high prevalence of HTNV (86.7%) among *A. agrarius* rodents during the autumn month of November. The average monthly HFRS cases in Korea from 2001 to 2020, revealed peak onset in the months of October, November, and December. Notably, November consistently had the highest number of reported cases, averaging around 120 cases per year (Tariq and Kim 2022). In Europe, over 4,000 cases of Hantavirus infection were recorded by the ECDC in 2019, which means that 0.8 out of every 100,000 people were infected. The primary etiologic agent in 98% of these cases was PUUV. Finland and Germany had the highest number of reported cases, accounting for 69% of the total (Koehler et al. 2022).

4. PATHOGENESIS

Hantaviruses exert a significant impact on target cells by inhibiting the apoptotic factor within them. This action leads to the impairment of endothelial barrier integrity, which is a hallmark of hantavirus disease. The underlying mechanism is believed to involve an excessive natural immune response, playing a central role in the pathogenesis of the disease (Munir et al. 2021). The integrity of the endothelial cell barrier is compromised due to an increased response of CD8+ T cells and elevated levels of vascular endothelial growth factor (VEGF). This results in the degradation of VE-cadherin, a crucial molecule responsible for regulating vascular permeability (López et al. 2019). Vascular leakage in microvascular beds that are infected by Hantavirus is caused by cytokines. The accumulation of mononuclear leukocytes is a micro-anatomical feature of Hantavirus infection (Muyangwa et al. 2015). Hantaviruses primarily infect vascular endothelial cells in humans, but they can also target epithelial cells, mononuclear phagocytes (MNP), follicular dendritic cells (DC), and possibly other cell types (Klingström et al. 2019). In individuals with severe HFRS or HCPS, the affected endothelium can lead to lung edema and potential lung failure. This can occur due to hyper-permeability, activation of the kallikrein-kinin system, or alterations in the endothelial glycocalyx (Kitterer et al. 2016). The other factors that contribute to the pathogenesis of both HFRS and HCPS are acute thrombocytopenia and platelet dysfunction. Additionally, the severity of the disease may be influenced by genetic predisposition, particularly related to HLA type (Avšič-Županc et al. 2019).

5. TRANSMISSION

The mode of hantavirus transmission and its circulation in nature can be influenced by climate change, particularly its impact on the population densities of the hantavirus reservoir host rodents (Douglas et al. 2021). Unlike other Bunyaviruses, hantaviruses do not rely on arthropod vectors for transmission. Rodents, insectivores, or bats that have persistent infections carry and transmit them to people, rather than being transmitted directly. Hantaviruses circulate in nature through horizontal transmission among endemically infected natural carrier hosts, such as mice, rats, and voles (Avšič-Županc et al. 2019). HFRS and HPS, which are caused by hantaviruses, are transmitted by rodents of the Muridae family, specifically the Sigmodontinae subfamily. Each hantavirus species is associated with a specific rodent species as its intermediate host. The incidence of these diseases is influenced by environmental factors that contribute to the reproduction and spread of rodents in endemic areas (Toledo et al. 2022). Humans act as spillover hosts, primarily acquiring infection by inhaling aerosolized excreta or secretions from rodents and insectivores that are infected with the virus (Watson et al. 2014).

It is important to consider the additional risk of person-to-person transmission. Unlike other hantaviruses, there is evidence of ANDV transmitting between individuals, although the efficiency of transmission is limited and accounts for a small portion of cases. The specific risk factors for secondary infections, include being a sex partner or sharing a room with a patient, as well as exposure to the patient's body fluids. This highlights the potential for person-to-person transmission of ANDV and sheds light on the factors contributing to secondary infections (Manigold and Vial 2014).

6. CLINICAL SIGNS

The clinical presentation and severity of HFRS varies depending on the hantavirus species involved. HFRS caused by Hantaan virus, Amur virus, and Dobrava-Belgrade virus exhibits a severe clinical course while Puumala virus infections typically lead to milder disease courses known as "nephropathia epidemica" (Koehler et al. 2021). Nephropathia epidemica (NE) is marked by acute kidney injury accompanied by thrombocytopenia and often proteinuria. The disease is also characterized by severe gastrointestinal symptoms, and intense back and abdominal pain, and can vary in severity from mild or asymptomatic cases to severe acute kidney injury, sometimes leading to a fatal outcome (Latus et al. 2015). Cardiac involvement with electrocardiographic (ECG) abnormalities and acute myocarditis has also been observed during NE (Kitterer et al. 2016). Hantavirus pulmonary syndrome is a severe and acute illness marked by respiratory failure, pulmonary edema, and cardiogenic shock. After exposure, there is an incubation period of 14-17 days. Early stages of HP may include gastrointestinal manifestations, headache, and chills (Mattar et al. 2015). Due to the similarities in their clinical presentations, HFRS and HCPS are often perceived as interconnected syndromes (Koehler et al. 2021).

The disease of HFRS has a five-phase clinical course: febrile, hypotensive, oliguric, polyuric, and convalescent. The febrile phase starts after 2 to 4 weeks of incubation and lasts for about 3 to 7 days. In this phase, patients have fever, headache, vomiting, abdominal pain, back pain, and visual problems. Towards the end of this phase, they may develop small red spots on the palate and redness of the eyes. The hypotensive or shock phase has a variable length, ranging from a few hours to 2 days. In severe cases, fulminant irreversible shock can occur, leading to approximately one-third of deaths. This phase is characterized by thrombocytopenia, leucocytosis, and pronounced hemorrhagic manifestations. The oliguric phase, lasting around 3 to 7 days, may lead to acute kidney injury (AKI) and is liable for half of the fatalities. Patients with AKI often require dialysis, and serum creatinine and urea levels become elevated during this phase. The start of renal function recovery is the polyuric phase, and the diuretic phase onset

is a good sign for the prognosis. The convalescent phase can extend up to 6 months. Children with HFRS may present with a clinical picture similar to adults but generally experience a less severe form of the disease. Abdominal manifestations are commonly reported in pediatric cases (Chandy and Mathai 2017). HCPS is considered more severe than HFRS. It typically follows a three-phase course: prodromal, cardiopulmonary, and convalescent. During the prodromal stage, patients may experience flu-like symptoms such as fever, chills, malaise, headache, vomiting, abdominal pain, and diarrhea, which can resemble other viral infections. The cardiopulmonary phase is characterized by a progressive cough, shortness of breath, and tachycardia. Patients is often presented with non-cardiac pulmonary edema and hypotension, and severe cases may require mechanical ventilation due to respiratory failure. Complications like cardiogenic shock, lactic acidosis, and haemoconcentration can lead to rapid deterioration and even death shortly after hospitalization. Survivors enter the polyuric phase, followed by the resolution of pulmonary edema, and most recover fully without any long-term effects (Chandy and Mathai 2017). However, diagnosing hantavirus infections based solely on clinical symptoms is challenging, particularly in cases with mild and moderate symptoms, as the early signs of the disease are nonspecific (Avšič-Županc et al. 2019).

7. TREATMENT

As of the current date, there are no antiviral drugs approved by the US Food and Drug Administration for the treatment of HFRS (Hantavirus Hemorrhagic Fever with Renal Syndrome) or HPS (Hantavirus Pulmonary Syndrome). Therefore, the approach to managing severe cases relies solely on providing supportive care. It is crucial to focus on maintaining proper fluid and electrolyte balance in these patients. In cases where HFRS patients experience severe kidney impairment, they may require extracorporeal blood purification, such as dialysis treatment. On the other hand, HCPS patients may need mechanical ventilation or even extracorporeal membrane oxygenation (Dheerasekara et al. 2020). The absence of FDA-approved drugs or vaccines remains the primary challenge in effectively controlling this lethal virus. Besides supportive care, there is hope in therapeutic approaches such as antiviral agents, DNA-based vaccines, and the use of polyclonal and monoclonal antibodies. These modalities have shown promise in neutralizing the hantaviruses and are being considered as potential treatments for hantavirus disease (Munir et al. 2019). Human ANDV immune plasma intravenous infusion appears safe for HCPS (Vial et al. 2015). Using mAb JL16 or MIB22 alone as monotherapy, or combining both in a cocktail, could be an effective treatment after exposure for patients infected with ANDV-induced HCPS. In small animal models, specific DNA vaccines have demonstrated protective effects against HCPS, as well as passive transfusion of polyclonal serum obtained from rabbit, duck, and human sources. In HCPS patients, the presence of abundant hantavirus-specific immunoglobulin G (IgG) during the early stages of the disease serves as a predictor for survival. Additionally, administering convalescent immune plasma from HCPS survivors to acute HCPS patients has shown to significantly reduce fatality rates. This demonstrates that antibodies make a significant and practical difference in controlling hantaviruses in vivo (Garrido et al. 2018).

8. PREVENTION AND CONTROL

To prevent the disease, the most important thing is to keep rodents away from where people live and work. This means getting rid of anything that rodents can eat or use to make nests, both inside and outside the house. It also means blocking any holes or gaps that rodents can use to get inside the house. Trapping and killing rodents is another way to control them. When cleaning areas that might have rodent droppings or urine, people should be careful not to breathe in the dust. They should wear rubber gloves and masks,

and use disinfectants to clean the area. To protect people from getting infected, especially those who are at high risk, vaccines against Hantavirus are needed (Dheerasekara et al. 2020). GRFT is a lectin that binds to sugars with many mannose units used as a topical microbicide for the prevention of hantavirus infection. It can block ANDV infection very well. It stops the virus from entering the cells by interfering with its envelope protein. 3mGRFT is a modified version of GRFT that works better than the original one against ANDV and SNV infection (Kuenzli et al. 2018).

9. CONCLUSION

Hantaviruses are zoonotic viruses transmitted by rodents and can cause severe illnesses in humans, such as Hantavirus Pulmonary Syndrome (HPS) and Hemorrhagic Fever with Renal Syndrome (HFRS). The diseases have a significant impact on vascular endothelial cells, leading to respiratory failure and kidney injury. Climate change may influence hantavirus transmission, and person-to-person transmission of some hantaviruses has been observed. Diagnosis is challenging based solely on clinical symptoms, and there are no approved antiviral drugs or vaccines. Supportive care remains the main approach to managing severe cases. Preventative measures involve rodent control and proper hygiene to avoid exposure. Potential treatments under investigation include immune plasma infusions and therapeutic approaches like DNA vaccines and monoclonal antibodies.

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Seoul Virus: Clinical Picture and Treatment

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ABSTRACT

Seoul virus is a Hantavirus that caught the public attention initially during Korean war (1950-1953) and has an association with rodent populations and human health. A concise overview, exploring the various aspects of Seoul virus including its viral characteristics, epidemiology, ecology, pathology, clinical features, diagnostic criteria and treatment along with prevention has been provided. Seoul virus has a prevalence in urban environments where the brown rat (Rattus norvegicus) serves as reservoirs. Human are exposed to this virus through inhalation of contaminated aerosols pr direct contact with rodent excreta. Clinical manifestations of Seoul virus are discussed in detail ranging from asymptomatic cases to severe conditions described as Hemorrhagic fever with Renal syndrome (HFRS) and Hantavirus Cardiopulmonary syndrome (HCPS). The features associated with HFRS are fever, nausea, vomiting, headache, backache, petechiae and internal bleeding. The patient may go into shock. Pneumonia, cardiogenic shock and pulmonary oedema are associated with HCPS. The diagnosis of Seoul viruses is done by ELISA, serological tests, hemagglutination test and IFT. The treatment is only providing symptomatic care and supportive along with monitoring of vitals. There is currently no approved specific medical therapy available. Strategies for rodent control and prevention of human infections include the role of public health initiatives, education and community engagement. In conclusion, a comprehensive exploration of Seoul virus, bridging gap between epidemiology, ecology, pathology, clinical aspects, diagnostic and preventive measures have been provided in this chapter.

Keywords: Seoul virus, Hantavirus, Rodents, HFRS, HCPS, ELISA test, Prevention.

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1. INTRODUCTION

The disease resembling hantavirus infection, which was originally mentioned in Chinese writings 900 years ago, initially caught the public attention during the Korean War (1950–1953). Korean hemorrhagic fever, also known as hemorrhagic fever with renal syndrome (HFRS), struck more than 3000 United Nations personnel. Cause of disease remained unclear until Lee et al. (1978) reported on Hanta virus (HTNV) which was found in lungs of the virus' natural reservoir, the striped field mouse (Apodemus agrarius) (Lee et al. 1978; Brummer-Korvenkontio et al. 1980; Nichol et al. 1993; Vapalahti et al. 2003; Heyman et al. 2009). Severe illness can be induced by pathogenic hantaviruses having fatality rates ranging from 12% (HFRS) (Heyman et al. 2009) to 40% (HCPS) (MacNeil et al. 2011). In nature, these viruses are carried by a particular rodent host species. Both illnesses are acute febrile infections that are typically contracted by inhaling dust or aerosols infected with rodent excreta or viruses (Jonsson et al. 2010). Renal failure and various haemorrhagic symptoms, from petechiae to severe internal bleeding, are characteristics of HFRS. Cardiovascular dysfunction and pneumonia are HCPS features. A typical result of hantavirus infection appears to be increased permeability of the microvascular endothelium (Klempa 2009). There are currently around 28 hantaviruses known to infect humans and cause conditions including pulmonary oedema, severe hemorrhagic conditions and acute renal failure.

2. VIRAL CHARACTERISTICS

All of viruses that cause HFRS are members of the Hantavirus genus of Bunyaviridae family. Hantaviruses are enveloped particles having a diameter of 90–120 nm. The genome is divided into medium, large and tiny segments. A nucleocapsid protein along with large protein and two glycoproteins are coded by these segments.

Arthropods including ticks, sandflies, and mosquitoes are responsible for spreading the majority of the Bunyaviridae family's viruses to humans. On the other hand, rodents propagate all hantaviruses and they are transmitted to humans through rodent urine, saliva, and feces aerosol. Also, they are transmitted from rodents to rodents by the same mechanism. Although the vast majority of evidences militate against ectoparasites' role in virus transmission, the matter is not entirely resolved. Since the Hanta virus was first discovered in a field mouse, Apodemus agrarius in Korea, an increasing number of novel but related viruses were discovered in various rodent species, as well as infrequently in acutely unwell humans. The results of serology employing the neutralization test (NT), monoclonal antibodies and indirect immunofluorescence test (IFT) have been used to classify these novel viruses. The hantaviruses were initially split into four distinct families or serotypes by these findings (Niklasson and Le Duc 1984). The genus of the primary rodent host and the serological grouping is is the same. Apodemus rodents are the source of the first serotype (Hantaan virus), Rattus rodents are the source of second serotype (Seoul virus), serotype 3 is composed of isolates from Clethrionomys (Puumala virus), and serotype 4 is referred to the isolates from Microtus (Baek et al. 1988). A belt from Norway in the west to Sweden, Finland, the Soviet Union, China, and Korea to Japan in the east is where HFRS is endemic. Throughout this belt, there is variation in the clinical severity of HFRS. In Asia, there is a severe variant (KttF) with major hemorrhagic signs and mortality, while in Europe, there is a milder type (nephropathia epidemica) that has minimal hemorrhagic manifestations. This type is of little to low lethality (Lee 1982). Both types of the disease were found in the former Soviet Union. Given that several cases of Korean Hemorrhagic Fever have been identified in eastern European nations like Greece and Yugoslavia, for example, the line between a serious disease and a benign condition is not quite clear-cut. Asia has recorded cases of clinical sickness brought on by the Seoul virus, commonly known as the urban rat virus. Both serologically and clinically, Hantaan virus infection is closely connected to Seoul virus disease. In contrast to patients infected with the Hantaan virus, the patients suffering from Seoul-

related viruses have lower mortality rate. The taxonomy of Bunyaviridae family members divides these viruses into genera and different viruses based on serology, such as NT (Bishop et al. 1980).

3. EPIDEMIOLOGY

In the majority of the world's regions, hantavirus antibodies have been discovered in humans and rodents (Leduc et al. 1986). However, only cases of patients who were clinically unwell have been documented from Europe and Asia. The number of cases that are fatal in Korea each year ranges between 300 and 900 and the fatality rates that were estimated previously was at 7 to 15%. Mortality rate has decreased to 5% over the past ten years due to better and efficient medical care (Lee 1982). The incidence rate in China has grown recently (perhaps as a result of better surveillance) and in 1982, 60,000 cases were reported with 5% fatality rate. There have been up to 168 cases per 100,000 population recorded annually in highly endemic regions of China (Song et al. 1984). The most endemic districts of Sweden have documented an incidence rate of 30 per 100,000 residents during such peaks, which happen every 3–4 years. Infection occurs year-round in areas of far eastern Asian locations but the peak incidences are reported in hot summers (May to July) and in mild winters (October to December). The bulk of occurrences in Scandinavia and the European Soviet Union region happen from October to April. there are up to 30% of people of older age groups who have antibodies, as has been reported in Sweden. This means that the case-to-infection ratio may be around one to ten (1:10). The majority of clinical cases are men of working age. The male to female sex ratio exceeds up to 2:1 in many places (Niklasson and LeDuc 1987). Farmers and woodworkers, soldiers and hunters are among the groups that are most frequently affected. A common perception is that there is low prevalence in children as compared to adults. All HFRS survivors are believed to recover without long-term effects, however some patients have been noted to have chronic hypertension and persistent renal impairment. According to renal biopsies tests, GFR and renal function tests, the prognosis of nephropathia epidemica is good. Within 3 months' majority of the patients slowly restore their renal function. In Some patients, it may take a prolonged time of up to 8 months for renal impairment (Settergren et al. 1990). People who work with artificially and sometimes naturally infected laboratory rodents have had a number of laboratory infections. In a Moscow institute, 113 lab employees were affected by an outbreak in 1961. Finland reported making similar findings. Hantaan virus transmission attempts to laboratory rats were followed by an outbreak in Seoul (Settergren et al. 1990).

4. ECOLOGY

Hantaviruses, in contrast to other Bunyaviruses, do not spread through arthropod vectors but rather through persistently infected rodent or insectivore hosts including bats as well (Fig. 1). The ecology of hantavirus and their geographic dissemination are correlated with dispersion of their natural habitat. In 1976, Apodemus agrarius, a field mouse was the first mammal which the HTNV (a hantavirus prototype strain) was isolated from (Lee et al. 1978). When the HFRS etiological agent was first discovered in South Korea, research studies were conducted worldwide that resulted in additional new HFRS-associated viruses to be recognized. Hence, it has been recorded that hantaviruses are able to spread not just across the Europe and Asia but also in the Americas and Africa.

It is generally acknowledged that spontaneous host infection is undetectable and does not result in disease. Although this is the case, some researches have shown various detrimental effects of hantavirus infection on survival of hosts. Gradual growth of infected animals and the existence of histological alterations in infected tissues were also recorded. The virus and host co-evolved, hantaviruses are usually closely connected to a single rodent species (Ahlm et al. 2000). Other animal infections include those of

moose, red fox, domestic cats and dogs are regarded as a spillover with a negligible or zero risk of human infection. The diverse biogeographic and anthropogenic stresses on the environment appear to be a major cause of spillover infections of sympatric hosts, however, since many cases of this phenomenon have been reported and this is also dangerous for public health as excessive infection promotes natural reassortment and the creation of new species of hantavirus (Plyusnin and Morzunov 2001).

5. PATHOGENESIS

Despite the presence of viral antigen in different organs, viral infections mostly affect renal or pulmonary endothelial cells and macrophages in both humans and animals (Hughes et al. 1993). Animals, in contrast to humans, frequently carry the virus throughout their lifetimes and are still capable of spreading it to other animals and people. As a result, our knowledge of viral pathogenesis has been constrained by the absence of obvious disease in the natural host (Mackow and Gavrilovskaya 2001). As the Syrian hamster model is utilized for ANDV and HCPS, therefore, it is not appropriate for HFRS and there had never been an animal model for HFRS. Increased vascular permeability, acute thrombocytopenia, and significant microvascular bed permeability are the main pathophysiologic events in both HFRS and HCPS (Vapalahti et al. 2003). The vascular endothelium is where hantavirus replication takes place,

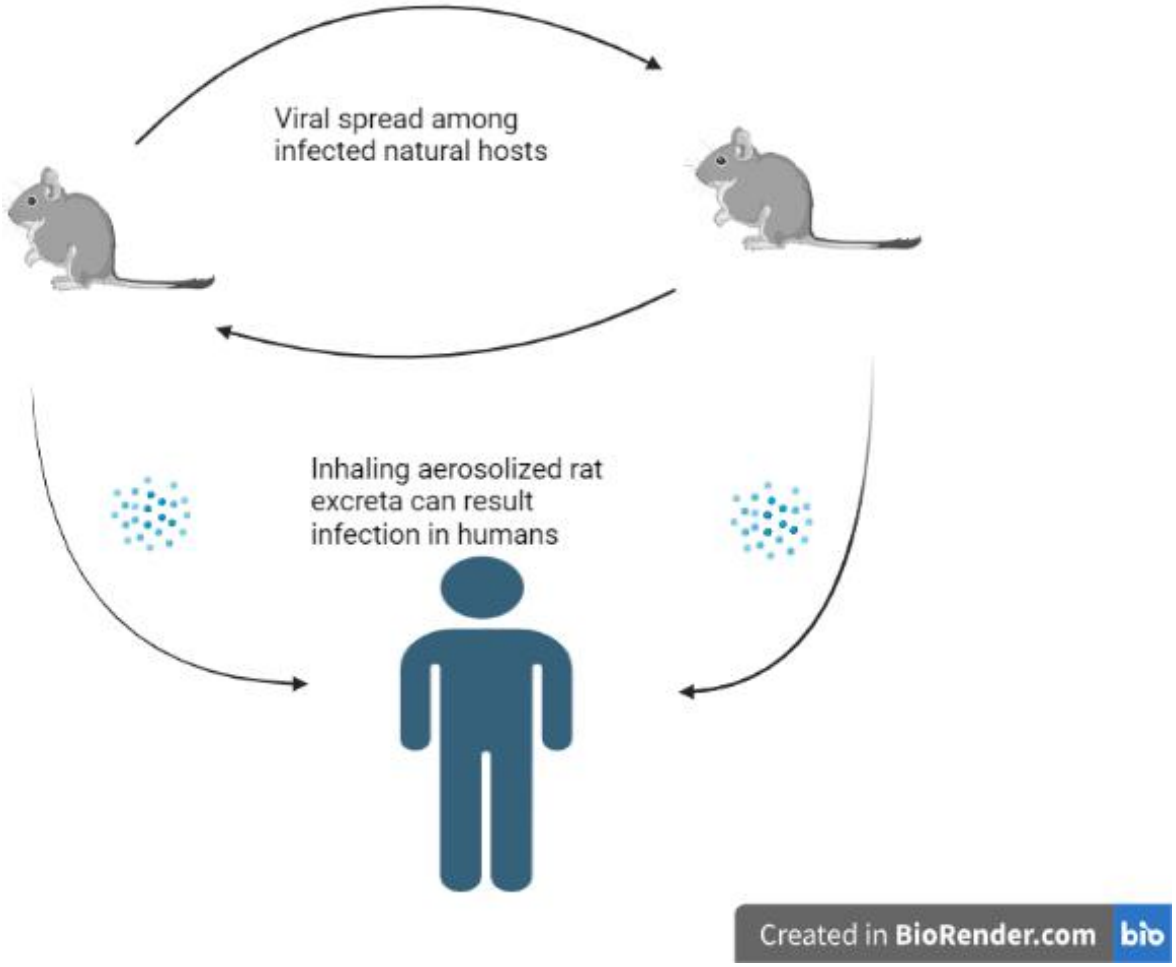

Fig. 1: Spillover infection to humans.

However, it doesn't appear to have a direct cytopathic effect. Since the virus replication cycle is very sluggish and late sepsis develops 5 to 10 days after infection (Terajima et al. 1999). This suggests that the virus persists rather than progressing in an acute lytic manner like other viral hemorrhagic fevers do. The viral antigen was found in the human kidney tissues of NE patients combined with inflammatory cell infiltrations and tubular damage, pointing to the possibility that immune response and viral replication are both implicated in tissue harm. The primary location of enhanced expression of numerous cytokines and the adhesion of endothelial molecules detected is the peritubular region of the distal nephron (Temonen et al. 1996). In acute NE, the renal involvement is characterized by significantly reduced renal plasma flow and glomerular filtration rate. Massive proteinuria is caused by increased glomerular permeability, which is a symptom of tubular dysfunction (Ala-Houhala et al. 2002). After the inhalation of infected aerosols, at first there is a communication of surface proteins with integrin receptors on the membranes of target cells. The exact mechanism by which virus spread throughout the human body is yet unknown. It has been demonstrated that human endothelium cells can be infected by pathogenic which includes SEOV, HTNV, PUUV, SNV as well as non-pathogenic hantaviruses which includes Tula virus, Prospect Hill virus. However, they do so using various integrin receptors (αvβ1 versus α5 β3) (Gavrilovskaya et al. 1999). Given that they express 3-integrin receptors and are found close to epithelial cells, immature dendritic cells likely play a crucial role in viral spread (Peebles and Graham 2001). They are also capable of acting as carriers to deliver the virus through lymphatic ducts to local lymph nodes from where they can further travel to endothelial cells after undergoing further replication (Schönrich et al. 2008). Virus replication is permitted by these cells particularly in the macrophages and CD8+ T cells which triggers immunological activation. It has been demonstrated that pathogenic hantavirus-infected cells exhibit increased viral titers due to a delayed type I interferon response (Schönrich et al. 2008). Antiviral innate immune responses can create inflammatory cytokines and chemokines, which can be a double-edged sword. Patients with both DOBV and PUUV infections had higher serum levels of interferon, interleukin-10, and TNF. Additionally, the patients suffering from more severe clinical condition of the disease had considerably high levels of TNF and interleukin-10 (Saksida et al. 2011). Interleukin-6 and tumor necrosis factor levels are increased in NE patients, although transforming growth factor-1 levels are low, indicating a milder type of the disease. In late stages of an acute infection, the overexpression of converting growth factor-1 points to a beneficial immunoregulatory function (Sadeghi et al. 2011). Cytotoxic T cells may cause capillary damage in NE patients by immunopathology, as well as through elevated levels of nitric oxide and tumor necrosis factor (Groeneveld et al. 1995; Linderholm et al. 1997). Hantaviruses, as opposed to other viruses that can cause haemorrhagic fever, cause the maturation of infected dendritic cells which results in a potent T-cell response during acute infection (Kilpatrick et al. 2004). The cytotoxic T-lymphocyte response, which coincides with the development of clinical illness in NE patients, increased the number of activated CD8+ T cells and reversed the CD4+ versus CD8+ T-cell ratio (Chen and Yang 1990; Kilpatrick et al. 2004). The negative impact of the immune response in HFRS-infected individuals is caused by the immune response of T helper type 1 and T helper type 2, proinflammatory cytokines in higher levels and inadequate regulation of them by their regulatory cytokines (Schönrich et al. 2008). Platelet dysfunction, immune responses and the dysregulation of endothelial cell function are all thought to play a role in the complicated multifactorial pathogenesis of the hantavirus. Above that, it was demonstrated that a genetic susceptibility to severe HFRS disease was correlated with HLA type, although different hantaviruses were linked to various HLA haplotypes. It has been demonstrated that the HLA-B8 DRB103:02 haplotype is particularly related with a genetic susceptibility to a more harsh form of HFRS that is brought on by PUUV (Mäkelä et al. 2002). Following ANDV infection, the same HLA haplotype was once more associated with a severe course of HCPS (Ferrer et al. 2007). Additionally, HLA-B*35 was more frequently found in individuals with severe illness development from DOBV infection, notably in cases where the patient died. The same HLA type has

previously been linked to a severe form of HCPS brought on by SNV (Korva et al. 2011). Fig. 2 shows the increase vascular permeability in response to viral infection.

6. CLINICAL PICTURE

Humans infected with hantaviruses may develop one of two clinical conditions, HFRS or HCPS, depending on whether the virus is from the Old World or the New World. Because separated capillary beds—renal medulla capillaries in HFRS and pulmonary capillaries in HCPS—are predominately damaged, the hantavirus-associated illnesses differ from one another. However, all hantavirus infections begin with identical first symptoms, such as a rapid onset of high fever, malaise, myalgia and other flu-like symptoms. Increased vascular permeability causing hypotension, thrombocytopenia, and leucocytosis with a left shift are additional common variables of HFRS and HCPS (Khaiboullina et al. 2005).

7. HAEMORRHAGIC FEVER WITH RENAL SYNDROME

The severity of the clinical signs and symptoms of HFRS may vary from asymptomatic to mild to moderate to severe and depends on the disease's etiological agent. Generally speaking, HFRS brought on by HTNV, Amur/Soochong virus, or DOBV are more severe and have fatality rates ranging from 5 to 15%, whilst SEOV produces intermediate disease and PUUV and SAAV bring on mild disease with mortality rates of less than 1%. However, a single PUUV infection case could be severe, a single HTNV infection could be mild, and infections are typically associated with subclinical seroconversion (Linderholm and Elgh 2001; Vaheri et al. 2013). The five unique phases of a typical course of HFRS are febrile, hypotensive, oliguric, polyuric, and convalescent. The illness begins suddenly with a high fever, chills, headache, backache, abdominal pains, nausea, and vomiting after an incubation period

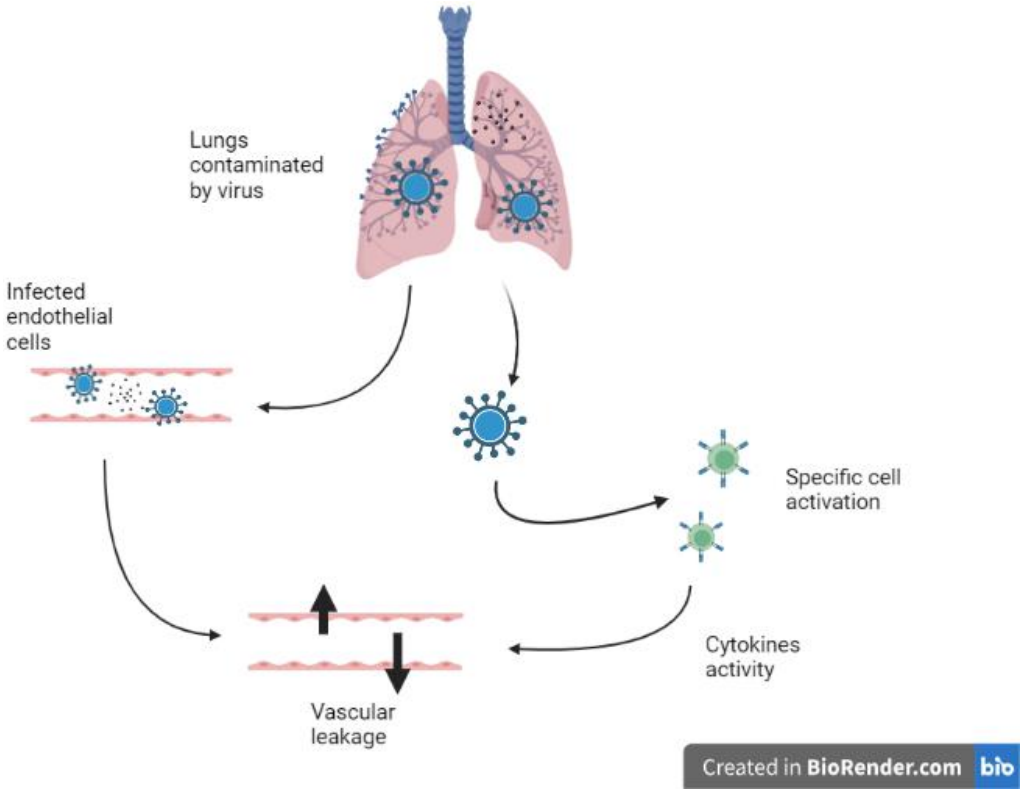

Fig. 2: Increased vascular permeability in response to virus infection.

of two to four weeks. There are commonly reports of lethargy and visual abnormalities (typically blurred vision). This febrile period may last from 3 to 7 days. Conjunctival hemorrhages and fine petechiae start to appear on the palate at the end of this period. A few hours to two days can pass during the hypotensive period. Majority deaths by HFRS are linked to severe irreversible shock at this stage and the severe cases can be characterized by hypotension and the patient even may go into shock quickly. This phase is characterized by thrombocytopenia, leucocytosis, and the beginning of severe hemorrhagic illness. Blood pressure returns to normal during the 3–7-day oliguric phase but kidney function temporarily deteriorates, causing azotaemia, oliguria, proteinuria, microscopic haematuria and even anuria. Patients with significant symptoms in oliguric phase, that is typically accompanied by stomach and back pain, need to have haemodialysis treatment. Elevated serum creatinine and urea levels are typical test results. Renal function begins to improve and urine output rises throughout the polyuric phase. The patient has a good prognosis when the diuretic phase starts. Patients can pass many litres of urine per day during this time, which can extend for days or weeks. It is challenging to distinguish between the five phases of HFRS in milder cases brought on by SEOV. Acute hemorrhagic symptoms and shock are uncommon in NE, but about one-third of patients have petechiae and other minor hemorrhagic symptoms. Instead of a full-blown shock episode, hypotension is detected. Overall, NE is frequently misdiagnosed because its clinical history is frequently atypical and more closely resembles a febrile sickness with stomach pain (Kanerva et al. 1998; Settergren 2000). A mild variant of HFRS brought on by an infection with SEOV has a clinical appearance and progression remarkably similar to HFRS brought on by HTNV. Though hepatitis is typically absent in other hantavirus infections, SEOV infections are frequently accompanied by it (Kim et al. 1995; Jonsson et al. 2008).

8. HANTAVIRUS CARDIOPULMONARY SYNDROME

HCPS is a more serious illness with fatality rates that range from 30 to 50 % compared to HFRS. Clinical symptoms of HCPS can range from mild hypoxemia to respiratory failure with cardiogenic shock, and the disease typically proceeds through three phases: prodromal, cardiopulmonary, and convalescent (Enria et al. 2001). Rapid development of bilateral infiltrates and coexistence of pleural effusion can result in respiratory failure and necessitates mechanical ventilation. Lactic acidosis, significant hemoconcentration and cardiogenic shock worsen this stage in more severe cases. Within hours of being hospitalized, patients can pass away. Patients that make it through the disease's initial phase enter the poly-uric stage that can be followed by the pulmonary oedema's remission. The recovery is typically full and without any aftereffects, despite the fact that the recovery is delayed, there are frequently complaints of weakness, exhaustion and poor exercise tolerance by the patients (Enria et al. 2001; Schönrich et al. 2008; Jonsson et al. 2010). Following this, cardiopulmonary phase quickly advances with sudden onset of a growing shortness of breath with cough and tachycardia. Hypotension and acute pulmonary oedema may also occur in the patients. Although lung and renal disease are typically attributed to HFRS and HCPS, respectively, growing medical understanding of clinical developments of HFRS and HCPS leads to the conclusion that the two conditions can overlap partially. In particular, there are increasingly more occurrences of HFRS with lung involvement and HCPS with renal and/or hemorrhagic involvement (Hughes et al. 1993; Kanerva et al. 1998; Linderholm and Elgh 2001).

9. DIAGNOSIS

Only a few cell lines have been used to effectively produce hantaviruses, with Vero E6 being the most popular. Virus isolation from humans or animals typically necessitates many steps. Before the viral

antigen is found in cells, it takes many weeks of blind transit. Therefore, in general clinical practice, isolation of virus is not employed for patient diagnosis but in epidemiological research to recover novel agents, it can be used. Haemagglutination inhibition test and the IFT are the major conventional immunological tests that are used to diagnose the HFRS. Enzyme-linked immunosorbent assay (ELISA) is also used to diagnose the HFRS. To detect the particular immunoglobulin the majority of regular laboratories currently use IFT. IFT can also be used IFT can also be used to detect the presence of specific antibodies in acute and the serum of recovering correspondents in the clinical diagnosis in establishing the diagnosis. Antibodies attain peak at the end of second week and can last up to 30 years, IFT detects these antibodies that start to manifest in the first week (Glass et al. 1991). The first serum sample had very high IgG titers titers in many patients of nephropathia epidemica (Niklasson et al. 1990). Only 50% of individuals with clinical nephropathia epidemica exhibit a fourfold raise in titer titer, according to IFT. If a particular IgG is present, it may indicate a past infection rather than the current state of the patient because in highly endemic parts of Sweden the prevalence rates of antibodies may exceed up to 30% in the older age groups (Niklasson et al. 1987). The patients of nephropathia epidemica have antibodies detectable by techniques like ELISA or NT or IFT lasting 20 to 50 years, as seen in KHF patients. Sero-epidemiology is therefore advantageous because lifelong exposure to the virus is shown by the existence of antibodies revealed by these sensitive assays. However, early IgG antibody detection, a lack of antibody titre ascent with high prevalence rates of antibodies can hinder accurate identification of patients. A g-capture IgM ELISA recently was created and tested (Jiang 1983). In first few days following the commencement of the disease, specific IgM was found and patients continued to be IgM positive for several months. With its excellent sensitivity and specificity, the IgM ELISA now is the most appropriate diagnostic test for patients. Two (Seoul and Hantaan virus) of three serologically different viruses that cause human disease, can only be distinguished by NT.

10. TREATMENT

The focus of care is on providing supportive treatment as there is currently no specific Food and Drug Administration-approved therapy for HFRS or even HCPS in the U.S. For close observation and clinical management, the patients with severe HFRS and HCPS are advised to be transferred to an intensive care unit. Maintaining fluid and electrolyte balance as well as circulatory volume is critical for anuric or leaky capillary patients and must be monitored very carefully for electrolyte balance, the function of kidneys and diuresis. Dialysis may be necessary for HFRS patients with significant renal failure, which is linked to pulmonary oedema and excessive fluid retention. Platelet transfusions may be done if there is significant bleeding and thrombocytopenia (Linderholm and Elgh 2001; Jonsson et al. 2010). In HCPS, it's important to regulate fluids, use pressors properly, and provide supplemental oxygen when necessary (Krüger et al. 2001). Ribavirin was successful in treating suckling mice infected with HTNV and was indicated to carry anti-hantaviral action (Huggins et al. 1986). Clinical investigations on HFRS patients from China has shown that at the beginning of symptoms if ribavirin is given in initial 5 days, it can significantly decrease the mortality rate dramatically (Huggins 1989; Huggins et al. 1991). In the treatment of HFRS in China, ribavirin has widely been used. It has been confirmed in a recent study by Rusnak et al. that giving IV ribavirin in early course of HFRS lessens the severity of renal insufficiency and the incidence of oliguria (Rusnak et al. 2009). Ribavirin given intravenously has also been investigated for the treatment of HCPS. However, ribavirin medication provided no therapeutic effect for the patients in a few small trials (Chapman et al. 1999; Mertz et al. 2004).

11. PREVENTION

The main source of Seoul virus are the wild rats. A chance could be present that rats migrating via, say, international shipping could transmit this human illness around the world. In addition to attempting to

reduce this risk, the prevention of HFRS disease now rests on evading the recognized endemic habitat and decreasing the exposure to rats and their excrement. Expeditions to eradicate rodents can prove to be very costly and challenging but they have occasionally been successful (Yanagihara and Gajdusek 2019). An effective and intact vaccination has received first preference in HFRS research because of the illness's severity and some regions' high occurrence rates. Trials using an inactivated vaccine based on the Hantaan virus that was created in accordance with the Japanese encephalitis vaccine protocol are now being done (Lee et al. 1991). Animals that had received vaccinations were protected from Hantaan virus infection. The vaccines contain antigens of Hantaan virus and were produced in recombinant vaccinia virus (Schmaljohn et al. 1990). Nevertheless, the scarcity of appropriate animal models hinders the development of vaccines against all hantaviruses, regardless of vaccination method. The most pressing issues that need to be addressed right now are firstly the therapeutic interventions to be made in patients with severe shock and life-threatening hemorrhagic cases. Secondly the arbitration of entire clinical spectrum of infections. Furthermore, issue of the consequences like CVS and renal damage as well as the creation and production of a reliable vaccine.

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Simian Foamy Virus; ZOONOSIS

15

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ABSTRACT

Foamy viruses are complex and ancient retroviruses belong to genus spumavirus of reteroviridae family prevalent to nonhuman primate species. Simian foamy virus is found to have a zoonotic significance. Humans acquire SFV by means of frequent occupational and non occupational exposures with infected animals and their body fluids. Humans have no clear clues of pathogenesis yet and no pronounced clinical signs have appeared so far. A persistent latent infection in humans is obvious which may remain unnoticed as there is no adverse clinical picture of SFV infection in naturally infected humans. As SFV has non zoonotic origin before, but several evolutionary phases in cross species result in its zoonotic outcomes. Since studies have declared the ability of retroviruses to emerge from non pathogenic into pathogenic form, so well precautions are decisive to deter zoonotic SFV.

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1. INTRODUCTION

The retroviridae family comprises of two subfamilies and eleven genera based on their phylogenetic analysis (Coffin et al. 2021). Among the subfamilies are Spumaretrovirinae and Orthoretrovirinae. Retroviruses are well recognized for causing a variety of exogenous and endogenous diseases in vertebrates (Maeda et al. 2008; Goff 2013) such as malignancies associated with lymphomas, sarcomas, leukemias and various other pathogenic tumors of mesodermal genesis. They are also involved in cancer development in mammary tissues, liver, kidneys, lungs, and immunodeficient diseases such as AIDS (Acquired Immunodeficiency Syndrome) and autoimmune diseases (Coffin et al. 2021). However, there are some retroviruses which approved to be non-pathogenic.

Foamy viruses (FV) are also known as Spuma or Syncytial viruses which belong to the genus Spumavirus of the Reteroviridae family (Pinto-Santini et al. 2017). They are complex forms of archaic viruses with the origin of non-human primates (NHP). They are ubiquitous in their spontaneous natural hosts which take in cats, horses, cows, bats, and other non-human primates (Meiering and Linial 2001). They are not endemic in humans but many cases of human infections by foamy viruses have been reported so far. These oldest known viruses have been revealed to be co-evolved with the non-human primate species (NHPS) at a minimum of 60 million years ago (Switzer et al. 2004; Pinto-Santini et al. 2017). These are classified as feline foamy virus (FFV), bovine foamy virus (BFV), equine foamy virus (EFV), chiropteran foamy virus (CFV), simian foamy virus (SFV) and prototype foamy virus (PFV) which are well described by (Pinto-Santini et al. 2017). It is thought that all others have rare or even no significance as zoonotic pathogens except simian foamy viruses. Simian foamy viruses (SFV) comprise a third complex group of retroviruses (Buseyne et al. 2018). Primarily simian foamy viruses (SFV) are the pathogens of non-human primates, but their genetic modifications with time have made it a zoonotic infectious agent.

SFV's genome contains 3 retroviral genes i.e. *gag*, *pol,* and *env*, and 2 regulatory *tas,* and *bet genes. Gag*, *pol,* and *env* mRNAs are transcribed by *viral promoters and enhancers* located on *5'LTR* followed by splicing of *pol,* and *env* mRNAs. *Basal transcription of tas and bet is initiated by the internal promoter (IP) followed by activation of the second promoter in long promoter* transactivator *Tas. Activation of 5'LTR occurs, by Tas protein assembly but Bet protein is highly expressed and still is poorly understood. High* mutations in retroviruses are reported, mainly associated with error-prone reverse transcriptase.

The first ever case of SFV in a human was reported in 1971 in a Kenyan patient which give rise to the question of where this virus came into human cells. In Later years many cases of SFV were reported in hunters, laboratory personnel, and women in different regions of the world where there had been a good interaction between human and non-human primate populations. Researchers have reported that SFV was transmitted to humans through the bites of apes, gorillas, and small monkeys (Achong et al. 1971). In occupational and non-occupational ways of exposure to these NHPs veterinarians, lab attendants, zoo keepers, hunters, and pet owners are at risk of interspecific transmission of SFV.

Why are they called foamy or syncytial viruses? It is because they can produce rapid cytopathic effects (CPE) in the host's body tissue, leading to immediate syncytium formation and cell death ultimately (Linial 1999). Although SFV is not very common in the human population, it can be a source of other serious diseases. SFV can persist in humans for more than 20 years which creates a long-term illness in man. This chapter depicts the complete overview of the simian foamy virus with its history, genetic structure, and its increasing importance with the zoonotic perspectives, along with diagnosis and care management to save humans from these infections.

2. BACKGROUND HISTORY

Foamy viruses (FV) belong to retroviruses and are the ancient type of viruses. Due to their complex structure and dissimilarities to other types of retroviruses, they are categorized as the subfamily of

retroviruses, the Spumaretrovirinae. Foamy viruses are pervasive in their natural hosts mainly including nonhuman primates, cats, and cows. Human pandemics caused by HIV-1 (retrovirus) and influenza a (orthomyxovirus) originated from zoonotic infections.

In 1971, the very first foamy virus in humans was isolated from a human cell culture from a Kenyan patient with Nasopharyngeal Carcinoma (Achong et al. 1971). Phylogeny showed that it has the origin from the East African chimpanzee subspecies (*Pan troglodytes schweinfurtii*) and is named prototype foamy virus. However, interspecific transmission from chimpanzees to humans remained unclear (Murray and Linial 2006). In the 1970/80s many researchers reported contrary results about SFV occurrence in the human population reflecting the significant percentage of nonspecific serological activity and lack of confirmatory tests (Meiering and Linial 2001; Gessain et al. 2013). In 1995, the first confirmed evidence of the presence of SFV in humans was reported based on specific antibody tests and molecular assays in 3 monkey governesses and laboratory technicians (Schweizer et al. 1995). Different other groups of researchers have reported similar findings in multiple workers occupationally related to nonhuman primates and zoos from the USA, Gabon, Canada, and China (Gessain et al. 2013). SFV infection was also reported in 50 persons (mostly hunters) in Cameroon who had direct contact with the blood or blood fluids of NHPs. The majority of them were bitten by apes (gorillas, chimpanzees, and small monkeys (*Cercopithecus nictitans)) during hunting practices.* Recently SFV infection in women was also reported in the Democratic Republic of Congo (Switzer et al. 2012). Simian foamy viruses (SFV) were considered to be transmitted from nonhuman primate (NHP) hosts to humans in comparison to other retroviruses (Switzer and Heneine 2011; Khan 2009). To confirm the mode of transmission different studies have been carried out in different areas of the world where human and nonhuman primates interaction was high. In North America, Europe, Africa, and Asia's densely populated areas, the human population is settled near the richest biodiversity reservoirs so nonhuman primates have become part of their daily life (Sandstrom et al. 2000; Switzer et al. 2004). In cities, nonoccupational means of exposure include the form of pets, parks, and animal marketing areas (thousands can be seen) which are likely to transfer inter-species diseases like simian foamy viral diseases (Jones-Engel et al. 2006; Southwick et al. 2005). In occupation situations veterinary clinics, research laboratories, and hunting areas appeared to be potential sites for the transfer of cross-species diseases. It is appealing to note that human and NHP interaction is very high in Asiatic regions as compared to other areas of the world. Human and macaque companionship dates back to 25000 years in Southern Asia (Engel et al. 2013). Human-macaque mutualism in the context of routine life due to common geographical area is putting humans in danger of viral interspecies transmission. However, In Africa, bush meat hunting is a potential risk factor for SFV transmission to humans (Betsem et al. 2011).

Different studies declared that in nonhuman primates SFV seropositive can reach 75-100% in adults and SFVs can be in high concentrations to be present in the saliva of diseased animals. The potential sources of zoonotic transmission of SFV are apes, New World monkeys, and Old World Monkeys. Humans appeared to be more susceptible to apes' SFV than old-world monkeys' SFV and New World monkeys' SFV. Humans are more susceptible to SFV strains coming from their genetically related nonhuman primates (Switzer and Heneine 2011).

In humans, more than 100 cases of zoonotic SFVs are reported however not being considered as natural hosts. In humans, persistent infection can be caused due to Zoonotic transmission of SFVs (Gessain et al. 2013).

3. GENOMIC STRUCTURE

SFV's genomic organization includes three retroviral gag, pol, and env genes arranged from the 5' end and two regulatory tas and bet genes (Fig. 1). Viral promoters and enhancers are located on 5'LTR (long

terminal repeat) that transcribe gag, pol, and *env* mRNAs followed by splicing of *pol and* env *mRNAs.* Basal transcription of tas and bet is initiated by the internal promoter (IP) chased by activation of the second promoter in long promoter *transactivator* Tas that is needed for transcription from 5'LTR. Tas is also helpful in the regulation of transcription from IP. Activation of 5'LTR occurs when Tas proteins assemble (*Meiering et al. 2001)*. The other protein Bet is highly expressed and non-*structural but still is poorly understood (*Russell et al. 2005; Delebecque et al. 2006; Gärtner et al. 2009; Jaguva Vasudevan et al. 2013). Assays of western blotting showed that antibiotics are produced in Naturally-infected NHP that gives a strong reaction to Gag and Bet proteins. In FV in vitro detection, anti-Gag and anti-Bet antibodies proved to be useful (Pinto-Santini et al. 2017).

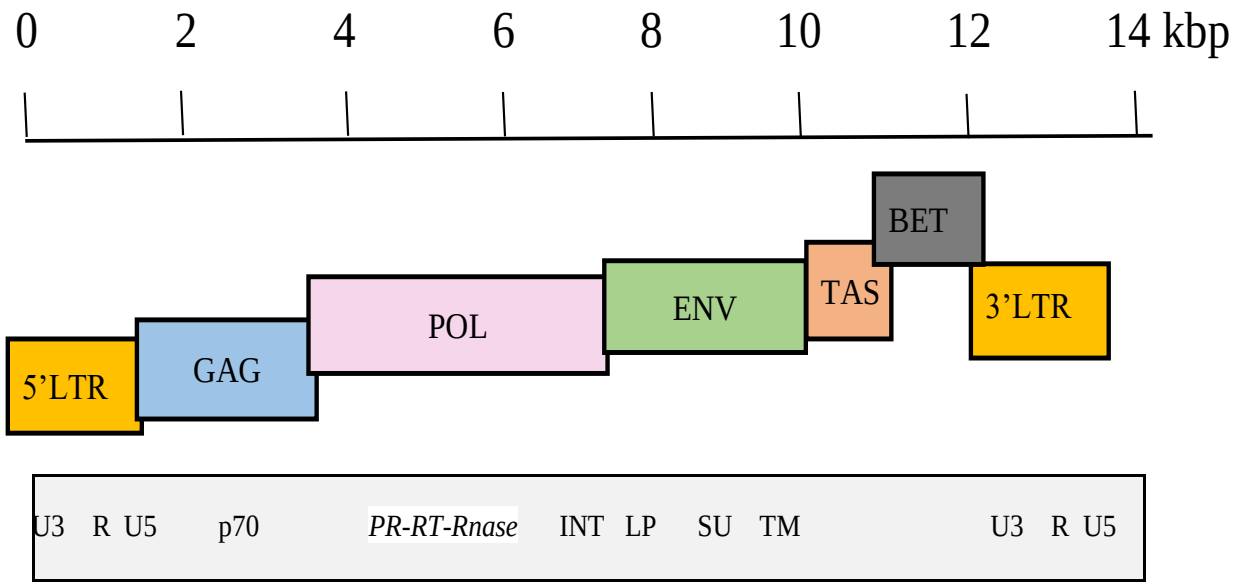

Fig. 1: Pictorial description of SFV genome (Chimpanzee strain). SFV genome is characterized by two flanking long terminal repeats (*LTR*) *that* contain 3 regions (a unique 3′ (U3), repeated (R), and *unique 5*′ (U5)). gag codes for both the shorter p70 protein and the full-length (74 kDa) gag protein. The protease (PR)-reverse transcriptase (RT)-Rnase H protein and the integrase (INT) are encoded by pol. The leader peptide (LP), surface glycoprotein (SU), and transmembrane protein (TM) are all encoded by env. tas and bet collectively code for regulatory proteins. Transactivator Tas binds to the 5'LTR and initiates the transcription of the structural genes gag, pol, and env.

Gag protein showed more similarity at the amino (N) terminus to other retroviruses as compared to the carboxylic (C) terminus (Linial et al. 2005). Just one cleavage near C terminus is reported resulting in ca. 3 kDa peptide, P3. A virus becomes non-infectious if a point mutation removes the Gag cleavage site resulting in a Gag full-length protein (Enssle et al. 1997). Cleavage is possibly needed for the configuration of leaved Gag protein and its function, however, it is not been proven yet. Maybe the P3 peptide has a significant role in replication. As almost half of formed Gag proteins are cleared, this leads to the existence of Gag doublet in Western blots (Pinto-Santini et al. 2017).

A high mutation rate in retroviruses has been reported. However, an interesting fact about foamy viruses is that their genome is highly conserved in personnel of the same kind of species in comparison to other retroviruses (Schweizer et al. 1999). Mutations in retroviruses are mainly associated with error-prone reverse transcriptase (RT). In vitro and cell culture examination of PFV RT has resulted in the similarity of PFV RT and recombinant HIV-1 RT in vitro (Boyer et al. 2007; Gärtner et al. 2009). However, a higher fealty RT probably has a supporting role in observed genome stability in FV. PFV recombination

is reported as a frequent event by template switching is significant as an error-prone RT, recombination may have a contribution to virus evolution. Recombinant viruses have been identified in SFV-infected OWM through sequence analyses of *gag* and *env* genes is strong evidence to prove the point of recombination in natural infection (Feeroz et al. 2013; Richard et al. 2015). The process of recombination, template switching, and recombination coupled with the documented interspecies transmission of FV in NHP give rise to the consideration of viral recombination of FV in co-infected animals of host species (Ghersi et al. 2015) (Fig. 2). In NHPs, co-infection with multiple SFV species has been reported. However, no case of coinfection and infection from recombinant SFV has been reported in humans to date (Leendertz et al. 2008; Liu et al. 2008).

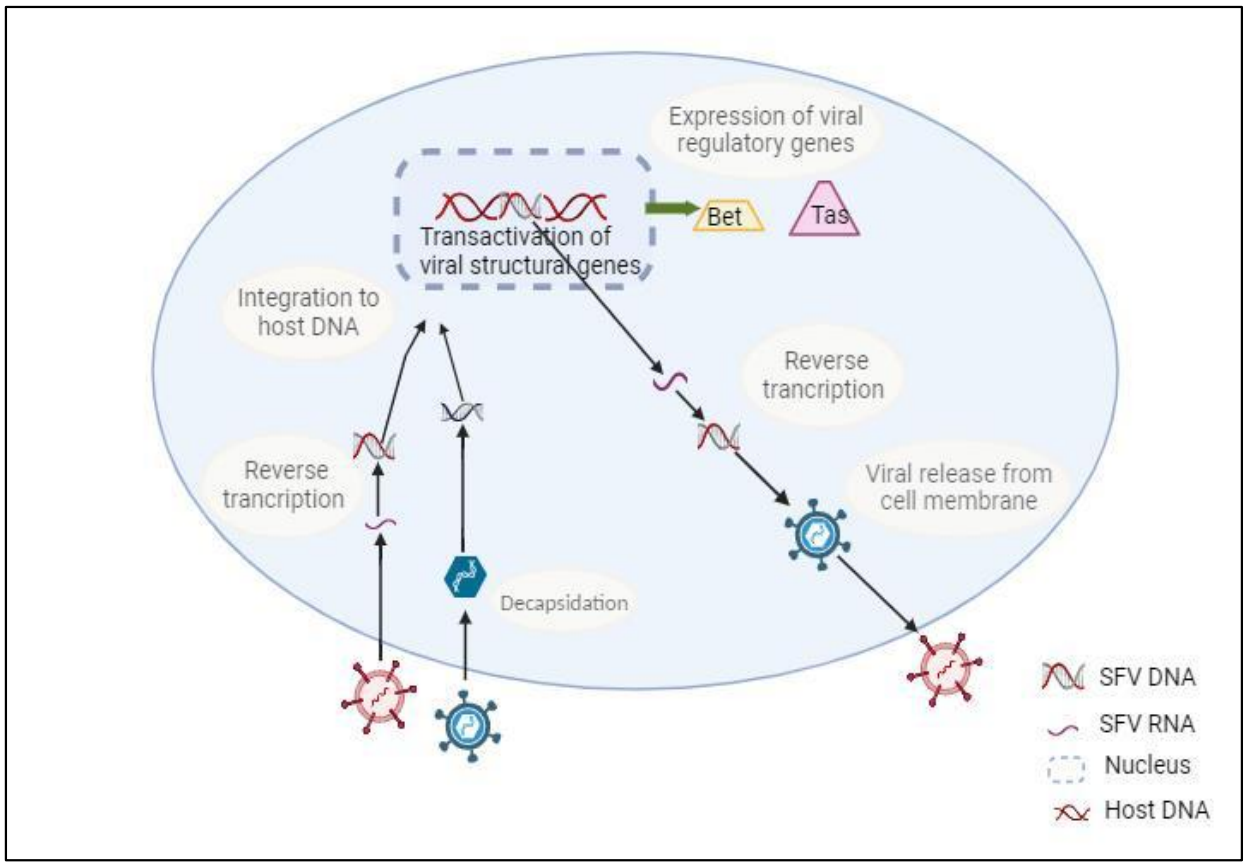

Fig. 2: Life cycle of SFV infection is stared with the decapsidation of RNA/DNA genome. In RNA containing SFVs reverse transcription occur followed by incorporation of DNA into host cell. *tas* and *bet* transcription induced by cellular activation of internal promoter followed by the activation of second promoter positioned on LTR by transactivator Tas resulted in the synthesis of Gag, Pol and Env proteins. After assembling and reverse transcription produce both DNA and RNA particles.

4. HOST SPECTRUM

Foamy viruses (family reteroviridae with the genus of spumavirus) can cause disease in a pervasive range of mammalian species, primarily non-human primates 10. Simian foamy virus has a zoonotic potential that leads to causes human infections. In them, the most obvious susceptible hosts are primates which includes monkeys and apes. The prevalence of this virus is more than 70% in monkeys

and apes 15. Simian foamy virus is more prevalent in their natural hosts than in humans. It infects a broad range of animal species mainly the non-human primates, monkeys, wild red colobus, and chimpanzees (Murphy and Switzer 2008). Moreover, SFV persists and causes asymptomatic infections in cats, sea lions, horses, hamsters, and cows (Wormser 2004). Among the non-human primates which harbor complex multiple strains of SFV are prosimians, baboons, African green monkeys, apes, macaques, and chimpanzees (Wormser 2004). Over time, the cross-species evolutionary modifications of the virus result in the infection in humans through various interactions with wild animals and non-human primate's species. But still, humans are rarely infected by this virus as its prevalence is not in domesticated animals. But still, as far as the genetic basis are concerned, it is well known that humans and monkeys are closely related species through their similarities in genetic makeup. The documented research claims that humans living or working in areas near the natural habitats of non-human primates are more likely to get viral entry into the body (Jones-Engel et al. 2008). However, evidence of natural infections in humans through foamy viruses is still lacking.

5. TRANSMISSION

Almost 60% of human infections are of animal origin which infects humans through numerous exposures either direct or indirect. In animals, the cross species Exogenous retroviruses have various routes of transmission from infected to healthy individuals, the most likely are through direct contact, bites, infected saliva, milk, blood, sexual contact, and perinatal routes (Pinto-Santini et al. 2017; Coffin et al. 2021). While the endogenous routes of viral transmission is vertical via the inheritance of germ-line proviruses (Coffin et al. 2021). The exact mechanism of transmission for foamy viruses is still needs to be known (Dhama et al. 2014). However, various research data suggest that the zoonotic simian foamy viruses are prevailing agents in non-human primates species. They are transmitted to humans through frequent occupational and non-occupational contacts with the infected animals, their body fluids, tissues, blood, or saliva (Khan 2009). The primary cause of viral entry to the human body is bite from NHP animals. These human bites are increasing with a great interest in hunting activities and increasing the load of the population of all NHP species in various geographical regions. In the significant blood-borne transmission SFV disseminates in humans during whole blood transfer, from SFV-infected humans. In this way, simian foamy virus is becoming a major health threat to human society.

6. PATHOGENESIS

The simian foamy virus is an endemic, zoonotic, and less prevalent retrovirus. Studies verified that only 2 to 3 % of humans get infected by SFV who are caretakers of non-human primates or lab workers dealing with the virus directly (Switzer et al. 2004). The exact pathogenesis characteristics related to SFV in humans are still unknown due to very minute data available. Worldwide, there are few humans affected by SFV which is mentioned in the literature. In this regard, the available analysis of a few subsets has not revealed the true picture of medical conditions associated with SFV (Hahn et al. 2000; Switzer et al. 2004; Brooks et al. 2007). Despite the very little information, some of the research data tried to elaborate on the pathological conditions caused by SFV in humans. It suggested that humans get the virus in through the NHP bites (gorillas, green monkeys, apes, chimpanzees etc.). The incubation period of SFV is highly variable from person to person. It may vary from 6 months to up to 3 years or more even. However, the virus's potential to cause significant infections in humans is lacking so far and needs to be understood deeply. Apparently, infected humans lack specific health problems (but it's according to limited personal

data), but deep *in-vitro* studies confirm a massive destruction of body cells caused by SFV in both monkeys and humans as well. The bites of non-human primates end with scars and significant wounds on different exposed parts of the body. Viral load is preferably seen in peripheral blood circulation and thus disseminated to the whole body. The virus specifically resides in the epithelial cells of the oral mucosa (Murray and Linial 2006; Falcone et al. 1999; Murray et al. 2008). SFV effects the liver, mucosa cells, and respiratory pars of the body during the course of infection (more commonly observed in non-human primates) (Ghersi et al. 2015; Muniz et al. 2017). Overall it is confirmed that SFV infection in humans is not as active as in non-human primates (Schweizer et al. 1997). The appropriate information for SFV pathological effects in humans is still unclear and further experiments are needed to confirm the exact path of pathogenesis in the human body.

7. VIRUS DETECTION

As the Simian foamy virus is an uncommon and limited studied virus, the specific detection methods or tests are not designed so far. To find the route cause of disease, we need subsets for analytical parameters. There are several biological and biochemical test methods for the diagnosis of viruses. The most reliable diagnostic techniques are serological and molecular testing. The simian foamy virus has a potential to cause a long-term non-significant infection in the human population as well. The samples from buccal mucosal epithelial cells, liver tissues, and blood especially from the peripheral body parts are obtained. The most preferred specimen is oral swabs where a huge number of the simian foamy virus are present. Most of the viral diagnostic practices are obtained from non-human primates which are the natural target animals for SFV. (Santos et al. 2019) elaborately described an experimental effort that in 2013, a large study has conducted on different genera of non-human primates to detect 192-bp *pol* sequence of SFV by using molecular technique i.e. PCR (polymerase chain reaction). In this experiment, the sample was collected from the peripheral blood mononuclear cells (PBMC) from wild monkeys and other NHPs (Ghersi et al. 2015). The conducted PCR assay results showed 100% sensitivity of the PBMC specimen from the western blot. Most of the samples were declared western blot positive which showed both sensitivity and specificity in wild non-human primate species (Santos et al. 2019).
Another detective method is serological testing in which specific antibodies are screened against simian foamy virus in the body. These antibodies include IgG and IgM which are specific immunoglobulin proteins. The research evidence by Hussain et al. (2003) showed a high level of seroprevalence among Asian and African NHP species, but it do not imply on humans until extensive deep research has to be done on the human population.

8. PREVENTION AND CONTROL

Zoonoses is a substantial public health problem which arises through a number of diseases which are common in different species of living things. It is a direct health hazard to human population leading to death. Among all of the human infections, almost 61% are of zoonotic importance in nature (Taylor et al. 2001). The interactions among humans, animals and the environment impose a significant role in the emergence and re-emergence, evolution and transmission of pathogens. With time, pathogens become genetically more stable and cause massive damage to the health and economy of the world. According to a survey study, there are about 2.4 billion estimated cases of zoonotic illness with the average of 2.7 million deaths of humans per year (Grace et al. 2012). In this way, there are certain prerequisites which are compulsive to adapt to minimize the adverse effects of pathogenic ailments over the globe.

Commonly, most of the zoonotic infections are transmittable from animals to humans by different means. Simian foamy virus is an emerging potentially zoonotic virus which is directly originating from wild animals. Humans need a comprehensive information of the SFV to carry out necessary measures to restrict the pathogen's survival and genetic stability.

9. INNATE IMMUNE CONTROL

In vitro investigations declared that Interferons are the molecules which are potent fighting force against viral diseases. Usually, they represent as the first line defence to the invading pathogens. SFV's can be easily sensed by the hematopoietic cells of human's defense system (Rua et al. 2012). It induces the production of higher levels of interferon-1 in blood. Interferon-1 (IFN-1) contains endosomal toll-like receptors which make it able to detect SFVs genome following the SFV uptake into the body (Rua et al. 2012). Moreover, these antiviral factors of interferon-1 hinders the virus replication inside the human body (Rua and Gessain 2015).

10. ADAPTIVE IMMUNE CONTROL

Foremost, the serum of infected individuals (experimented in rhesus macaques) have neutralizing antibodies which play crucial role to inhibit the SFV transmission and its infection (Williams and Khan 2010). Thus it aids *in vivo* adaptive control of SFV infections. There is no significant data showing the consequential events of immune system in humans after the SFV infection. However, antibodies have been found in SFV infected human's blood, saliva and urine samples which clearly depicts the adaptive immune control in human population against SFV (Rua and Gessain 2015).
Secondly, the neutralization event of Interferon-gamma with the activated PBMCs (Peripheral Blood Mononuclear Cells) in infected individuals leads to increase the viral expression (Falcone et al. 1999). It up-regulates the MHC-1 (Major Histocompatibility Complex-1) against SFV invading and replication inside the body (Colas et al. 1995). MHC-1 express the pathogen more efficiently and alert the immune system to virus infected cells of the body.

11. OTHER SALIENT CONSIDERATIONS

- SFV infected individuals are advised to not to donate blood to other individuals
- Use of PPE. As it spread more among humans who are occupationally linked to wild animals, veterinarians, butchers, hunters etc. They should adapt necessary measures while handling with the infected wild animal species such as washing of hands, use of gloves, properly covered body, cleaned hunting or other medical equipments, and proper repeatedly blood testing.
- Any cuts on skin should not be contaminated with infected animal's body fluids
- Minimize the usual contacts with wild animals (especially NHPs)
- Do not domesticate the non-human primates species
- Public awareness for zoonotic perspectives of SFV
- Adequate cooperation at regional, national and international level
- Proper wildlife monitoring committee
- Conservation of environment
- Adapt one health concept
- Availability of quick diagnostic facilities
- Ensure a safe food chain, especially for meat consumption

- Lunching of various educational programs related to zoonosis and hygiene

12. CONCLUSION

The greater part of human infections come from animal origin. SFV is at emerging state of infectious disease in humans. It has emerged through various evolutionary phases which enable its genomic stability. So far, it is an open gate to investigate various parameters of SFV emergence and control. However, the future of the SFV is completely unknown in the human population. There has not been any specific pathogenesis and apparent clinical picture in humans so far. That's why most of the basic parameters are yet to be investigated to conclude the outcome of zoonotic SFV infections. Some prerequisites and post-infection considerations are necessary to opt to deter the adverse effects of SFV.

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Rabies- A Zoonotic Disease

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ABSTRACT

Rabies, one of the earliest recognized viral diseases, causes encephalitis in humans and other mammals. It is the biggest public health risk that firstly appeared about 4,000 years ago and is considered one of the deadliest diseases with 100% death rate in the twenty-first century. It is a zoonotic and neglected disease that causes around 60,000 human fatalities annually throughout the world. More than 99% of cases of rabies in humans involve dogs. Rabies lyssa virus belongs to the family Rhabdoviridae. After infection takes place within the neuronal cell the virus starts using host machinery, as it reaches cells of the spinal cord, brain stem, and sensory ganglia where replication occurs. Incubation periods vary greatly among different species from days to years. After the incubation period, prodome stage appears characterized by pain, numbness, and itching at the site of the bite, pyrexia, fatigue, and headache. Changes in behavior become apparent like anxiety, agitation, insomnia, and depression. The prodromal phase is followed by the neurological phase which causes hallucinations, disorientation, paralysis, hydrophobia, hyperventilation, hypersalivation, and seizures followed by coma and death. An antemortem diagnosis is done by detection of rabies antigen and with serological testing. Once the clinical signs of rabies become obvious it is difficult to cure the disease and becomes fatal for both animals and human. However, rabies can be prevented by wound cleaning and administration of pre and post exposure vaccine.

Keywords: Rabies virus, encephalitis, lyssavirus, rabies prevention, virus transmission, rabies vaccine.

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1. INTRODUCTION

Rabies, one of the earliest recognized viral diseases, causes encephalitis in humans and other mammals (Scholand et al. 2011). It first appeared about 4,000 years ago and is considered one of the deadliest diseases with 100% death rate. It is the biggest public health risk in the twenty-first century except for Antarctica. Each year, thousands of deaths are documented, with the majority of cases being reported in Asia and Africa. Dog bites are the primary cause of nearly in all human instances of rabies. Neurotropic viruses of the genus Lyssa virus are responsible for its onset. Although zoonotic but it is a neglected disease in humans and animals. Children between 5 and 14 years are frequent victims (Rivera et al. 2018). Children under the age of 15years frequently die of dog bites in Africa and Asia. According to preliminary data, rabies causes around 60,000 human fatalities annually throughout the world. With such a big number, it can be inferred that rabies causes a yearly economic loss of over 4 billion dollars and leads to the loss of over 2 million disability-adjusted life years (DALYs). More than 99% of cases of rabies in humans involve dogs. Therefore, preventing dogs, especially stray dogs, from roaming freely can help stop the spread of rabies. In America, rabies has been successfully eradicated in both dogs and terrestrial species, while in Western Europe; rabies has been successfully controlled in canine populations (Banyard et al. 2014).

1.1. EPIDEMIOLOGY OF RABIES

Rabies is present all over the world except Antarctica. Over 95% of human deaths occur in Asia and Africa. Annually approximately 60000 deaths occur worldwide. In 2015, India (approximately 20,847) followed by China (approximately 6000) and the Democratic Republic of Congo (approximately5600) had the most cases (Coudeville et al. 2015).

1.2. RABIES IN PAKISTAN

Rabies is one of the leading animal-transmitted diseases in the sub-continent. In Pakistan alone, rabies contributes to about 2000 to 5000 deaths in a year (Mughal and Ali 2018). Unfortunately, only one method is applied for prevention which is killing stray dogs and an immunization program for the victims (Khan et al. 1976). Due to failure in controlling rabies, it remains endemic in Pakistan (Nawaz et al. 2022). Factors like in-adequate medical training, lack of awareness, and shortage of availability of vaccines contribute to a high mortality rate (Mubashir and Hussain 2021).

1.3. RABIES IN INDIA

India has the greatest rate of human rabies in the world. The number of cases increased since 2001, because of high stray dog's population. An estimated 20,000 people die every year from rabies in India, more than a third of the global total (Dyer et al. 2012).

1.4. RABIES IN AUSTRALIA

Australia is officially declared as rabies-free zone. However, the Australia Bat Lyssa Virus (ABLV) was discovered in 1996 (Makita et al. 2019).

1.5. RABIES IN UNITED STATES

Canine rabies was eradicated from the US but it is still present in wild animals. From 1960 to 2018, about 125 human rabies cases were reported in the United States out of which about 36 (28%) cases were

Fig. 1: Children playing with stray dog. A picture captured in a village in Pakistan.

because of dog bites during international travel. Among 89 infections present in the US, 62 (70%) are reported to be because of bats. In 2021, only one case of human rabies was recorded in the US in nearly 3 years (Pearson et al. 2019).

1.6. RABIES IN EUROPE

Very few cases of rabies are reported annually in Europe.

1.7. RABIES IN UNITED KINGDOM

The United Kingdom was declared free of rabies in the early 20th century except for rabies-like European bat 2 lyssavirus (EBLV-2) in a few Daubenton's bats (Easmon 2003). In 1902, last death from indigenous rabies was reported from UK (McIntyre et al. 2003). Since 2000, there have been4 deaths reported due to rabies that were transmitted due to dog bites in international travels.

1.8. RABIES IN SWEDEN AND NORWAY

Sweden and Norway were declared free from rabies in 1886. Rabies antibodies were found in bats but no virus was found (Tryland et al. 2022).

1.9. RABIES IN MEXICO

Mexico was certified by WHO as being dog-transmitted free rabies in 2019 because no case of dog-human transmission was recorded in 2 years.

2. ETIOLOGY OF RABIES

Rabies virus belongs to the family Rhabdoviridae, and order Mononegavirales. It is a negative-stranded RNA virus having bullet shape. It consists of three genera of animal viruses including, Lyssa virus, Ephemer virus, and Vesiculo virus. Genus Lyssa virus includes Rabies virus, Mokola virus, Duvenhage virus, European bat virus 1 & 2, and Australian Bat virus. The RNA genome of Lyssa viruses is 12 kilo bases long and not divided into segments. It is of negative polarity, encoding 5 viral proteins (3' to 5') including nucleoprotein N, phosphor protein P, matrix protein M, glycoprotein G, and polymerase L. Its size ranges from 100-300nm long and 75nm in diameter (Hyatt et al. 1998).It is composed of two functional and structural units:
The outer envelope is made up of a lipid bilayer. Spike-like projections corresponding to G-Protein trimmers are present on it. These spikes recognize and bind cell receptors. While G-protein is important for Lyssavirus pathogenicity and also for induction of immune response (Juozapaitis et al. 2007).
The internal ribonucleocapsid (RNP) is made up of genomic RNA associated with protein N, polymerase L, and its cofactor protein P. This internal structure ensures genomic transcription and replication in the cytoplasm. Ribonucleocapsid is of helical structure (Granzow et al. 2010).
The matrix protein M is present in the middle of ribonucleocapsid and envelope. It is responsible for the bullet-shaped morphology of the virus and its budding (Granzow et al. 2010).

3. PATHOGENESIS AND CLINICAL PRESENTATION OF RABIES

3.1. PATHOGENESIS

The virus is excreted in the saliva of an infected animal and deposited through the skin into subcutaneous tissue and muscles of the host (Suja et al. 2016). After entry, the virus binds to the cell receptors. It replicates within striated muscles or connected tissue at the site of inoculation and then enter peripheral nerves by a neuro-muscular junction (Chakrabharti 2007). After infection takes place within the neuronal cell the virus starts using host machinery, as it reaches cells of the spinal cord, brain stem, and sensory ganglia where replication occurs (Fooks, Banyard et al. 2014). Then the virus travels by fast axonal from the spinal cord to the brain, and up to this stage, no clinical sign appears as insufficient viral antigens are present to trigger an immune response of the body. After reaching central nervous system (CNS), the virus replicates extensively and, in this stage, clinical signs appear and it can become fatal for the animal (Banyard et al. 2014). Extensive infection spreads in the brain and leads to virus dissemination by neurons into different body sites. Rabies virus now reaches peripheral sites and eventually reaches non-nervous tissue like taste buds, olfactory cells, thymus, salivary glands, and pass in to oral and nasal secretions (Chakrabharti 2007). The salivary glands are innervated by the parasympathetic nervous system by submandibular ganglion and glossopharyngeal nerves, sympathetic innervation by the superior cervical ganglion, and by the afferent innervations (Banyard et al. 2014). On invading the brain, virus damages the brain stem and medulla causing nerves to undergo degeneration. Ultimately, paralysis of various muscles and clinical signs become visible (Chakrabharti 2007).
Atthe microscopic level, neural degeneration and perivascular infiltration occur. Formation of Negri Bodies is the characteristic feature for the identification of rabies (Chakrabharti 2007). They are granulated structures observed on the site of replication.

4. INCUBATION PERIOD

Incubation periods vary greatly among different species. Generally, it ranges from 1-3 months in dogs. In some cases, it is also extending up to years. In human sit mostly lasts for 3-8 weeks, and sometimes more than 6 months (Iowa 2015). Incubation period variation depends upon factors including the age of the animal, virulence of the virus, virus concentration, severity of bite, and distance of bite from CNS (Chakrabharti 2007). The nearer the bite is from the CNS more rapidly infection develops and clinical signs appear (Baron 1996). It also depends upon the species of animal. The virus hides in safe sanctuaries in the host during prolonged incubation periods (Suja et al. 2016).

5. CLINICAL STAGES AND SYMPTOMS OF RABIES

5.1. RABIES IN HUMAN

Five stages of rabies are found in humans, incubation, prodrome, acute neurologic period, coma, and eventually death (Baron 1996). After the incubation period, prodome stage appears characterized by pain, numbness, and itching at the site of the bite, and nonspecific clinical signs are likely to appear including pyrexia, fatigue, and headache. Changes in behavior become apparent like anxiety, agitation, insomnia, and depression. The prodromal phase is followed by the neurological phase which causes hallucinations, disorientation, paralysis, hydrophobia, hyperventilation, hypersalivation, and seizures followed by coma and death (Iowa 2015).

5.2. RABIES IN DOG

In animals, rabies is mostly differentiated into two forms based on signs and symptoms; furious (encephalitic) and dumb (paralytic) rabies. Another type, atypical rabies, is also observed.

5.2.1. FURIOUS RABIES

It is characterized by aggressive or excited behavior. In this condition dogs tends to bite inanimate and animate objects, does not obey their master, have violent and frenzy behavior, tend to bite inedible things (like stone, and wires), bite other animals and humans, unusually stay alert, tend to bite imaginary objects, drooling of saliva, pupil dilation, lacrimation, hydrophobia, hallucinations, aerophobia. Paralysis of pharyngeal and laryngeal muscles leads to the paralysis of throat muscles hence dog may be unable to swallow food and drink water (Chakrabharti 2007).
As the condition becomes severe, dog becomes more aggressive, photophobia occurs, excessive sweating, protrusion of tongue, characteristic change in the bark, dyspnea, ascending paralysis and coma. This condition may last for as long as 10 days, and eventually death occur (Chakrabharti 2007).

5.2.2. DUMB RABIES

Paresthesia and weakness are characteristic of the onset of the disease (Suja et al. 2016). In this form there is paralysis of the lower jaw, tongue, larynx, and hindquarters, the dog can’t bite but the saliva is still infected. Dogs are unable to bark due to the paralysis of throat muscles. Dog produce voices like howling. Moreover, dogs can’t close their mouths because of the hanging of lower jaw. Excessive gagging may also be observed (Chakrabharti 2007).In the terminal stages, the dog shows progressive weakness and paralysis

and ultimately proceeds to coma and death This form lasts for up to 1-7 days. To more or less extent, rabies virus also affects other animals like cats, horses, cattle, sheep, goats, and pigs (Chakrabharti 2007).

5.2.3. ATYPICAL RABIES

This type is mostly associated with bat bites. It may have symptoms of both furious and dumb rabies. These variations make it very difficult to recognize rabies disease (Rod Brouhard 2021).

6. DIAGNOSIS OF RABIES

Even if a patient may exhibit symptoms that are highly typical for rabies, such as behavioural changes or trouble swallowing clinical observation and examination cannot confirm the diagnosis and can only raise suspicion of rabies. The only way to make a conclusive diagnosis of rabies is to find the virus or some of its particular components using the recommended standard laboratory tests from the WHO and OIE WHO (2013).
In both humans and animals, brain tissue is the ideal specimen for post-mortem diagnosis. The only way to reliably identify an infection in a patient who is suspected of having the disease is intra-vital testing of rabies in animals, that even though it is generally discouraged. The foundation of intra-vital diagnostics in suspect human patients is virus or viral RNA detection (CDC 2011).

7. FINDING THE RABIES ANTIGEN

The fluorescent antibody test (FAT) is most widely used primary diagnostic test for rabies diagnosis in humans and animals. This test is based on antigen detection and regarded as the gold standard for diagnosing rabies by the WHO and OIE. An impression smear formed from a composite sample of brain tissue is treated with anti-rabies serum or globulin that has been fluorescently labelled with fluorescein isothio cyanate (FITC). The fluorescence of certain clumps of rabies virus antigen can be used to identify them under a reflected light (incidental light) fluorescence microscope. The precision, sensitivity, and speed of the FAT allow for results to be routinely obtained within 1 to 2 hours of receiving the specimen. A direct rapid immune histochemistry test (dRIT) is an alternative to fluorescence microscopy (Mani and Madhusudana 2013).

7.1. DIRECT MICROSCOPY: HISTOLOGICAL IDENTIFICATION OF CHARACTERISTIC CELL LESIONS

Histological studies (Seller's Technique) on smears taken from different regions of the brain show aggregation of virus particles called "Negri bodies" which are intra-cytoplasmic inclusion bodies specific to rabies infected neuronal cells. Negri bodies range in size from 3 30mm in diameter. These bodies are often circular or oval, and are profoundly eosinophilic with distinctive basophilic granules that are frequently grouped in the shape of a rosette inside the eosinophilic matrix (Ravisse et al. 2017).
Seller's method on unfixed tissue smears is a straightforward, quick test, but it only works on fresh samples and has a relatively poor sensitivity. Staining methods for paraffin-embedded sections of brain tissue take longer, are more expensive, and are less accurate. Histological techniques are much less sensitive than immunological methods, especially in the case of autolyzed specimens, and are no longer recommended for primary diagnosis, both in humans and animals (Ponfa et al. 2016).

7.2. CLINICAL EVALUATION

When evaluating a suspected case of rabies, healthcare professionals typically consider the following clinical factors:

7.3. CLINICAL SIGNS AND SYMPTOMS

7.3.1. EXPOSURE HISTORY

To assess the risk of rabies transmission, a detailed study of the patient's history is necessary. The main topics of discussion should be possible animal contact, especially bites and scratches, as well as any trips to areas where rabies is an endemic disease.

7.3.2. INCUBATION PERIOD

The rabies incubation period can last anywhere from a few days to several years. The amount of time that has passed since the patient may have been exposed to the virus is crucial since it can assist in predicting the possibility of rabies infection (Sajjad et al. 2017).

7.3.3. DIAGNOSTIC TESTS

Typically, laboratory testing is necessary for a rabies diagnosis. The direct fluorescent antibody (DFA) test is used to find the rabies virus in skin biopsy samples taken from the nape of the neck. Additionally, viral RNA can be found in saliva, cerebrospinal fluid, or tissue samples using the reverse transcription-polymerase chain reaction (RT-PCR) (CDC 2011).

7.3.4. PROGNOSIS

Once rabies clinical symptoms appear, the condition is nearly invariably fatal. Since there are so few confirmed cases of survival, prompt post-exposure prophylactic delivery and early diagnosis are crucial (Nadeem and Panda 2020).

7.3.5. POST-EXPOSURE PROPHYLAXIS (PEP)

PEP entails meticulous wound cleaning, rabies vaccination, and injection of rabies immunoglobulin (RIG) for those who have experienced high-risk exposures. To increase the possibility that rabies symptoms won't manifest, PEP should be started as soon as possible.

8. LABORATORY TECHNIQUES FOR RABIES DIAGNOSIS

Laboratory methods that can identify the presence of the virus or its antibodies in the body are frequently used to diagnose rabies. Here are a few typical methods used in laboratories to identify rabies (Rao 2019).

8.1. DIRECT FLUORESCENT ANTIBODY (DFA) TEST

The most popular and trustworthy laboratory test for rabies diagnosis is DFA. It involves using fluorescent dyes that precisely bind to the rabies virus antigens to stain samples of brain tissue from the suspected animal or human. The diagnosis is supported by the discovery of fluorescently labelled viral particles (Fooks et al. 2018).

8.2. POLYMERASE CHAIN REACTION (PCR)

The PCR method is used to detect and amplify the genetic material (RNA) of the rabies virus. It is a very sensitive technique that can find very small amounts of the virus. PCR is frequently applied to samples of cerebrospinal fluid, saliva, or brain tissue (Isloor et al. 2018).

8.3. SEROLOGY

These tests are frequently used to verify prior virus exposure or to evaluate the efficacy of rabies immunization. The IFA is most popular serological test for rabies WHO (2013). Other test is ELIZA and RFFIT (Rapid Fluorescent Focus Inhibition Test).

8.4. VIRUS ISOLATION

In this method, the rabies virus is grown in laboratory animals (such as mice or cell cultures) by injecting brain tissue samples or other body fluids into the animals. Virus isolation is less frequently employed than other diagnostic techniques because it takes time and sophisticated equipment (Huang et al. 2018).

8.5. HISTOPATHOLOGY

Brain tissue samples from probable rabies patients can reveal distinctive changes through histopathological analysis, including inflammation and the presence of inclusion bodies (Negri bodies). This method is often used in conjunction with other laboratory tests because it cannot reliably confirm a diagnosis on its own.

9. IMMUNOHISTOCHEMISTRY (IHC)

The rabies virus antigen can be found in formalin-fixed tissues using IHC procedures, which are sensitive and specific. Before being embedded in paraffin and sectioned onto formalin-fixed paraffin-embedded slides, tissues treated in formalin must first be processed using standard histologic techniques. Specifically designed anti-rabies monoclonal or polyclonal antibodies are used to identify the rabies viral antigen. Compared to histologic staining techniques like hematoxylin and eosin (H&E) and Sellers stains, IHC testing is more sensitive and precise (Alizadeh et al. 2019). Fig. 2 and 3 shows the positive and negative results for the presence of virus inside the brain neural cells.

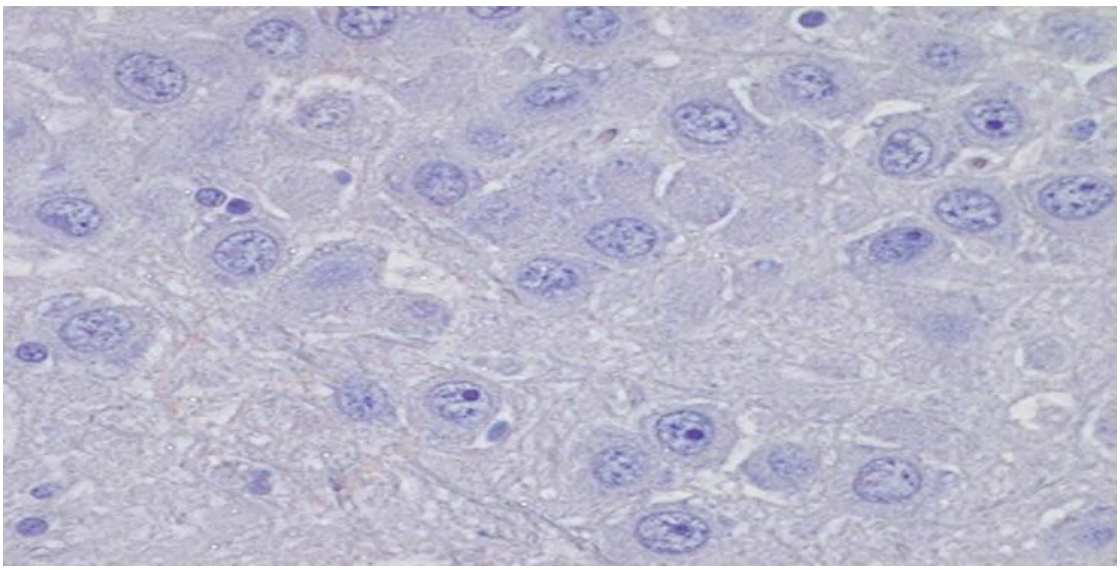

Fig. 2: Brain neural cells with intracytoplasmic inclusions that have been infected with rabies. Using the Streptavidin-biotin complex staining technique, the red stain denotes the presence of rabies viral antigen.

10. SEROLOGICAL TEST

There isn't currently a widely used serological test for identifying human rabies. The direct fluorescent antibody (DFA) test, which includes evaluating brain tissue samples for the presence of the rabies virus, is the only procedure that can be relied upon to accurately diagnose rabies. Usually, this test is carried out after death. The most frequent way to identify rabies in live animals is by looking for certain clinical signs and symptoms and a history of possible virus exposure. The signs and symptoms of rabies can resemble those of other neurological disorders, but they are not unique to rabies. The use of serological techniques, such as enzyme-linked immunoassays (ELISAs), to find rabies antibodies in blood is possible, although these tests are not thought to be diagnostic for an ongoing rabies infection (Singh et al. 2017).

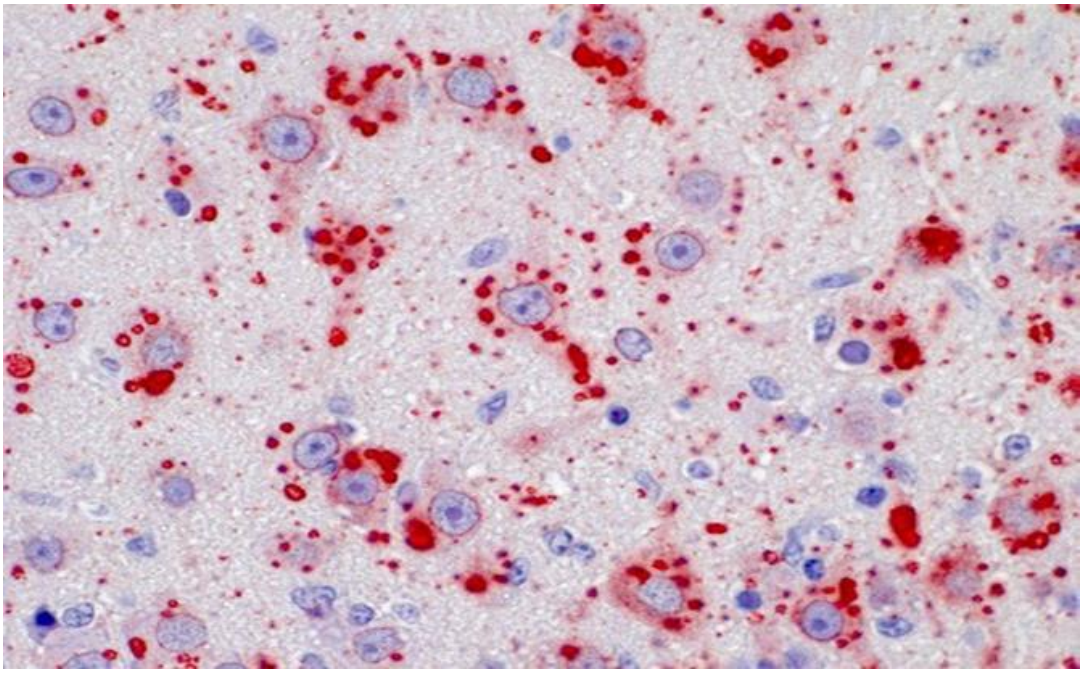

Fig. 3: A result of negative IHC. IHC examination of brain tissue revealed no rabies viral antigen, indicating that no rabies virus was present.

11. DIFFERENTIAL DIAGNOSIS

Here are some conditions that may be considered in the differential diagnosis of rabies.

11.1. OTHER VIRAL ENCEPHALITIDES

Symptoms of rabies can also be caused by illnesses like herpes simplex encephalitis, West Nile virus encephalitis, and Japanese encephalitis. Additionally, these disorders may show neurological signs, a fever, and a change in mental status (Warrell et al. 2017).

11.2. BACTERIAL MENINGITIS

Symptoms of bacterial infections, such as meningococcal meningitis or pneumococcal meningitis, which include fever, headache, stiff neck, and altered mental status, can resemble those of rabies. However, the onset of these illnesses is frequently more abrupt, and they may be accompanied by other infection-related symptoms (Harris and Wittler 2017).

11.3. TETANUS

Tetanus is a bacterial infection brought on by the toxin-producing bacteria *Clostridium tetani*, often known as lockjaw. Muscle spasms, breathing issues, difficulties swallowing, and rigidity of the muscles are possible symptoms. Tetanus and rabies are distinct diseases, yet they could exhibit some of the same neurological signs (Sykes and Creedon 2021).

11.4. GUILLAIN-BARRÉ SYNDROME (GBS)

A rare form of inflammatory disease called GBS damages the peripheral nerves. In severe situations, it might result in paralysis, numbness, tingling, and muscle weakness. Due to neurological symptoms, GBS can occasionally be confused for rabies, however, there are usually no signs of violent behaviour or hydrophobia (Göktepe et al. 2016).

11.5. ACUTE INTERMITTENT PORPHYRIA

The accumulation of porphyrins in the body characterizes this uncommon hereditary condition. Abdominal pain, neuropsychiatric abnormalities, and autonomic dysfunction are possible symptoms. Seizures and neurological symptoms that match those of rabies can occur in severe cases (Lau 2019).

12. TRANSMISSION

There are various routes of transmission of zoonotic agents. Some are transmitted through skin contact without any breakage in the skin's integrity i.e., sarcoptic mange. In case of some diseases breakage in the skin's integrity is essential for transmission like rabies (Acha 1987). A study conducted in the USA in 2009 showed that there were 6690 cases of rabies reported. Wildlife accounts for 93% of the reported cases while that of the domestic animals was7% (Palmer et al. 2011). The saliva of mammals may also contain the rabies virus which may be transmitted through the bite of a rabid mammal. Many cases of rabies from the bites of domesticated animals i.e., cats or rabid cattle had been reported. Various studies from Asia suggest dog bites as the common cause of rabies (Baer et al. 1963; Geneva 2005).

The host species of rabies virus are canine, livestock species, mongoose-associated rabies, felines, raccoon, skunks, vampire bats, and Coyotes(Lima 2013).

About 90% of the infections result from the bite of domesticated animals like dogs and cats due to their close association with human beings. Scratches on the skin infected with saliva have a 50% less risk of infection (Laothamatas et al. 2002; Rupprecht et al. 2008). Mucous membrane exposure and oral routes are ineffective (Abelseth et al. 1971). Intranasal exposure to aerosol droplets is quite dangerous because the olfactory nerve spreads directly to the brain, but natural transmission through this route rarely occurs (Fashinell et al. 1973; Phillpotts et al. 2006). Aerosol inhalation of the rabies virus was observed in a laboratory worker working on the production of a vaccine from brains of rabid sheep and in people inhabited in caves by infected bats (Gibbons 2002).

- Human-to-human rabies transmission is rare but some cases are reported i.e. Donor tissues infected with rabies used for transplantation, similar is the case of recipients of corneal graft (Burton et al. 1979; Fayaz et al. 1996; Wilde et al. 2007; Frisch et al. 2011).
- In some other cases related to the organ transplant from the donor died of rabies (Burton et al. 2005; Schwarting et al. 2010).
- No transfer of infection was recorded from the bite inflicted by rabies-infected humans. Contact of healthcare workers with urine, blood, feces, and non-infectious fluid doesn't cause exposure to disease.

Transmission of virus from mother to breastfed infant has been reported due to the viral secretions in breast milk (Dutta 1998).

- No transplacental transmission has been reported either naturally as well as experimentally in mammals, bats, and dogs (Allen et al. 1963; Montes et al. 1973; Howard 1981).
- Some cases of human rabies during pregnancy have been reported but infants survive through PEP and in some cases without any PEP (Leitritz et al. 1977; Lumbiganon and Wasi 1990; Dacheux et al. 2008).
- There is a risk of transmission of rabies from bats to terrestrial animals.
- Rabies can be transmitted to rabies-free zones and far-off places by the transportation of rabid dogs or other mammals to that area (Wilde et al. 2004; Clifton 2010).

12.1. TREATMENT

Once the clinical signs of rabies become obvious showing that the virus has affected the nervous system, then it is difficult to cure the disease and becomes fatal for both animals and human (Acha 1987).Rabies is a viral disease so no such treatment protocol has been discovered so far to treat this disease but through prevention and control strategies this disease can be prevented (Control and Prevention 2004).

12.2. PREVENTION

Yet the individual affected by the bite of a rabid animal can be prevented from catching the disease, through prophylactic measures taken before the virus could reach the nervous system WHO (2011). WHO stresses on instant and thorough washing of wounds with soap and clean water. After washing apply disinfectants as this reduces the viral load and removes saliva from the wound (Baer et al. 1963).
World Rabies Day was first organized in 2007 by CDC and Alliance for Rabies Control in collaboration with WHO, PAHO, and OIE. This is an important initiative for rabies-affected countries. This includes awareness campaign about rabies through print media and electronic media, seminars and workshops in educational institutes, walks, rallies, different competitions, and free vaccination camps for dogs (Costa 2009).Now it is celebrated every year to create awareness about rabies and preventive strategies to combat rabies.

12.3. CONTROL

Rabies in dogs has been controlled successfully throughout the America while in Western Europe it has been eliminated from dogs and wildlife. Dogs are the main cause of human rabies and accounts for 99% of rabies cases in humans. Therefore, our priority must be to control rabies in the dogs, especially in stray dogs. In this way, we can reduce human rabies cases (Reece and Chawla 2006; Wandeler et al. 2010; Meslin and Briggs 2013).

12.4. VACCINATION PROGRAM

Early neuron tissue vaccine was poorly immunogenic and was made from neuronal tissues of animals. Several doses of vaccine are administered to induce sufficient immunity. Later on in 1940s, these vaccines were replaced by highly immunogenic and safer CCVs (cell culture-derived vaccines) (Warrell 2012).
Pre-exposure prophylaxis (PrEP) is important for individuals travelling to endemic countries. After PrEP, a booster dose is necessary to keep antibody titer high. Booster doses should be administered following the guidelines from the manufacturers (Gautret and Parola 2012).

PrEP vaccine three doses are given through the intramuscular route or intradermal route on following day 0, 7, and 21 (Keates 2010). Table 1 shows the post exposure rabies vaccination regimens recommended by the WHO and the advisory committee on immunization practices by Regimen.

Table 1: The post exposure rabies vaccination regimens recommended by the WHO and the advisory committee on immunization practices by Regimen**.**

	No. of Vaccine Doses	Administration Route	Schedule of Injection
Pre-Exposure Prophylaxis			
Routine intramuscular	3	Intramuscular	At Days 0, 7,21or 28 (single doses)
Routine intradermal	3	Intradermal	At Days 0, 7, 21, or 28 (single doses)
Post Exposure Prophylaxis			
Essen	5	Intramuscular	At Days 0, 3, 7, 14, 28 (single doses)
Zagreb	4	Intramuscular	At Days 0 (double doses), 7, 21 (single dose)
Reduced Four doses	4	Intramuscular	At Days 0, 3, 7, 14 (single dose)
Modified Thai Red Cross	8	Intradermal	At Days 0, 3, 7, 28 (two doses)
Post-exposure Prophylaxis for Vaccinated People			
Two-dose intramuscular	2	Intramuscular	At Days 0, 3 (single dose)
Four-dose intradermal	4	Intradermal	At Day 0 (four doses)

13. PRE-EXPOSURE PROPHYLAXIS

PrEP is a feasible strategy in combating rabies, especially in cases resulting from disguised or unseen exposures and in cases of delayed PEP. The dog bite patients who have been previously immunized through PrEP don't need RIG. PrEP is highly recommended by the WHO for those people working in high-risk exposure conditions i.e., in research or diagnostic laboratories, veterinarians, wildlife officers, animal rehabilitators and handlers. Research shows that children are at high risk exposure to rabies, therefore WHO also recommends vaccination of Children in highly endemic areas (Warrell 2012).

13.1. POST-EXPOSURE PROPHYLAXIS

Unfortunately, there is a lack of awareness in developing countries like Pakistan, Sri Lanka, Bangladesh etc (Dodet, Goswami et al. 2008). In Pakistan, private institutes use cell culture vaccines for PEP while rabies immunoglobulin (a life-saving biological agent used for PEP) is not available in any government institution because of its high cost (Chotani et al. 2004).

According to WHO Standards, the categorization of wounds after the bite will be helpful in further management. According to the severity of the bite it is categorized as category I: it is a non-bite and requires no PEP),category II: It is of moderate risk and skin integrity breaks, requires wound cleaning and vaccination, category III: high risk, multiple wound and provide rabies immunoglobulin and vaccination (Geneva 2005).

Two types of regimens are used for rabies PEP, first is the Modified TRC Regimen (intradermal application)which is mostly used in developing countries and is economical, the second is Essen regimen used intramuscular (WHO 2013).

The medical professional must be trained in the rabies wound classification and WHO-approved PEP protocols. Also, the provision of a free supply of rabies immunoglobulin and Cell culture vaccine should be ensured (Geneva 2005; Dodet and Bureau 2006).

The following are the guidelines of WHO for PEP (Organization 2000; Geneva 2005).

1. According to WHO recommendations instant and thorough washing of wounds with soap or any other detergent is recommended after a dog bite. If nothing is available then wash the wound extensively with fresh water.

2. WHO classified the RIG into three classes that have been made so far: ERIG (equine rabies immunoglobulins), HRIG (human rabies immunoglobulins), pERIG (highly purified equine rabies immunoglobulins). These RIGs should be administered at the wound site to neutralize the rabies virus before it affects the nerve endings.
3. Vaccination playsan important role in PEP.WHO recommended the use of a cell culture vaccine instead of a nerve tissue vaccine.
The primary goal in the twenty-first century is to increase cooperative efforts to eradicate canine rabies, which will reduce human fatalities (Banyard 2013). In many countries, canine rabies has been eliminated but in underdeveloped countries it is still present (Meslin and Briggs 2013).
The multidisciplinary approach should be the main emphasis of the strategy plan for eliminating canine rabies. It includes representatives from the governmental and private sectors, such as decision-makers, vaccine producers, veterinary professionals, researchers, and medical professionals (Taylor and Prevention 2013).
This collaborative multidisciplinary approach to combat rabies is also called the One Health Approach. It is an important step to combat rabies through mass vaccination and solicitous management of dogs (Attlan et al. 2011).

13.2. CULTURAL BELIEFS AND TRADITIONAL MEDICINES USED FOR RABIES

Globally, people have different beliefs and traditional medicines that are widely used to treat a variety of injuries and illnesses, including dog bites, and exposures that are risky for rabies. However, the beliefs and efficacy of most traditional remedies used for rabies prevention or treatment have not been demonstrated in controlled trials or proven in community-based surveys (Wallace et al. 2022).
In the first century A.D., the Roman scholar Celsus recommended that rabies was transmitted by the saliva of the biting animal. He incorrectly recommended keeping the patient underwater as a rabies treatment. The rabies killed those who did not drown. Other cruel treatments for rabies included using a hot poker and a "hair-of-the-dog" to burn open sores. In homeopathic medicine, the concept of *"similar,"* or *"like cures like,"* is used. The patient swallowed or applied rabid dog hair to the wound. While a hair-of-the-dog may cure a hangover, it did nothing to cure rabies. The usage of "mad stones" to treat rabies in 18thcentury America attracted the greatest interest. Mad stones are calcified hairballs that are discovered in ruminant animals' stomachs, including those of cows, goats, and deer. It was believed that they might extract the lunacy from the bite wound, rendering them therapeutic. Madstones was highly regarded and considered more valuable than rubies and were passed down through generations as '*family jewels*'. In 1805, a mad stone sold for $2000 in Essex County, Virginia (O'Niell 2017).
When a person or their animals are bitten by a dog in India, low-caste tribes adore the Hindu deity Hadkai Mata as the mother of Rabies. This concept might influence people's attitudes and behaviors about rabies prevention, even though it has never been studied. Hindus say that human rabies is typically the goddess's attempt to chastise disobedient individuals and improve interpersonal relationships. There is a basic understanding of the biochemical mechanisms of infection that result in rabies as a physical illness. If her victims go through the required phase of moral development, Hadkai Mata is thought to be able to heal rabies. Although there is no opposition to standard post-exposure prophylaxis, those who choose conventional treatment first usually put off getting it. The widespread vaccination of dogs has been greeted with some opposition since it is believed to interfere with the goddess's control over them by enraging, and sending them to bite wrongdoers. To effectively reduce dog rabies in this area, it is likely essential to address these cultural attitudes (Hampson et al. 2022).
Compared to 90% of persons in other countries, the majority of dog bite patients in Pakistan did not seek hospital care following a dog bite. This mindset and behavior significantly contribute to the rise of rabies-

related mortality in Pakistan. Additionally, it has been noticed that some people avoid going to hospitals in favor of traditional rabies cures and spiritual healers. Additional accounts of a prospective rabies patient seeking a spiritual healer in India and Africa exist. They may have investigated several spiritual healers, many of whom offer services at no cost. It is usual in Pakistan to send the victim to a spiritual leader or shrine after they have been bitten by a dog to receive blessings and take part in a "dam" (spiritual healing rite). As part of this procedure, the patient continues to receive spiritual care at the shrine across numerous visits spaced over a few weeks. If the patient's health doesn't get better in some situations, they might be isolated and kept away from other people. The patient unfortunately succumbs to his or her injuries in the end (Hussain et al. 2020).

Studies have shown how important multidisciplinary strategies are for containing and eradicating zoonotic illnesses like rabies. This includes the significance of comprehending various cultural and religiously mediated ways in which humans relate to animals; searching for points of agreement and mutual understanding; and developing context-tailored, linguistically accurate, locally acceptable, feasible, and effective strategies (Hampson et al. 2022).

14. CONCLUSION

The multifaceted nature of rabies demands a comprehensive approach encompassing epidemiology, pathogenesis, clinical presentation, diagnosis, and preventive strategies. Rabies, a disease with a history spanning over 4,000 years, continues to exert a significant toll on public health, particularly in Asia and Africa, where the majority of human deaths occur annually. The economic burden of rabies, estimated at over 4 billion dollars per year, highlights the urgency of addressing this neglected disease. The epidemiological landscape of rabies reflects a global presence, with over 95% of human deaths concentrated in Asia and Africa. India, China, and the Democratic Republic of Congo are particularly affected, demonstrating the need for region-specific interventions. In Pakistan, the endemic nature of rabies is exacerbated by inadequate medical training, low awareness, and a shortage of vaccines. The reliance on the indiscriminate killing of stray dogs as a preventive measure reflects a failure in controlling the disease.

Diagnostic methods, including the Direct Fluorescent Antibody Test (FAT), Polymerase Chain Reaction (PCR), and histopathology, play pivotal roles in confirming rabies. The importance of prompt post-exposure prophylaxis (PEP) cannot be overstated, as clinical symptoms signal an almost invariably fatal outcome. The lack of awareness in developing countries, such as Pakistan, underscores the need for education and accessible PEP, including rabies immunoglobulin and cell culture vaccines. Preventive measures, including vaccination programs and the One Health Approach, are vital for controlling rabies. Successful efforts in canine rabies control in developed regions serve as models for implementation in underdeveloped countries. Pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) guidelines, as outlined by the World Health Organization (WHO), provide a framework for effective intervention.

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Zika Virus: An Arboviral Disease

17

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ABSTRACT

The Zika virus (ZIKV) has emerged as a serious threat to global health. To fully understand the virus's epidemiology, virology, dynamics of transmission, clinical symptoms, implications for public health, and preventive and control measures, extensive research and collaboration have been conducted. The virological investigation compares strains from Asia and Africa and highlights distinctive features present in the virus's genome to investigate the genetic variability of ZIKV lineages.

The chapter delves into the complex processes of Zika virus transmission, specifically highlighting the primary carriers—Aedes aegypti and Aedes albopictus mosquitoes. It elucidates not only the conventional vector-borne pathways but also non-vectoral modes like blood transfusion and sexual contact. It comprehensively details the diverse clinical manifestations of ZIKV infection, placing particular emphasis on the profound impact on expectant mothers and its link to neonatal Zika illness. Symptoms vary from mild, resembling dengue fever, to severe neurological complications, presenting a spectrum of health challenges.

The significance of ZIKV for public health is underlined, underscoring the critical requirement for effective preventive and control interventions. The chapter advocates for a comprehensive plan that includes mosquito control methods, vaccine development, and public awareness initiatives to lessen the spread of ZIKV. The paper also examines the challenges and potential solutions for managing and preventing ZIKV, including mechanical, chemical, and biological approaches to mosquito population reduction.

The final sections of the chapter delve into ongoing research and progress in treatment strategies for Zika virus (ZIKV), exploring potential treatments and their mechanisms of action. The abstract concludes by underscoring the critical importance of collaboration among academia, policymakers, and the global health community. This collaboration is essential to collectively address the multifaceted challenges posed by ZIKV and mitigate its adverse impact on public health.

Keywords: Zika Virus, Arboviral disease, Virology, Transmission dynamics, Clinical manifestation, public health implications, Prevention and control strategies

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1. INTRODUCTION

After being discovered in 1947 in Uganda, the Zika virus (ZIKV) was initially restricted to equatorial Africa and Asia for 60 years, but it was first discovered outside this region in 2007 on Yap Island. From there, the virus spread to other Pacific Islands in 2013–2014, then to Latin America in 2015, and finally to North America in 2016. Its connection to fetal microcephaly caused made it a health emergency in 2016. (Ramos da Silva and Gao 2016; Song et al. 2017). The United States' Center for Disease Control and Prevention (CDC) has confirmed 4,944 and 36,367 cases of Zika Virus in USA. Infection with ZIKV has so far been documented in 66 countries. ZIKV, which has been identified as a neurotropic virus, has been connected to several diseases, primarily in countries that were exposed to it during the Federated States of Micronesia pandemic in 2007, which showed up as a variety of neurological problems. The most noticeable consequence of ZIKV infection that has been noticed is the abrupt increase in fetal microcephaly incidence in Brazil (Ramos da Silva and Gao 2016).

A Brazilian outbreak that was characterized by a rash-like skin eruption accompanied by pyrexia and a dramatic rise in the number of infants and fetuses with microcephaly at the end of 2015 made the Zika virus (ZIKV), which was first identified 70 years ago, a public health concern (Duffy et al. 2009; Teixeira et al. 2016). Since then, researchers from all over the world have been frantically trying to understand the pathogenesis of ZIKV infection. They are particularly interested in discerning the differences between the infection brought on by the first described strain of African MR766, which only caused a few mild symptoms. Additionally, they aim to compare it to the infection found in Asia in 2007 on Yap Island of the Federated States of Micronesia and later in French Polynesia in 2013, which resembles the infection in Brazil. Nearly every day, fresh scientific data about ZIKV is made public (Duffy et al. 2009; Bradley and Nagamine, 2017; Krause et al. 2017).

In Uganda's Zika Forest, ZIKV was initially discovered in a monkey in 1947 and an Aedes africanus in 1948 (Lanciotti et al. 2008). In the following years, the outbreak occurred in individuals across several regions of Africa as well as South and Southeast Asia (Wikan et al. 2017) Based on the area, Zika virus virus outbreaks from 2007 to 2015 had differential influences. Only modest symptoms such as a fever, headaches, and skin rashes were reported by the majority of Yap Island's inhabitants during an epidemic in 2007 (Khatri et al. 2018.) In 2013, the virus was transmitted to French Polynesia (Cao-Lormeau et al. 2016).

ZIKV was discovered for the first time in Brazil in 2015. The number of infants and fetuses with microcephaly had accelerated by the end of the year (Cardoso et al. 2015). Infections with Zika virus infection was deemed a Public Health Emergency of International Concern by the World Health Organization (WHO) in February 2016 (Heymann et al. 2016) and the United States Center for Disease

Control and Prevention (CDC) confirmed the link between ZIKV infection and microcephaly in April 2016 (Rasmussen et al. 2016).

2. VIROLOGY

This far, description of the ZIKV lineages from Asia and Africa have been published. The variants isolated from samples in Brazil between 2015 and 2016 were strikingly identical to the Asian strains as well as the French Polynesia strain (Giovanetti et al. 2016; Sheridan et al. 2018). A part of the Flavivirus genus and the Flavivirus family, ZIKV is an arbovirus which also includes the following viruses: Dengue virus (DENV-1 through DENV-4), West Nile virus (WNV), Japanese encephalitis virus (JEV), and Yellow fever virus (YFV) (Gubler and Musso 2016).

Single full gene encodes (ORF), less than 11 kb in size, makes up the ZIKV genomes. It comprises seven non-structural proteins, such as NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5, in addition to various structural proteins, as well as the capsid, envelope glycoprotein (E), membrane (M), or premembrane (prM), are also present like other flaviviruses. Depending on its newly disclosed 3.8 structure, the E protein's amino acids near Asn154 show significant variation from those of other flaviviruses (Sirohi et al. 2016). This glycoprotein possesses a glycosylation site for ZIKV at Asn154, while DENV has two glycosylation sites at Asn67 and Asn153 that influence viral assemble, escape, and pathogenicity, correspondingly (Ruiz Jimenez et al. 2022).

ZIKV encompasses an Asn154-based glycosylation location that has been connected with neurotropism. Differences in the glycosylation sites may be accountable for alterations in the phenotypic expression, pathogenicity, viability, and virulence of different strains of ZIKV (Beasley et al. 2005). However, it's uncertain whenever the variations arose in the initial isolated strains —possibly pushed on by the rapid spread African strains lacking specific glycosylation regions. The Asian and African lineages of ZIKV differed in 59 amino acids, with 10% of these mutations appearing in the prM region, as per a comprehensive examination of the available isolates (Wang et al. 2016).

One of the NS proteins named NS1, which also features N-glycosylation sites, is essential for the proliferation and subsequent invasion of flaviviruses (Muller and Young 2013). There seem to be distinctive electrostatic prospects between ZIKV, DENV, and WNV that may be included in the ZIKV NS1 due to the structural changes that have been recently discovered. The discrepancies in pathogenicity between these viruses and other ZIKV strains may be elucidated by these data. Numerous isolates from Brazil exhibited an NS1 mutant region as compared to other Asian strains, albeit the technique used in this study seemed uncertain. Other distinctive aspect of the ZIKV structure is its resilience along a temperature range, from 4 to 40°C (Kostyuchenko et al. 2016).

3. TRANSMISSION

The most prevalent vectors of ZIKV infection in humans are *Aedes aegypti* and *Aedes albopictus* mosquitoes, which are the major means of transmission. The first cycle of transmission is only seen in non-human primates classified as sylvatic, while the second cycle of transmission is through the human-mosquito-human cycle (urban cycle) (Petersen et al. 2016). In Brazil, ZIKV has recently been found in marmosets and capuchin monkeys, the majority of whom are kept as pets (Favoretto et al. 2016).

Recently, further transmission paths have been identified. After the ZIKV epidemic in South America, autochthonous transmission that was not aided by a mosquito has been documented in Brazil and Colombia, including an HIV-positive individual (Calvet et al. 2016). It has also been reported that ZIKV may be sexually transmitted through vaginal, oral, and anal intercourse, and that the virus can be found in

saliva, urine, and semen samples (D'Ortenzio et al. 2016). In a case reported in Italy (Venturi et al. 2016), sexual transmission of the ZIKV from Thailand was documented. Brazil has documented blood transfusion transmission from an asymptomatic donor (Cunha et al. 2016).

4. CLINICAL SIGNS

The incubation period of the Zika virus is reported to be 3-12 days, and in about 80% of the cases, the infection is asymptomatic (Ioos et al. 2014). The asymptomatic patient poses a great threat and is considered a perilous source of virus transmission (Musso et al. 2014). Initially, for 2-7 days, the mild "dengue-like" symptoms are shown by the virus, followed by a wide range of symptoms. The more noticeable signs and symptoms are a slight fever, arthralgia, edema of the extremities, headaches, retro-orbital pain, and maculopapular rashes (Heang et al. 2012). Furthermore, the major clinical symptom that characterizes the Zika virus is the eruption of maculopapular rashes, observed in around 90% of patients. Although the rash remains for 2-14 days, the fever generally lessens within one or two days after the onset of the rash (Mallet et al. 2015).

Normally, the fever is low, but in Brazil, the incidence of severe pyrexia, around 39º C, has also been reported (Zanluca et al. 2015). Regarding the symptoms of the Musculo-skeletal system, the Zika virus causes muscle, joints, and low-grade back pain. The pain is usually observed in the knees, ankle joints, and hands for one week and normally reduces after a week (Cao-Lormeau et al. 2014). Frequently, non-purulent conjunctivitis has also been observed in many cases of Zika virus infection. Other symptoms include vomiting, nausea, dizziness, and retroorbital pain (Moghadam et al. 2016) Infants and Children are also susceptible to Zika virus infection, and similar signs are observed in them as in adults (Lebov et al. 2018).

Likewise, in adults, Children, and infants; it causes arthralgia, characterized by irritability, walking with a limp, or sometimes extreme pain while walking, thus reluctance to walk (Fleming-Dutra et al. 2016). In addition, several congenital infections are linked to the Zika virus. It affects pregnant women in any trimester and causes microcephaly in infants. In Brazil, it has been reported that there was a link between microcephaly and the Zika virus in newborns and even in dead infants (Melo et al. 2016). Children born with microcephaly caused by the Zika virus have been linked to muscle atrophy in many cases in Brazil (Ventura et al. 2016). Similarly, infection with this virus during pregnancy negatively impacts the fetus's outcomes. It causes placental inefficiency, in vitro growth restriction of the fetus, and injury to the central nervous system (Mayor 2016). Moreover, the Zika virus is also responsible for neurological problems, including meningoencephalitis and acute myelitis (Carteaux et al. 2016).

5. PUBLIC HEALTH IMPORTANCE OF ZIKA VIRUS

The Zika virus has emerged as a significant public health concern due to its potential adverse outcomes and rapid spread (Panchaud et al. 2016). Understanding its importance in public health is crucial for implementing effective prevention and control measures. Zika virus infection leads to various diseases and conditions in humans, causing significant health impacts and burden on healthcare systems (Noorbakhsh et al. 2019).

One of the primary concerns associated with Zika virus infection is its effect on pregnant women and their unborn babies. When a woman in pregnancy is infected with the Zika virus, it is transmitted to the fetus, leading to a condition known as congenital Zika syndrome (Chan et al. 2016). This syndrome is characterized by a range of severe neurological abnormalities, including microcephaly, where the baby's head size is significantly smaller than average, indicating improper brain development (Melo et al. 2016).

Additionally, congenital Zika syndrome results in other birth defects, such as eye abnormalities, hearing loss, impaired growth, joint and muscle problems. These conditions have long-term implications for affected infants and their families, requiring specialized care and support (Pomar et al. 2019).

Apart from congenital Zika syndrome, Zika virus infection also causes several diseases and conditions in non-pregnant individuals. Most infected individuals, approximately 80%, do not exhibit any symptoms and are asymptomatic (Paixao et al. 2018). However, those who do develop symptoms may experience mild to moderate flu-like symptoms such as fever, maculopapular rash, joint pain, muscle pain, asthenia, headache, conjunctivitis and peripheral edema at extremities These symptoms typically last for few days to a week and are generally self-limiting (Pomar et al. 2019).

In some rare cases, Zika virus infection leads to more severe complications. One of the notable complications is Guillain-Barré syndrome (GBS), a rare neurological disorder characterized by muscle weakness and potential paralysis. GBS occurs when the body's immune system mistakenly attacks the peripheral nervous system, leading to nerve damage and subsequent muscle weakness (Mier-y-Teran-Romero et al. 2018). Although the association between Zika virus infection and GBS is still being studied, evidence suggests a link between the two, highlighting the importance of monitoring and early detection of GBS cases during Zika outbreaks.

In addition to GBS, other potential complications of Zika virus infection include meningoencephalitis, an inflammation of the brain and meninges, and autoimmune manifestations These complications are relatively rare but underscore the need for further research to fully understand the spectrum of diseases associated with Zika virus infection (Schwartzmann et al. 2017).

The public health importance of the Zika virus lies in its potential to cause significant harm to individuals, particularly pregnant women and their unborn babies. The devastating consequences of congenital Zika syndrome highlight the urgency of prevention and control efforts to minimize the risk of transmission. Preventing Zika virus infection among pregnant women is crucial in reducing the incidence of congenital Zika syndrome and its associated disabilities (Rice et al. 2018).

Furthermore, Zika virus outbreaks also strain the healthcare systems, particularly in regions with limited resources. The need for specialized care and support for infants with congenital Zika syndrome places a significant burden on healthcare providers and facilities (Bailey and Ventura 2018). Investing in surveillance systems, research initiatives, and public health interventions is essential for effectively addressing the public health impact of Zika virus infection (Bailey and Ventura 2018).

6. PREVENTION & CONTROL

Preventing and controlling the spread of the Zika virus is of utmost importance to safeguard public health. There is a need for a comprehensive approach which encompasses various strategies aimed at reducing mosquito populations, implementing personal protective measures, and developing effective vaccines to prevent Zika Virus infection and spread. The viral infection can be haltered by using following strategies (Poland et al. 2018; Singh et al. 2018).

6.1. MOSQUITO CONTROL STRATEGIES

Mosquito control strategies play a crucial role in preventing the transmission and spread of the Zika virus. *Aedes* mosquitoes, particularly *Aedes aegypti* and *Aedes albopictus,* are the primary vectors responsible for transmitting the virus to humans (Gasperi et al. 2012). These mosquitoes are highly adaptive, capable of breeding in small water containers, and have a preference for biting humans. By implementing effective mosquito control measures, we can significantly reduce the population of these vectors and minimize the

risk of Zika virus transmission (Von Seidlein et al. 2017). There are various strategies to control mosquitos transferring this virus. These strategies encompass various methods aimed at controlling mosquito populations, preventing their breeding, and protecting communities from the mosquitoes (Hajra et al. 2016). Effective mosquito control requires the implementation of mechanical, chemical, and biological measures (Araújo et al. 2015). Following are the ways, which could be adopted to curb the mosquito spread of disease.

6.1.1. MECHANICAL CONTROL OF MOSQUITOS

Mechanical control measures are long-standing and cost-effective techniques widely employed in various countries for mosquito population control. These methods involve the removal of objects that collect stagnant water, as they serve as breeding grounds for mosquitoes. Ensuring proper cleanliness of streets, maintenance of buildings and housing units, and promoting personal and community hygiene are integral aspects of this approach. Encouraging the use of mosquito nets on windows and employing mosquito-proof water storage options are also effective strategies. Ovitraps, which are low-cost and require minimal upkeep, can be utilized to reduce mosquito populations (Barrera et al. 2014). It is crucial to raise public awareness about identifying and eliminating potential mosquito breeding sites within residential areas. By adopting a hygienic lifestyle and actively preventing mosquito bites and breeding sites, the risk of mosquito-borne diseases such as Zika virus can be significantly reduced (Bancroft et al. 2022).

6.1.2. CHEMICAL CONTROL OF MOSQUITO

Chemical control measures are employed to combat mosquitoes, primarily targeting their nervous system. The chemicals like Pyrethroids, organochlorides, and organophosphorus compounds are commonly used (Van Den Berg et al. 2012). However, the use of Imidacloprid, thiacloprid, and thiamethoxam demonstrate good efficacy against mosquito larvae and adults. The fogging with insecticides is utilized outdoors to kill the insects, but it can lead to resistance development in mosquitoes (Maciel-de-Freitas et al. 2014). Likewise, the use of chemicals also poses other challenges, including resistance development, bioaccumulation, and negative impacts on non-target organisms like other arthropods, birds and mammals in the environment. However, prioritizing a comprehensive analysis of the benefits and costs is essential before implementing widespread insecticide use (Uragayala et al. 2014). Moreover, there are certain repellents which proved efficacious against in mosquito control studies, such as N,N-Diethyl-meta-toluamide (DEET) and p-menthane-3,8-diol, offer protection against mosquito bites and also proved safe for pregnant women (Kline and Schutze 2016). Additionaly, the Insect growth regulators (IGRs), such as methoprene and pyriproxyfen, also provide effective and environmentally safe larvicidal options (Khan 2021). IGRs like pyriproxyfen have shown promise in autodissemination strategies against Zika virus vectors (Unlu et al. 2017). Ensuring judicious use of appropriate chemicals can effectively control mosquito populations and mitigate the spread of diseases like Zika virus (World Health Organization 2016).

6.1.3. BIOLOGICAL CONTROL OF MOSQUITO

Biological control measures have been explored as an alternative to chemical methods for controlling mosquito populations and preventing the spread of the Zika virus (Niang et al. 2018). Several biological approaches have shown efficacy in combating mosquitoes on a large scale. One method involves the use of bacteria, such as *Bacillus thuringiensis* subsp. *israelensis* (Bti) and *Bacillus sphaericus* (Bs), which

produce toxins that specifically target mosquito larvae (Singh et al. 2018). These bacteria have been commercialized as insecticides and are widely used in many countries. Another strategy involves the use of the intracellular bacteria *Wolbachia*, which can reduce mosquito lifespan and vector competence for the Zika virus. *Wolbachia*-infected mosquitoes have been released in certain areas to control mosquito populations (Lees et al. 2015). Fungi like *Metarhizium anisopliae* and *Beauveria bassiana* can also be employed as biocontrol agents against mosquitoes. These fungi infect and kill mosquitoes, and their spores can be sprayed to control mosquito populations (Tiago et al. 2014). Moreover, mosquitoes can also be controlled using other species of mosquitoes that prey on them, such as *Toxorhynchites splendens*, which feeds on mosquito larvae (Benelli et al. 2016). Additionally, copepods like *Mesocyclops* and *Macrocyclops* have also been used as mosquito biocontrol measures by preying on mosquito larvae (Singh et al. 2018). Finally, certain plant-derived products have been tested for their effectiveness against mosquitoes, including the use of plant extracts and essential oils with larvicidal and repellent properties These biological control measures provide environmental-friendly alternatives to chemical pesticides for controlling mosquitoes and reducing the transmission of the Zika virus (Souza et al. 2011).

6.2. VACCINAL CONTROL OF ZIKA VIRUS INFECTION

Preventing the transmission of Zika virus (ZIKV) requires controlling the vector population and implementing individual-level preventive measures like vaccines or strategies that interfere with non-vectoral transmission. Although there is currently no commercial ZIKV vaccine available, ongoing research shows promising developments in vaccine development (Wang et al. 2022).

Various vaccine platforms are being explored worldwide to develop an effective ZIKV vaccine. Over 40 vaccine candidates are under preclinical study, with 7 in phase I trials and one in phase 2b trial (Veljkovic and Paessler 2016). Researchers have found that antibodies generated against the hemagglutinin subunit 1 (HA1/H1) protein of influenza virus pdmH1N1 can neutralize ZIKV, suggesting the possibility of using the seasonal influenza vaccine to prevent ZIKV spread (Veljkovic and Paessler 2016).

Different types of ZIKV vaccines are being developed. Inactivated vaccines, created by killing the pathogenic organism and administering it with an adjuvant, are effective but require repeated immunizations. Inactivated ZIKV vaccines are currently in phase I clinical trials, showing promising protection in monkeys and mice (Sumathy et al. 2017). Moreover, the live attenuated ZIKV vaccines, created by weakening the virus through genetic or chemical manipulation, can modulate both arms of the immune system and provide protection with fewer doses. Studies with live attenuated vaccines have shown protection in mice, including pregnant mice and male mice protecting against testicular damage caused by ZIKV (Shan et al. 2017). DNA-based vaccines are also being developed, using the DNA of ZIKVA proteins, and are currently in clinical trials. These vaccines have shown safety and efficacy in initial studies (Morabito and Graham 2017). However, extensive research is underway to develop an effective ZIKV vaccine. Although commercial availability is yet to be achieved, the advancements made in various vaccine platforms offer hope for the future (Wang et al. 2022).

6.3. OTHER PREVENTIVE STRATEGIES

There are certain other preventing strategies for the control of Zika virus (ZIKV) keeping in mind the non-vector borne routes of transmission. Among which public awareness plays a vital role in eliminating breeding spaces for vector larvae through basic cleanliness measures. Sexual transmission of ZIKV necessitates safe sexual practices and refraining from intercourse for six months after the onset of

symptoms in male partners or diagnosis. Safe sex should be practiced in high-risk areas, and couples planning to conceive after visiting endemic regions should wait for at least 28 days (Musso et al. 2015).
Moreover, to minimize the incidence of ZIKV-associated microcephaly, parental care and the use of contraceptives should be promoted in ZIKV-endemic countries (Sharma and Lal 2017). Although ZIKV has been detected in semen and saliva, the advantages of breastfeeding outweigh the possible transmission risk, and infected mothers are advised to continue breastfeeding. Blood transfusion can also transmit ZIKV, if preventive measures are not taken. Various methods such as pasteurization, solvent/detergent treatment, and filtration can effectively reduce viral load in plasma-derived medicinal products (Blümel et al. 2017).
Additionally, the hygienic practices should be followed by health workers to minimize the spread of ZIKV within hospitals. In the initial week following ZIKV infection, avoiding mosquito bites and using bed nets are recommended. Travelers to endemic areas should be educated about the use of mosquito repellents and nets. Pregnant women are advised to avoid visiting such areas, and if they have already traveled, they should receive proper medical supervision (Lin et al. 2017).
Surveillance and monitoring should be done at entry points to prevent the introduction of ZIKV from endemic countries. Mosquito control programs combined with surveillance studies have shown effectiveness in preventing ZIKV cases Addressing vulnerable societies and considering climate change's influence on vector density are crucial in policymaking at the government level. Advance planning, infrastructure development, and collective efforts from both the government and the public are necessary for efficient prevention and control of ZIKV infection (Marano et al. 2016).

7. TREATMENT STRATEGIES

Preventing mosquito breeding is the primary strategy for controlling the Zika virus infection. Moreover, it is preferable to use palliative care to treat Zika virus infection, which includes rest and hydration intake. Although there is no drug of choice against the Zika virus, some drug classes, including paracetamol or Acetaminophen, can be used to treat fever and headache (Da Silva et al. 2018). However, salicylates are prohibited in children to prevent the development of Reye's syndrome. Besides, Acetaminophen, there are risks of hemorrhage complications associated with using another non-steroidal anti-inflammatory (NSAID) drugs, so they should not be used (Atif et al. 2016). Various molecules interfere with the life cycle of the Zika virus and can be used to treat the infection. Niclosamide and cyclin-dependent kinase inhibitors have significantly inhibited the Zika virus infection. These compounds have been found to stop viral replication, and when used with Emricasan, they show a synergistic effect (Xu et al. 2016).
Additionally, Chloroquine is another drug with FDA approval and can be used to treat Zika virus infection, particularly in pregnant women. It serves as a useful protective measure against the microcephaly caused by the Zika virus by blocking the initial phases of viral replication (Li et al. 2017). Similarly, another drug used to treat Zika virus infection is sofosbuvir. This drug has been seen to lower the concentration of the Zika virus in the blood, brain, and kidney because it prevents the Zika virus from replicating (Bullard-Feibelman et al. 2017). In the same way, Azithromycin, an antibiotic from the macrolide class, can also be used to treat an infection caused by the Zika virus because it effectively prevents viral replication. In particular, it is safe to treat pregnant women with the Zika virus infection (Retallack et al. 2016). Likewise, azithromycin and, sofosbuvir, Merimepodib also stop viral replication and have been shown to have strong antiviral effects against Zika virus infection (Tong et al. 2018).
In addition, the D2 and D3 dopamine receptor agonist bromocriptine can be utilized to treat Zika virus infection. It binds to the Zika virus NS2B-NS3 protease's active site and prevents the action of that enzyme (Chan et al. 2017). Apart from modern medicine, homeopathy and ayurveda can also be used to treat

infection caused by this virus because these preparations have shown effective results in treating the Japanese encephalitis virus, which belongs to a similar genus as the Zika virus (Bandyopadhyay et al. 2010). Herbal plants have therapeutic potential due to secondary metabolites, i.e., alkaloids which have antimicrobial properties and hence the part of prescriptions in many countries (Perumal Samy 2010). Considering the therapeutic potential of homeopathic medicine, the Eupatorium perfoliatum can be used to treat the infection of this virus because this drug can treat the symptoms experienced by patients with Zika virus infection. In addition to homeopathic medicine, Ayurvedic herbs, including *Tinospora cordifolia*, can also treat the infection that occurs due to Zika Virus (Saxena et al. 2016).

8. CONCLUSION

The Zika virus is a mosquito-borne viral infection that gained global attention due to its association with severe birth defects, particularly microcephaly. The virus can be transmitted through mosquito bites, sexual contact, blood transfusions, and from mother to child during pregnancy. Following the outbreak in the Americas in 2015 and 2016, significant efforts were made to understand and control the virus. These efforts included the development of diagnostic tests, mosquito control strategies, and potential vaccines.

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Crimean-Congo Haemorrhagic Fever Virus: A Silent Widespread Vector-Borne Disease and its Impacts on Public Health

18

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ABSTRACT

Crimean-Congo Haemorrhagic Fever (CCHF) is a viral disease transmitted to humans through ixodid ticks. This virus can cause severe and sometimes fatal illness in humans. The first documented case of CCHF was recorded in 1944 in the Crimean Peninsula. The disease is now widespread in many developing countries across Asia, the Middle East, Southeast Europe, and Africa. The infection is initially characterized by fever, low blood pressure, erythema, and conjunctival inflammation. Severe cases may exhibit disseminated intravascular coagulation, circulatory shock, hemorrhagic diathesis, and multi-organ failure before leading to death. CCHFV can spread among humans through various routes, including ticks serving as both transmitters and natural reservoirs of the virus. The World Health Organization (WHO) has classified CCHFV as a highly urgent infection due to its diverse range of vectors, the lack of effective medical prophylaxis for prevention and treatment, and a significant mortality rate. Improving international surveillance efforts for CCHF is essential to enhance global health security.

Key words: Crimean-Congo Haemorrhagic Fever, Hyalomma ticks, vector-borne, Pathogenesis, Transmission

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1. INTRODUCTION

Crimean-Congo Haemorrhagic fever (CCHF) is a viral disease that affects humans and is primarily transmitted through *ixodid* ticks around the globe. These ticks are generally found in regions including western China, southern Asia, and the Middle East to southeast Europe and most parts of Africa (Vorou 2009; Tekin et al. 2012). The CCHF virus can be transmitted horizontally and vertically between tick species. Horizontal transmission refers to the spread of the virus between ticks. In contrast, vertical transmission occurs when the virus is passed from an infected female tick to its offspring (Tekin et al. 2012; Bente et al. 2013; Gargili et al. 2017). Infection can be transmitted to humans through various means, including tick bites, crushing of ticks, and exposure to infected blood or tissues. Tick bites lead to transmitting CCHF viral infection in various susceptible hosts, including humans and animals. Though susceptible hosts may experience transient viremia indicating the presence of the virus in the bloodstream for a short period (Tekin et al. 2012; Spengler et al. 2016).

Moreover, transmission can occur through direct contact with infected individuals' blood or other bodily fluids, such as during healthcare procedures or the handling of animal carcasses (Nabeth et al. 2004). It's important to highlight that CCHF can manifest as a severe and occasionally fatal illness in humans. As the disease advances, more severe symptoms, including haemorrhage (bleeding), organ failure, and shock, can occur. Prompt diagnosis and proper medical care are of utmost importance when dealing with CCHF. Implementing stringent infection control measures, which include wearing protective clothing, using tick repellents, and avoiding contact with blood or other bodily fluids, is strongly advised to mitigate the risk of disease transmission (Tezer et al. 2010; Mostafavi et al. 2014). The World Health Organization (WHO) has classified CCHFV as a highly urgent infection, primarily due to its diverse range of vectors, significant mortality rate, and the lack of effective medical prophylaxis for prevention and treatment. The expansion of tick populations has triggered apprehensions about the potential spread of CCHFV to regions that were previously unaffected. This expansion could be influenced by various factors such as human activities, climate change, and the movement of infected animals or imported livestock (Gale et al. 2012; Aslam et al. 2016).

2. DISCOVERY OF CCHF

The first documented case of CCHF was recorded in the summer of 1944 when Soviet troops were reclaiming areas of the Crimean Peninsula that had been under German control. Those affected individuals displayed symptoms of acute febrile illness, characterized by bleeding and shock (Bente et al. 2013). Approximately 200 military soldiers were admitted to medical facilities for treatment, and the observed mortality rate was around 10%. In response to this outbreak, a team of investigators, led by Mikhail Chumakov, was dispatched from Moscow to conduct research. Chumakov, in collaboration with Lev Zilber, had previously identified the pathogen responsible for tick-borne encephalitis in the far eastern region of the Soviet Union in the late 1930s (Kuehnert et al. 2021). Investigators quickly established a connection between the newly observed illness and contact with ticks (Nasirian 2020; Kuehnert et al. 2021). They observed that the abandonment of cultivated land during the German occupation had led to an increase in the populations of hares and other wild hosts of *Hyalomma* ticks. Consequently, soldiers and farm laborers engaged in agricultural restoration were facing a significant number of tick bites. Chumakov and his colleagues demonstrated that the viral infection responsible for the illness, initially named "Crimean hemorrhagic fever," was transmitted through tick bites. They accomplished this by effectively inoculating psychiatric patients and army personnel with serum ultrafiltrates derived from patients or samples of pooled ticks (Watts et al. 2019; Fatima et al. 2023).

3. CAUSATIVE AGENT AND CLASSIFICATION

The *Bunyaviridae* family encompasses several genera, including *Orthobunyavirus*, *Hantavirus*, *Phlebovirus*, *Tospovirus*, and *Nairovirus.* The *nairovirus* genus is responsible for causing CCHFV (Appannanavar and Mishra 2011). The virus has a spike-like glycoprotein embedded in the virion's lipid membrane, which plays a crucial role in the attachment of the virion to cellular receptors. The CCHF virus has a genome consisting of three components: small (S), medium (M), and large (L) genomic segments, which are of negative-sense polarity. Inside the host cell, these genomic components are enveloped by nucleoprotein and RNA-dependent RNA polymerase (RdRp). NP and RdRp play a crucial role in initiating the transcription and replication of the viral genome (Nasirian 2020; Kuehnert et al. 2021). The Nucleoprotein (NP) of the CCHF virus is encoded by the S segment of its genome. The NP consists of a large globular domain that includes both the N-terminal and C-terminal sections of the polypeptide (Fig. 1). To enable the encapsidation of viral RNA, the nucleoprotein undergoes oligomerization, resulting in head-to-tail contacts that form a helical structure. These interactions play a pivotal role in the assembly of the virion and the packaging of viral RNA. The virus produces two types of I transmembrane glycoproteins, N-terminus glycoprotein (GP) and C-terminus glycoprotein (GC), through co-translational cleavage of a single polyprotein encoded by the M segment (Papa et al. 2002a; Nasirian 2020; Kuehnert et al. 2021).

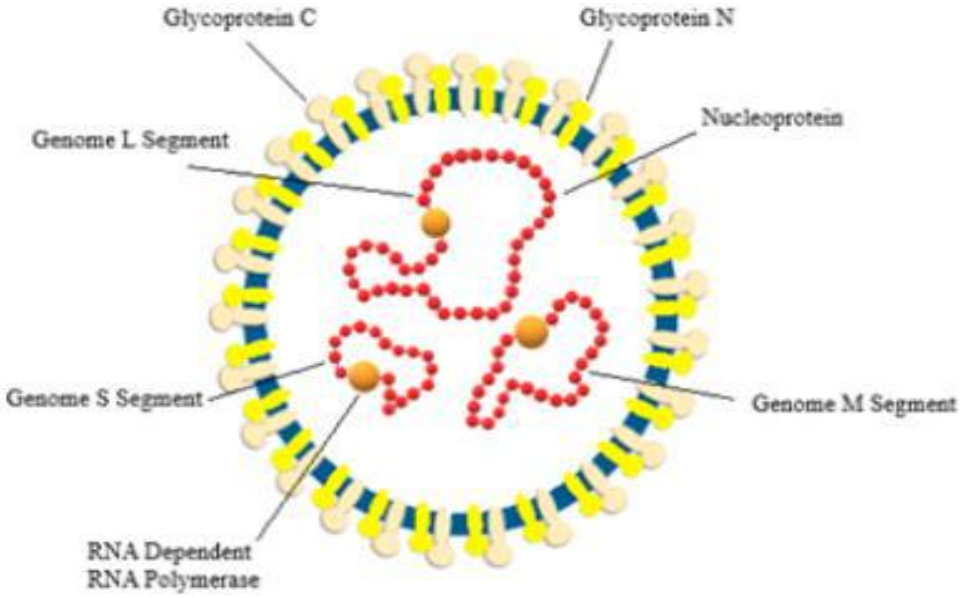

Fig. 1: Graphical presentation of CCHF virus. The virion has a spherical shape with an 80–100 nm diameter. The glycoproteins GP and GC are assembled into spikes scattered throughout the lipid membrane. Specifically, the virus has three single-stranded RNA-dependent RNA polymerase (RdRp), and the nucleoprotein encapsulates RNA genome segments (small, medium, and large).

The glycoproteins of CCHFV stand out due to their abundance of cysteine residues, indicating the presence of numerous disulfide bonds and a complex secondary conformation. The N-terminus of Gn demonstrates features resembling mucin and possesses the potential for substantial O-glycosylation (Papa et al. 2002b; Bertolotti-Ciarlet et al. 2005). The C-terminal cytoplasmic tail of GC is notable for its two zinc fingers, which

can bind to viral RNA. The genetic sequence of the L segment consists of a single reading frame that spans over 12,000 nucleotides (Bertolotti-Ciarlet et al. 2005). An OTU domain is located near the polyprotein's N-terminus, followed by components resembling viral topoisomerase, leucine zipper motifs, and a zinc finger. This sequence encodes a polyprotein of nearly 4,000 amino acids. Towards the C-terminus, the polyprotein contains an RdRp catalytic domain, which exhibits significant sequence homology with the Dugbe virus, another member of the *Nairovirus* genus (Honig et al. 2004a).

4. GEOGRAPHICAL DISTRIBUTION

Human infections with CCHFV have been documented in more than 30 countries spanning Asia, the Middle East, southern Europe, and Africa (Table 1). The first recorded case of CCHF was identified in Bulgaria in 1950, leading to its designation as a recognized infection from 1953 onwards. During the period between 1953 and 1974, a total of 1,105 clinical cases of CCHF was reported. Subsequently, from 1975 to 1996, the number of patients decreased to 279 (Avšic-Zupanc 2008; Papa et al. 2004 and 2011a; Nasirian 2020; Kuehnert et al. 2021). A study carried out in Greece revealed a seroprevalence of 11.6% (34/294) in sheep and 32.9% (139/422) in goats. Similarly, an epidemiological investigation in Novosibirsk, Russia, indicated an antibody prevalence rate of 3.1% among individuals residing in the vicinity (Papa et al. 2010 and 2011b). In 2002, the inaugural case of CCHF emerged in the northern region of Turkey, particularly within the province of Tokat. Subsequently, CCHF was categorized as a notifiable disease in 2003. Subsequently, the annual occurrence of clinical cases has surpassed the cumulative count in all other European countries combined. Numerous instances of human CCHF cases have been documented in the middle and eastern Anatolia regions (Karti et al. 2004; Maltezou et al. 2010; Yilmaz et al. 2008). In 2006, a sero-epidemiological study was undertaken in the endemic regions of Tokat and Sivas. The findings revealed a seroprevalence of 12.8% among rural populations and 2% among urban populations. A study conducted in specific regions found that 79% of the tested domestic livestock had antibodies specific to CCHFV (Gunes et al. 2009). Additionally, a 20% CCHFV positivity rate in Hyalomma ticks was found using an antigen capture ELISA conducted by Vector-Best in Novosibirsk, Russia (Gunes et al. 2011). Furthermore, in 2007, a minor epidemic occurred in the Thrace region of European Turkey, where no prior outbreaks had been documented. An enzyme-linked immunosorbent assay (ELISA) detected CCHFV-specific antibodies in humans, revealing a seroprevalence rate of 5.26% (Midilli et al. 2009).

Within the Eastern Mediterranean Region of the World Health Organization (WHO), which includes 22 countries, there have been documented sporadic human cases and outbreaks of CCHF in several countries. These countries include Iran, Kuwait, Pakistan, Oman, Sudan, Afghanistan, Saudi Arabia, Iraq, and the United Arab Emirates (Malik et al. 2013; Nasirian 2020; Kuehnert et al. 2021). Furthermore, serological investigations conducted on livestock have detected infection in Egypt, Tunisia, and Somalia (Al-Abri et al. 2017; Nasirian 2020; Kuehnert et al. 2021). Outbreaks of infection have been reported in Pakistan, Afghanistan, and Iran, particularly in the border areas of these countries with large populations of nomadic people and their livestock who migrate frequently (Shahhosseini et al. 2021). The exchange of animals and their skins between Iran, Pakistan, and Afghanistan is believed to significantly contribute to the transmission of CCHFV to individuals involved in activities such as handling livestock or their skins, slaughtering infected animals, being close to the tick or patients of CCHF. In 1998, the first documented case of CCHFV was recorded in Afghanistan, and currently, it is prevalent with an average annual incidence of 5–50 cases in humans (Jawad et al. 2019; Ince et al. 2014). Antibodies to CCHFV were initially determined in cattle and sheep in Iran during the early 1970s (Keshtkar-Jahromi et al. 2013). The first confirmed case of CCHF in humans was identified in August 1999 in Iran, when a patient receiving medical

care at a hospital in the southwestern region country died from severe gastrointestinal bleeding (Mardani et al. 2009).

In 1976, the first reported case of CCHFV in Pakistan was documented in Rawalpindi. Since then, there has been a biannual increase in the incidence of CCHF cases in the country (Sheikh et al. 2005). Pakistan is considered an endemic country for CCHF and ranks 4th in terms of prevalence of infection in Asia, following Turkey, Iran, and Russia (Ince et al. 2014). The initial recorded instances of CCHF in Iraq trace back to 1979, with a reported 10 cases and 7 fatalities near Baghdad (WHO 2015). In 1980, several occurrences were documented in Halabja, situated in Iraq's Sulaimani province (Ghareeb and Sultan 2023). In Sudan, the first case of CCHF was recorded in 2008, affecting healthcare personnel in a medical facility in the Kordofan locality. An outbreak in Kordofan resulted in a cumulative count of 10 reported cases. Serosurveys conducted in this region unveiled the existence of CCHF infection in eight individuals who submitted serum samples (Aradaib et al. 2010). In the Gulf region, a study conducted between December 1979 and October 1982 in two hospitals in Kuwait revealed that 4% of serological samples tested positive for CCHFV (Perveen and Khan 2022). A study in Mecca, situated in western Saudi Arabia, during 1989-1990 involved a serological investigation of abattoir workers. This investigation disclosed 40 human cases of CCHFV, resulting in 12 fatalities (El-Azazy and Scrimgeour 1997). A study identified that exposure to animal tissue or blood in abattoirs was a significant risk factor, whereas tick bites did not display a substantial association. In the United Arab Emirates, CCHF was initially documented in 1979, with six instances reported among hospital personnel in Dubai (Baskerville et al. 1981). Table 1 shows the number of cases across different regions of globe.

Table 1: Number of CCHFV cases reported around the globe

Country	Year	Reported Cases	References
Albania	2001-2006	25	Papa et al. 2002a.
Afghanistan	2009	60	Aslam et al. 2023
Afghanistan	1998	19	Sahak et al. 2019
Afghanistan	2000	25	Sahak et al. 2019
Bulgaria	1953-1974	1105	Papa et al. 2004
Bulgaria	1975-1996	279	Papa et al. 2004
Bulgaria	1953-2008	1568	Papa et al. 2004
China	1965-1994	260	Aslam et al. 2023
India	2010-2019	34	Aslam et al. 2023
Iran	2012	870	Keshtkar-Jahromi et al. 2013
Iraq	1989-2009	6	Aslam et al. 2023
Iraq	2010	11	Aslam et al. 2023
Iraq	2021	33	Aslam et al. 2023
Iraq	2022	1085	Aslam et al. 2023
Oman	2014	18	Aslam et al. 2023
Oman	2015	16	Aslam et al. 2023
Pakistan	1976	14	Sahito et al. 2022
Pakistan	2014-2020	356	Sahito et al. 2022
Russia	1999-2020	2361	Volynkina et al. 2022
Russia	2000-2020	385	Volynkina et al. 2022
Turkey	2002	2508	Yilmaz et al. 2008
Turkey	2002-2007	1820	Yilmaz et al. 2008
Turkey	2008	688	Yilmaz et al. 2008

5. VIRUS TRANSMISSION AND CLIMATE CHANGE

The CCHF virus is carried by ixodid ticks and can be transmitted both horizontally and vertically among tick species. Hyalomma ticks, which feed on a variety of hosts throughout their life cycle at different stages of development, play a pivotal role. During their feeding process, infected ticks can transmit CCHFV to susceptible hosts, including humans (Fig. 2). Viruses can spread among ticks through transstadial, transovarial, or venereal routes, making ticks both transmitters and natural reservoirs of the virus (Gunes et al. 2011; Nasirian 2020; Kuehnert et al. 2021; Shahhosseini et al. 2021). Transstadial transmission refers to the passage of viruses from one developmental stage to the next within the tick's life cycle. Transovarial transmission involves the transfer of the virus from infected female ticks to their offspring through eggs. Venereal transmission occurs during mating between infected male and uninfected female ticks. Initial surveys of ticks collected from wild and domestic animals are essential for identifying potential reservoir species (Telmadarraiy et al. 2015).

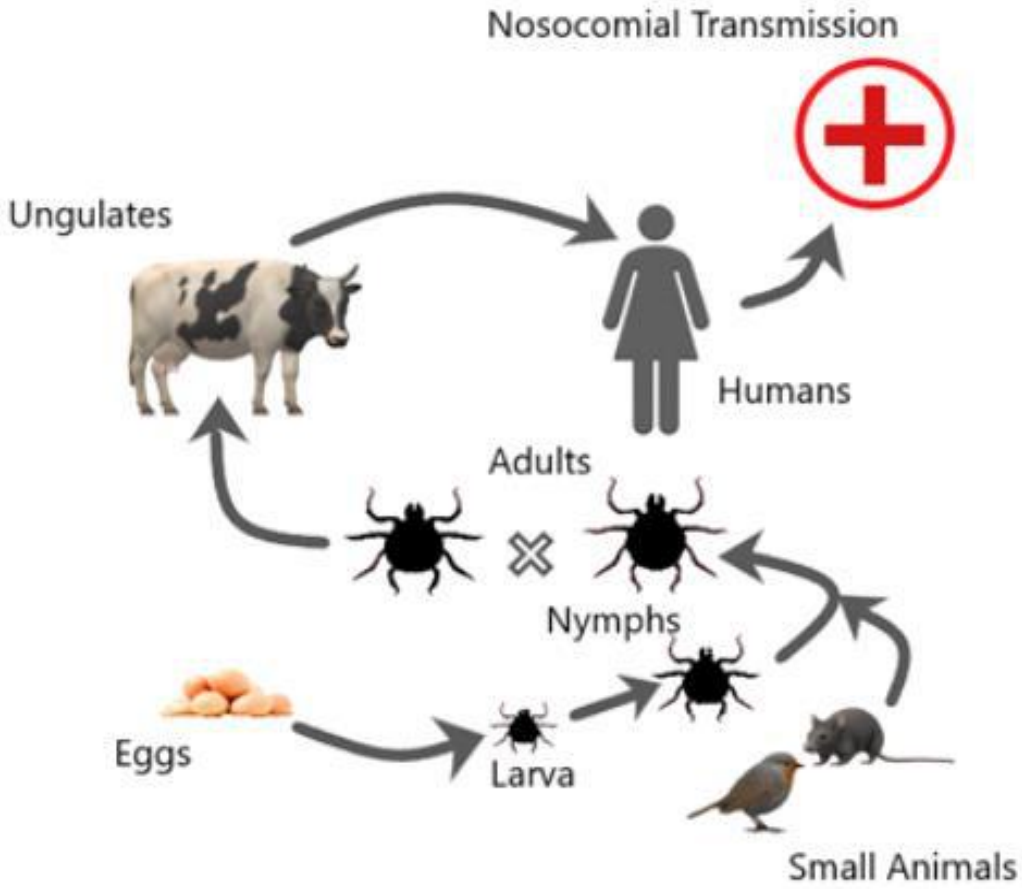

Fig. 2: *Hyalomma spp.* tick life cycle and nosocomial transmission. *Hyalomma* species follow a two-host life cycle, commencing as nymphs on small creatures such as birds and rodents, before transitioning to larger animals and vertebrates, including humans. Notable sources of human infection encompass nosocomial transmission, direct exposure to CCHFV-infected ticks, and contact with infected animals. Factors such as heightened human mobility, the migratory patterns of vertebrate hosts, and the influence of climate change on the migration behaviors of small animals could potentially contribute to an increased prevalence of CCHFV infection within the population.

Competent tick vectors for CCHFV are characterized by their ability to support viral replication in various developmental stages, including larva, nymph, and adult. They can facilitate the transmission of viruses from mature females to their eggs and from adult males to females during copulation (Gargili et al. 2017; Bernard et al. 2022). The virus attains its highest concentrations in the tick's reproductive organs and salivary glands (Valcárcel et al. 2023). When an infected tick bites a mammal, the virus multiplies within the host's tissues, spreading through the bloodstream and potentially infecting other ticks. The risk of virus transmission increases with prolonged attachment of a feeding tick over several weeks, enabling transmission from an infected tick to a host or from an infected host to uninfected feeding ticks (Kuehnert et al. 2021; Shahhosseini et al. 2021).

Hyalomma ticks exhibit a wide geographic distribution, encompassing various habitats such as savannahs, steppes, semi-deserts, farms, foothills, and river floodplains. The acceleration of mean annual temperatures, especially in late fall, could expedite the molting process of ticks, allowing nymphs to mature into adults before winter. This adaptation increases their survival chances during colder months and potentially facilitates their movement to adjacent regions. Consequently, this can enhance the virus's survival and dissemination among ticks (Ergonul 2006; Papa et al. 2002a). Various factors, including rising winter temperatures, reduced winter precipitation, elevated summer evapotranspiration, and the availability of suitable animal hosts, can influence the expansion and migration of tick ecosystems to higher latitudes. Environmental alterations, such as the conversion of floodplains to agricultural lands, changes in grazing patterns, and the conversion of marshy deltas in farming areas, can create more conducive environments for *Hyalomma marginatum* ticks. Research has demonstrated a connection between high infection rates and habitat fragmentation, as well as small agricultural fields in Turkey (EFSA 2010; Estrada-Peña and Venzal 2007; Vorou 2009). Avian migration, which can transport infected ticks, along with the movement of livestock or other species infested with ticks, can potentially aid the spread of CCHFV to new tick habitats. These dynamics underline the intricate interplay between environmental changes, tick populations, and the transmission of CCHFV (Estrada-Peña and Venzal 2007; Vorou 2009).

While the possibility of migratory birds transmitting diseases to previously unaffected European regions is generally considered low, reports from Spain in 2010 indicate the presence of CCHFV-infected ticks (Gale et al. 2012). The spread of CCHFV from endemic to non-endemic areas can result from the convergence of isolated strains with those found in Mauritania and Senegal. However, a lack of fundamental comprehension of interactions between ticks, hosts, and the virus, as well as other factors influencing tick and viral epidemiology, has impeded the development of comprehensive risk assessment models (Estrada-Pena et al. 2012a, b; Vorou 2009).

6. PATHOGENESIS AND CLINICAL PRESENTATION

Following inoculation, the virus undergoes replication within dendritic cells and adjacent tissues, subsequently migrating to local lymph nodes. From there, dissemination occurs in various tissues and organs, including the spleen, liver, and lymph nodes, facilitated by the lymph and blood monocytes. As the infection progresses, tissue macrophages become involved upon infection of receptive parenchymal cells (Peters and Zaki 2002; Geisbert and Jahrling 2004). Notably, a substantial occurrence of apoptosis is observed throughout the disease, resembling patterns seen in other forms of septic shock, even in the absence of lymphocyte infection. The initiation of the extrinsic coagulation pathway is prompted by the production of tissue factors on the cell surface. Within this context, hepatic dysfunction may precipitate intravascular coagulation disruption, leading to reduced levels of coagulation factors, a characteristic

manifestation of CCHFV infections termed diffused intravascular coagulopathy (Geisbert and Jahrling 2004).

In addition to platelet and endothelial cell destruction, CCHFV has demonstrated the capability to induce inflammatory and immunological responses that contribute to hemorrhagic diathesis (Chen and Cosgriff 2000; Peters and Zaki 2002). The release of cytokines, chemokines, and other proinflammatory agents by infected monocytes and macrophages is chiefly responsible for these alterations (Bray 2007; Ergonul et al. 2006). The incubation period for CCHFV typically spans 1 to 9 days, during which the victim typically undergoes a non-specific prodromal phase lasting less than one week. The common manifestations during this phase encompass elevated body temperature, headache, general discomfort, joint and muscle pain, nausea, abdominal discomfort, and occasionally diarrhea (Bray 2007). Initial symptoms often encompass fever, low blood pressure, conjunctival inflammation, and a skin rash or erythema. As the disease advances, patients may develop signs indicative of worsening hemorrhagic diathesis, such as petechiae, bleeding from mucous membranes and conjunctiva, hematuria, emesis of blood, and melena. Complications may include circulatory shock and disseminated intravascular coagulation (Ergonul et al. 2006).

Hemorrhagic diathesis and multi-organ failure are frequently observed prior to death, often occurring within 1-2 weeks after the onset of symptoms. It is important to note that the severity of the disease tends to be milder in pediatric patients (Tezer et al. 2010). Laboratory tests commonly reveal abnormalities such as decreased platelet counts (thrombocytopenia), reduced white blood cell counts (leukopenia), and elevated liver enzymes. Anemia typically does not manifest during the initial stages of the illness but may develop as the condition progresses. Coagulation irregularities present as prolonged bleeding time, prothrombin time, and activated partial thromboplastin time. Furthermore, there may be an elevation in fibrin degradation products and a decline in fibrinogen levels (Mostafavi et al. 2014).

7. EXPANSION OF CCHF CASES

The transmission of CCHFV can occur through contact with the bodily fluids of infected individuals during the initial 7 to 10 days of infection. Health authorities have reported clusters of cases, highlighting the importance of adhering to standard barrier nursing techniques to prevent the spread of the virus (Athar et al. 2005; Maltezou et al. 2009). It's important to note that individuals may travel both before and after the onset of clinical symptoms (Leblebicioglu et al. 2016). Traveling before symptoms emerge can pose diagnostic challenges, as suspicion of the disease may be lower, leading to delayed recognition. Traveling after the onset of symptoms is common among individuals with CCHF. The virus is more prevalent in humans in geographically isolated areas, and the occurrence of the disease is often linked to past tick bites or contact with livestock. Rural areas with high tick activity levels are particularly vulnerable, as ticks are carried by domesticated and wild animals that serve as hosts. This allows for transient viremia and the maintenance of the virus in the natural environment. Measures such as patient isolation and fundamental barriers have been implemented to effectively contain the emergence and spread of diseases like CCHFV, which can result in significant outbreaks (Kuehnert et al. 2021; Shahhosseini et al. 2021).

Hosts, especially migratory birds, and the growth of host populations play a significant role in the dispersal of ticks (Randolph 1998). Changes in tick populations often correspond to the movement of birds or an increase in the number of host animals. The expansion of tick populations across different geographical areas can be attributed to two primary factors. Firstly, ticks carrying the infection can be introduced to separate countries, potentially leading to human-to-human transmission and initiating a chain of disease spread (Shahhosseini et al. 2021). Secondly, non-infected ticks can be introduced to new regions if they

are transported there, where they might establish local populations capable of sustaining the virus transmission. While birds might have a limited role in the transmission cycle of CCHFV, they are still considered important potential vectors for introducing the virus. Cases of *Hyalomma marginatum and Hyalomma rufipes* ticks have been identified in countries like Hungary, Germany, and the U.K., likely brought by migratory birds (Chitimia-Dobler et al. 2016; Hornok and Horvath 2012; Jameson et al. 2012; Shahhosseini et al. 2021). An interesting example is the transportation of *Amblyomma variegatum* ticks to the Caribbean from CCHFV-endemic Senegal through livestock. An anomaly is observed with *Rhipicephalus bursa* ticks, as they seem to propagate a distinct genetic lineage of the CCHFV organized under the Europe 2 clade.

It's important to highlight that *Hyalomma* ticks have also been discovered to carry strains belonging to this clade (Dinç er et al. 2017). The vector competence of *Rhipicephalus* ticks has not been definitively established. The presence of *R. bursa* could indicate either their ability to transmit the virus or the prevalence of R. bursa in regions where strains from the Europe 2 clade are present (Gargili et al. 2017).

The movement of domestic and wild animals plays a critical role in the spread of viruses. While certain borders may impose restrictions on the movement of infected animals due to geographical or political reasons, the transportation of animals between regions, particularly livestock, can contribute to the dissemination of diseases (Spengler et al. 2016). In the initial documentation of CCHF in Abbottabad, Pakistan, there was a noticeable influx of livestock migration to the region, potentially involving infected sheep, which led to the identification of the primary case (Saleem et al. 2009). Multiple CCHF outbreaks have been reported in connection with Eid-ul-Adha, a significant religious celebration in the Muslim community, during which many livestock is imported and subsequently slaughtered in urban areas (Mallhi et al. 2016). Moreover, the movement of livestock and other animals, including deer, across hunting estates can serve as a vector for tick transportation. This situation could potentially lead to the establishment of a CCHFV reservoir or the introduction of infected ticks. This concern is underscored by instances such as the discovery of mature *Hyalomma spp*. ticks on a horse that was imported to England (Akuffo et al. 2016). To counter the risk of viral or tick-borne pathogen transmission through animal importation into non-endemic areas, several strategies can be implemented.

8. CCHF RISK ASSESSMENT, OPTIMIZATION, AND REDUCTION

The lack of a comprehensive understanding of virus maintenance in natural habitats, their transmission to human populations, and the intricate interconnections between these processes represent a significant research gap in the context of CCHFV. This holistic framework should guide research efforts toward a health-focused approach to addressing CCHF. In addition to epidemiological, ecological, virological, and vector biology studies, mathematical modeling will play a crucial role in implementing the framework and conducting thorough risk assessments. When incorporated into a framework, modeling techniques can effectively identify critical knowledge gaps, thus aiding in prioritizing epidemiological studies, laboratory-based investigations, and mitigation strategies. The modeling of viruses transmitted by ticks has historically been challenging due to the complex interactions among vectors, hosts, and viruses. Nonetheless, mathematical models have the potential to integrate the biology of hosts, vectors, and viruses, thereby facilitating the identification of key factors that influence disease likelihood.

The tick-host system of CCHF exhibits several characteristics that contribute to non-linear transmission responses, potentially leading to disease outbreaks. Despite the detailed understanding of many processes, it's crucial to comprehend the mechanisms underlying rapidly changing exposure risks. Co-feeding ticks can directly transmit the CCHFV virus to one another through certain hosts, bypassing the

need for the host to experience a viremic response. While feeding, ticks emit pheromones that attract other ticks to the same feeding site, promoting tick-to-tick transmission, a process further facilitated by the presence of tick saliva. The likelihood of co-feeding is positively correlated with the extent of tick infestation. Hosts heavily infested with tick nymphs and larvae are more likely to harbor co-feeding groups. Further research is essential to assess vector competence, which refers to the ability of vectors to acquire and transmit infections. Implementing traditional infection control protocols when handling potentially infected blood or ticks can significantly reduce the risk for individuals in these occupations. Secure tick removal methods involve mechanical techniques and can be performed using readily available tools in most areas (Coleman and Coleman 2017; Akin Belli et al. 2016). Managing diseases transmitted between humans and wildlife demands a multifaceted approach that encompasses various strategies. Preventive measures like translocation control, barriers, and proper husbandry practices play a pivotal role in managing diseases in both domestic and wild animals. Livestock animals, particularly those belonging to the *Bovidae* family, are preferred hosts for mature *Hyalomma* ticks. The interaction between animals, ticks, and humans provides additional opportunities for virus transmission. Understanding the risks associated with emerging and endemic diseases affecting animals and humans is crucial for making informed decisions and implementing preventive health programs for livestock (Booth et al. 1991).

The application of artificial acaricides on domesticated livestock has been a widely adopted approach for managing ectoparasites and ticks globally. Organophosphates are primary chemicals used for ectoparasite and acaricide management, including compounds like pyrethroids, macrocyclic lactones, amidines, and others (Eiden et al. 2017). Acaricides offer a cost-effective means of tick management and can be applied through methods like dips, footbaths, or traditional sprayers (Pavela et al. 2016). However, their effectiveness, cost-efficiency, sustainability, and worker safety can vary among different acaricides (De Meneghi et al. 2016). Unfortunately, the continuous and non-selective use of acaricides has led to the emergence of tick populations resistant to these agents, presenting a global challenge for tick management. Many countries have reported that practically all acaricides have become ineffective in recent times (Abbas et al. 2014; Nandi et al. 2018; Pohl et al. 2014; Li et al. 2004). This underscores the urgent need for alternative and sustainable strategies for tick control to effectively manage the spread of tick-borne diseases like CCHFV.

9. VACCINATION

A drafted roadmap proposed by the World Health Organization outlines alternative vaccination strategies for controlling CCHFV, considering the challenges faced in developing human vaccines. Initial pathway analysis for CCHF was formulated by a WHO working committee on research and development. This analysis includes a timeline for establishing standards and deployment goals for human vaccination. Various vaccine candidates for CCHFV have been developed, incorporating different antigenic variations based on strain and gene combinations (Papa et al. 2011; Tipih and Burt 2020). Establishing clinical markers of protection in this context is vital to facilitate the creation of countermeasures, including vaccines. However, vaccine development encounters several challenges. One major challenge is the diversity of strains, requiring the design of a vaccine that can effectively target the various geographic clades of CCHFV. Another hurdle is the assessment of safety profiles for experimental vaccines (Bente et al. 2013).

Successful wildlife vaccines have been developed and utilized in various scenarios. When designing vaccines for animal use, it's crucial to incorporate the DIVA strategy, which enables the differentiation between vaccinated animals and those previously infected. Immunization with these vaccines triggers the

production of antibodies in the host animal. These antibodies disrupt the biological activity of Bm86, resulting in reduced numbers, mass, and reproductive capacity of pregnant female ticks. The effectiveness of vaccines like TickGARD and Gavac in providing cross-protection against *Hyalomma dromedary* and *Hyalomma anatolicum* ticks in cattle has been demonstrated. However, their efficacy against other tick species, such as *Rhipicephalus appendiculatus* or *Amblyomma variegatum*, remains uncertain (Tipih and Burt 2020).

10. CONCLUSION

Understanding endemic regions and having access to comprehensive data are fundamental for grasping the distribution of disease. Ongoing enhancements in surveillance systems, diagnostic capabilities, and disease-related information mapping are contributing to a more nuanced understanding of CCHFV. The identification of new regions where CCHFV is circulating often hinges on documented cases of human infection. While the increase in disease reporting might be partially attributed to heightened awareness, it's unlikely that awareness alone can explain the observed rise. The potential for more frequent viral circulation within tick and animal populations remains uncertain and necessitates further investigation. Improving international surveillance efforts for CCHF is essential for enhancing global health security. By facilitating early detection and control of potential outbreaks or new introductions, international surveillance initiatives can contribute to mitigating the impact of CCHF and other viral hemorrhagic fever.

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Seroprevalence, Distribution Pattern and Control of Crimean Congo Hemorrhagic Fever (CCHF) with its Risk Factors in Pakistan and Neighboring Countries

19

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ABSTRACT

Crimean-Congo One of the most significant vector-borne illnesses with the potential to spread to humans after a tick bite is hemorrhagic fever (CCHF). In the Middle East and Asia, the disease is very common. contaminated tick bites, manual tick removal, and contact with contaminated tissue, blood, patients, or cattle during the acute viremic phase are risk factors for this disease. Clinical signs of the illness include fever, muscle discomfort, and increasing hemorrhages. Increased levels of creatinine phosphokinase (CPK), alanine transaminase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) are detected by biochemical testing. Pro-thrombin tests result in longer clotting times, and pathogenesis is mostly associated with epithelial destruction during viral replication and secondary cytotoxic molecule secretion. Endothelial activation is brought on by these substances, which leads to function loss. Infusions of plasma or blood are used in supportive therapy to treat or manage patients. Based on the most recent research, ribavirin, an antiviral medication that effectively prevents the disease, can be used to treat community-onset heart failure. Workers in healthcare are more likely to have infections. A thorough review of the viral epidemiology, zoonotic viewpoints, and important risk factors for community-acquired pneumonia (CCHF) in several Middle Eastern and Asian nations is provided in this book chapter. The pathophysiology and preventative measures of CCHF have also been examined, along with laws and policies pertaining to public education campaigns, research, and development projects that aim to prevent and control infections and are necessary on a worldwide scale.

Keywords: Prevalence, Africa, CCHF, transmission, ticks, Hyalomma.

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1. INTRODUCTION

Crimean Congo hemorrhagic fever (CCHF) virus is a lethal agent that is associated with CCHF fever. CCHF virus is present all over the over the world but most commonly it is present in West Africa, Europe, and Asia (Nasirian, 2020). Due to its endemic nature, this zoonotic disease poses a serious hazard to humans and livestock alike. It is a serious health concern since it can cause an acute and potentially fatal disease in humans (Shahhosseini et al. 2021). It has been linked to human severe hemorrhagic syndrome as well as sporadic infections in tourists visiting these regions (Gilbride et al. 2021). The virus that causes Congo hemorrhagic fever (CCHF) is called the Orthonairovirus, and it is a member of the Nairoviridae family and Bunyavirales order (Serretiello et al. 2020).

In nature, CCHFV often possesses a tick-vertebrate life cycle (Gargili et al. 2017a). In the CCHF cycle of distribution, many kinds of animals both domesticated and wild may serve as asymptomatic hosts of CCHFV, which is essential for feeding ticks that support the cycle of transmission to new populations of ticks (Fanelli and Buonavoglia, 2021). Seroepidemiological and serosurveillance have helped identify CCHFV hosts to identify endemic foci of viral transmission (Spengler et al. 2016).

Seroepidemiological investigations can be used to identify CCHF risk areas because the prevalence of antibodies in animals is a reliable predictor of the virus's presence or absence in a specific location (Sas et al. 2017). The main source of data for tracking naturally occurring virus transmission zones and identifying viral-exposed species is also serological surveys. There appears to be little chance of CCHFV infection in humans due to the absence of the virus and the absence of antibodies against people and animals alike (Mendoza et al. 2018). A substantial amount of study has been done on CCHFV hosts and their involvement in the survival and spread of the virus (Mertens et al. 2013). Recently, several kinds of organizations have released reports on in-depth serosurveys. Nonetheless, the majority of the research is local in nature and does not offer a thorough evaluation that spans wide regions or the entire world.

1.1. ABSTRACT

Crimean-Congo One of the most significant vector-borne illnesses with the potential to spread to humans after a tick bite is hemorrhagic fever (CCHF). In the Middle East and Asia, the disease is very common. contaminated tick bites, manual tick removal, and contact with contaminated tissue, blood, patients, or cattle during the acute viremic phase are risk factors for this disease. Clinical signs of the illness include fever, muscle discomfort, and increasing hemorrhages. Increased levels of creatinine phosphokinase (CPK), alanine transaminase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) are detected by biochemical testing. Pro-thrombin tests result in longer clotting times, and pathogenesis is mostly associated with epithelial destruction during viral replication and secondary cytotoxic molecule secretion. Endothelial activation is brought on by these substances, which leads to function loss. Infusions of plasma or blood are used in supportive therapy to treat or manage patients. Based on the most recent research, ribavirin, an antiviral medication that effectively prevents the disease, can be used to treat community-onset heart failure. Workers in healthcare are more likely to have infections. A thorough review of the viral epidemiology, zoonotic viewpoints, and important risk factors for community-acquired pneumonia (CCHF) in several Middle Eastern and Asian nations is provided in this book chapter. The pathophysiology and preventative measures of CCHF have also been examined, along with laws and

policies pertaining to public education campaigns, research, and development projects that aim to prevent and control infections and are necessary on a worldwide scale.

1.2. TRANSMISSION ROUTE OF CCHFV TO HUMANS

Infections with CCHF are enzootic and typically show no symptoms in a variety of animals. Humans are susceptible to the CCHF virus through tick bites, and contact with infected animals or their tissues or plasma (Papa et al. 2017). Hospital nosocomial epidemics are linked to environments with limited resources. For instance, in Al-Fulah, Kordufan, Sudan, a nosocomial outbreak was documented in 2008 following the hospital admission of a 60-year-old male patient who had previously worked as a butcher (Sargianou and Papa, 2013). Nurses who had cared for the index patient were infected with the virus because strict infection control procedures were not followed and personal protective gear, or PPE, was not used. However, those working in the veterinarian profession, abattoir, and livestock business have accounted for the majority of CCHF instances (Msimang et al. 2021). It has been demonstrated that numerous tick genera throughout are carriers of the virus. However, the majority of human illnesses are caused by ticks of the genus *Hyalomma*, possibly as a result of both larval and adult parasites relying on host blood during different stages of their development (Gharbi and Darghouth, 2014). Hyalomma ticks serve as CCHFV vectors as well as hosts. The adult *Hyalomma* ticks maintain CCHFV infection naturally through trans-ovarian and trans-stadial transmission, whereas the larvae and nymphs graze on ungulates, birds, or reptiles (Pascuccia et al. 2009). It is necessary to ascertain the function of reptiles as reservoirs and as capable hosts for the spread of CCHFV. Animals may acquire the CCHFV virus by being bitten by a virus carrier tick. The virus then spreads to ticks that are not affected as they feed on the blood of the afflicted host. Additionally, ticks can get infected directly by blood-feeding on the same host, and viral materials found in tick saliva hasten the spread of infection (Hart and Thangamani, 2021). However, the risk of contracting CCHFV is the same in all mammals. For CCHFV multiplication and transmission, birds are regarded as poor hosts because they frequently exhibit resistance to becoming viremic (Gargili et al. 2017b). Humans are typically thought of as CCHFV's accidental, dead-end hosts (Bente et al. 2013). The main ways that humans become infected are by tick bites, coming into touch with the cells and blood of virulent animals, and through contaminated human tissues, bodily fluids, or blood (Parola and Raoult, 2001). Transmission of CCHFV can also occur when cattle are travelled and migrate from affected regions to uninfected area (Fanelli and Buonavoglia, 2021). Changes in land use and restrictions on the movement and trading of affected livestock can both lessen the risk of CCHFV transmission (Obanda et al. 2021). In the Middle East, contact with contaminated blood from corpses through wounds or mucosal membranes of infected humans and animals was reported to be the most frequent mechanism of CCHFV transmission during several epidemics.

1.4. CLINICAL SYMPTOMS

The CCHFV infection primarily involves four distinct phases: the incubation phase, pre-hemorrhagic, hemorrhagic, and clinical convalescent (Papa, 2019). After infection, the incubation period endures three to seven days. The first 4-5 days of the illness are known as the pre-hemorrhagic phase. Headache, elevated temperature, abdominal discomfort, muscular pain, low blood pressure, and red face are the main symptoms (Fletcher, 2019). Severe symptoms such as skin lesions, ecchymosis, nosebleeds, gum bleeding, and nausea begin to manifest as the condition worsens (Leblebicioglu, 2010). Additional symptoms may include, vomiting, loose stool, mental disorders, and myocardial abnormalities. If the illness is not addressed, individuals may experience multiple organ failure and die. After 10–20 days of illness, survivors start the convalescent phase (Al-Halhouli et al. 2021). It can take a full year for CCHF survivors to fully recover.

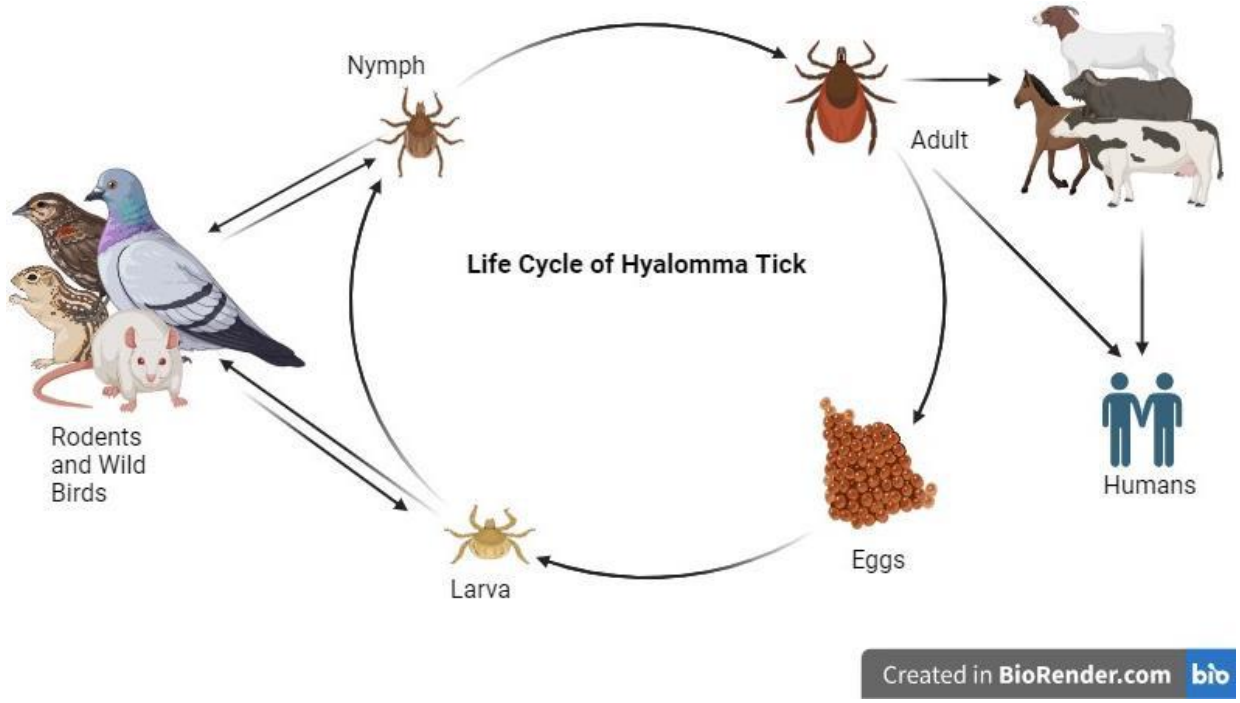

Fig. 1: Lifecycle of *Hyalomma* tick and potential transmission route of CCHFV.

1.5. DISTRIBUTION PATTERN OF CCHF VIRUS

1.5.1. PAKISTAN

With every passing year that goes by, there are more and more cases of CCHF throughout the nation. The virus was initially discovered in ticks infesting nearby cattle in the 1960s. The first recorded human incidence of CCHF was in Pakistan in 1976 (Lea, 2023). There were only 14 cases reported up till 2010. Following 2010, there was a sharp rise in the number of CCHF cases (Chinikar et al. 2012). Over 350 cases of the disease have been identified by the National Institute of Health, Islamabad, between 2014 and 2020 (Nisar et al. 2020). It was suggested that the fatality rate should be higher than 25%. Just 38% of these CCHF instances were recorded from the province of Balochistan, 23% from Punjab, 19% from Khyber Pakhtunkhwa, 14% from Sindh, and 6% from Islamabad, the nation's capital (Karim, 2020). Because people and animals interact closely in rural regions, the sickness was more common there. This disease become much contagious on Eid Ul Adha, occasion, when small and large ruminants are sold and consumed without sufficient examination of animal. Urban areas are more likely to be more affected than rural areas where population is less (Hurrem et al. 2015). In Pakistan, common strains from nearby nations like Iran, Afghanistan and India frequently circulate and propagate, and vice versa. Only 68% of the 248 cases that tested positive for CCHF in 2004 were reported from Sistan of Iran, and Baluchistan, Pakistan (Aslam et al. 2023). Up to 300 more cases each year were reported between 2004 and 2006 (Süss, 2011).

The spread of CCHF is largely being driven by a few risk variables. There are twice-yearly peaks from March to May and August to October due to rapid changes in the climate. The transmission of CCHF is facilitated by a number of factors, including inadequate sanitation, unclean abattoir’s, livestock being moved inside cities, nomadic lifestyles, and a shortage of medical personnel and trained animals (Wallace et al. 2002).

1.5.2. INDIA

The inaugural case of CCHF was found in the Indian state of Gujrat, and it was caused by a nosocomial illness connected to Pakistan on the other side of the border. According to a local livestock survey, tissue and serum samples were examined to determine the presence of *H. anatolicum* (Parihar et al. 2022). Of the 34 cases, eight secondary instances of CCHF were reported. Four Indian states had CCHF instances found in another study (Patil et al. 2022).

1.5.3. CHINA

Hemorrhagic fever cases were reported in western China in 1965 (Papa et al. 2022). Upon diagnosis, samples taken from humans, livestock, and ticks revealed the presence of the CCHF virus (Mourya et al. 2012). 260 individuals were found to have had CCHF infection between 1965 and 1994. Forty was the death rate. In Beijing, China, one imported occurrence was reported in 2013. The Chinese provinces also reported confirmed cases of the CCHF virus (Wang et al. 2019). In China's Inner Mongolia region, the CCHF virus was found in the ticks of camels and sheep. Only 447,848 cases were reported to have been infected by bunyavirales viruses between 1951 and 2021, with CCHFV and three other viruses being the viruses that were identified to generate the greatest illness burden (Teng et al. 2022).

1.5.4. IRAN

Based on the discovery of antibodies against CCHF in the serum of sheep, cattle, and people, the first incidence of CCHF was documented in Iran in the 1970s (Lotfollahzadeh et al. 2011). Viral antigens were discovered to be present in a sheep slaughterhouse in Tehran. The Ixodes genus of ticks was the virus's source. Since 1999, reports of human sickness have been made, and CCHF outbreaks have been documented in several parts of the nation. In 2000, the death rate was 20%; by 2007, it had dropped to 6%. In a study, 203 ticks were examined for the presence of CCHFV; despite being an endemic location, the Kerman province had no positive results (Watts et al. 2019).

1.5.5. AFGHANISTAN

There was a CCHF outbreak in the Afghanistan district of Herat in 2009. There were only 60 positive instances found. Native sheep and cow breeds found in the vicinity were found to have elevated blood IgG levels, suggesting possible pre-exposure (Samadi et al. 2020). In one investigation, ELISA identified 51 positive cases of CCHF; 11 patients of these instances passed away. They were shepherds and butchers (Lea, 2023). In the endemic year, the number of patients with CCHF climbed dramatically from June to September. This demonstrated that environmental variables and lifestyle choices are the main risk factors for the disease's spread. The border between Afghanistan and Iran is home to CCHF vector ticks, which raises the possibility of human CCHF infection (Sahak et al. 2018).

1.6. CONTROL OF CCHFV

The strongest defense against the transmission of CCHF disease is to reduce or prevent exposure to the virus (Mertens et al. 2013). To be more specific, the best human defense against CCHFV is body defense. When visiting or living in an endemic area, individuals should take personal precautions such as avoiding locations where tick vectors are common, especially when they are active, checking their skin and clothing frequently to remove any sticky ticks, and using repellents (Valente et al. 2015). Wearing long sleeves and

shirts with your jeans tucked into your boots is another method of preventing skin tick adhesion (Eisen, 2022). Meat typically undergoes acidification after slaughter or heating at 56 °C for half an hour to destroy or inactivate CCHFV. Consuming unpasteurized milk is not advised. People who work in high-risk fields like veterinary medicine, livestock husbandry, and slaughterhouses, as well as butchers and butlers, should take every measure possible to prevent exposure to CCHFV-infected ticks and infected animal tissues or fluids (Mitchell et al. 2020). These precautions include wearing gloves, gowns, and face shields. Healthcare professionals have a significant risk of contracting infections, especially while caring for patients who have gingivitis, areas of injection, noses, or vaginas (Vaughn, 2013). For the protection of healthcare professionals, safety precautions such as isolation, normal barrier-nursing procedures, and the use of gowns while in contact with healthcare clients or filthy environmental surfaces are advised. Strict biosafety protocols must be followed by laboratory personnel (Schwartz et al. 2022).

It is important to strengthen tactics such as laboratory capacity growth in areas of epidemic and areas at risk of CCHF growth, as well as surveillance utilizing defined case definitions. (Thi, 2015). To lower their chance of contracting CCHFV, both the general public and at-risk groups, such as those in high-risk occupations and the healthcare industry, should be aware of preventative measures. Individuals living in areas where the CCHF is prevalent need to be made aware of the routes of transmission, which include eating raw or undercooked meat right away after slaughter (Kalal, 2019).

It is directed that the aforementioned preventive and control measures be implemented as part of a multidisciplinary effort at the worldwide, national, and regional at particularly in places where CCHF is anticipated to develop. It is essential to develop and put into practice guidelines for early quick response treatments at the hospital, community, and patient levels (Ahmed et al. 2021). There should be an increase in laboratory capacity to enable CCHF to quickly confirm putative clinical cases (Greiner et al. 2016; Jahromi, 2014). It has proven successful in preventing CCHF in at-risk groups by emphasizing education to raise awareness.

Proficient and knowledgeable healthcare workers are vital to avoid, detect and take satisfactory procedures for dangerous transmittable diseases that directed a danger to the universal population. Supportive therapy is also a crucial component of case management. Early detection and analysis of CCHF is crucial for patient recovery as well as for the inhibition of potent nosocomial infections and transmission in the population. Healthcare workers must regularly undergo refresher training to reinforce sound public health practices and understand new developments in the field (Greiner et al. 2016).

Most endemic nations already treat CCHF patients with ribavirin, and new research indicates that this medication may be helpful (Ergonul, 2008). While additional studies have indicated encouraging outcomes, primarily linked to early therapy, the use of ribavirin for the treatment of chronic cardiomyopathy (CCHF) is still controversial because no modification in case casualty rates was observed. The majority of the information regarding the effectiveness of ribavirin is confined to case series and short observational studies, and methodological concerns have been brought up. We conclude that there is not enough information at this time to make a firm determination regarding the effectiveness of ribavirin (Elaldi et al. 2009). A well-designed multi-center, randomised controlled trial that takes severity criteria into account is desperately needed to offer evidence-based data about the efficacy of ribavirin, given the high fatality rates linked to CCHF(Huggins, 1989). Because of the possibility of autoimmune reactions, the use of inactivated suckling mouse brain vaccinations generally raises concerns (Al-Abri et al. 2017). Most cases of CCHF occur in low-resource countries, and the field's research has advanced relatively slowly.

More research may be conducted thanks to the recent genetic characterization of the CCHFV strain used to prepare vaccines. Although long-term field research will be necessary to demonstrate efficacy, a humanized vaccination against CCHF is necessary. Large-scale phylogenetic investigations and strong international collaboration among CCHF researchers are also necessary to produce the best immunogenic vaccine against CCHFV and will help achieve the goals of more effective treatment.

1.7. RISK FACTORS

The virus can be transmitted from one human to another through direct blood contact, body fluids of infected human and during handling of infected ticks (Sarwar, 2017).
There is minimal to no risk of tick exposure in regions outside the tick's geographical range. One of the primary risk factors for CCHFV exposure is either killing the diseased animal or breaking down and pressing the infected tick on the skin (Annex, 2012). Nosocomial infections represent another well-established risk factor. This is more common in healthcare professionals, especially when the condition is hemorrhagic. As mentioned before, this factor was demonstrated in January 1976 at the Central Government Hospital in Rawalpindi, Pakistan, where a nosocomial occurrence took place (Aslam et al 2023b). A shepherd was the source of the illness, which spread to a female doctor, a surgeon, an assistant surgeon, and other medical personnel. Another nosocomial epidemic happened at the Tygerberg Hospital in South Africa (Reddy et al. 2021). There, 33% of the medical staff contracted CCHF as a result of unintentional needle stick contact with the patient, and 8.7% contracted the infection from coming into touch with the patient's blood or other bodily fluids. One of the risk factors for CCHF is the droplet-respiratory route of infection (Whitehouse, 2007). Numerous examples of laboratory-acquired CCHF in Africa attest to this. Numerous instances of CCHF that were obtained from a laboratory in Africa provide evidence that laboratory personnel handling viral samples are also at a significant risk of contracting the illness. The Centers for Disease Control and Prevention have classified CCHFV as a BSL-4 pathogen in the US because to all of these factors.

2. DISCUSSION

This epidemic acutely demonstrated the lack of clear understanding of the fundamental concepts and principles of infection control among both healthcare personnel and hospital administrators. The Pakistani outbreak was eventually contained by a fruitful multidisciplinary association between the hospital's management, clinical microbiologists, and epidemiologists (Sydnor and Perl, 2011). This confirmed the vulnerability and restrictions of the health care system in a resource-poor country that are associated with bloodborne and other occupationally related pathogens.
To summarize, hospital staff who are responsible for patient care experience anxiety, confusion, and fear when a patient is admitted with a highly transmissible or catastrophic viral illness, such as meningococcal meningitis, rabies, or VHF (including that caused by the Ebola and CCHF viruses). With a basic understanding of CCHF and careful adherence to pertinent infection-control and standard barrier procedures, healthcare professionals can be assured that they are adequately safeguarded against this illness (Yousuf et al. 2018).
However, political will is one of the other factors needed to effectively combat CCHF (Sharma et al. 2022). While the medical community sometimes bemoans the sensationalization of some disease events by the media, in the case of the Ebola virus fever, the resulting publicity may have had a significant impact on political visibility and research priorities, ultimately resulting in the development of a new experimental vaccine for this uncommon but deadly infection. Despite being geographically considerably more widespread than the Ebola virus, CCHF has not received the same level of international attention. It would be beneficial to depict it as the "Asian Ebola virus" that it appears to be in order to get additional national, international, and scientific attention that could improve future attempts at prevention and control.

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Role of Wildlife in Emerging and Re-emerging Viral and Bacterial Zoonosis

20

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ABSTRACT

Zoonotic diseases highlight the interconnectedness of human, animal, and environmental health. Wildlife has historically served as a significant source of infectious illnesses that have the potential to infect humans. Wildlife account 71.8% of emerging and reemerging zoonosis. Wildlife trafficking and relocation, live animal and bushmeat markets, unusual food consumption, tourist development, access to petting zoos, and exotic pet ownership are the main factors in the emergence and reemergence of wildlife zoonosis. Along with these, anthropogenic activities and their impact on biodiversity, habitat destruction, changes in agricultural methods, and globalization of commercial activity are also major contributors of wildlife zoonosis. Although actual human-pathogen transmission is relatively rare, once it happens, human-to-human transmission can keep the infection going for short period of time or even permanently. Pathogens that exhibit this type of transmission include the Ebola virus, influenza A, severe acute respiratory syndrome, and the human immunodeficiency virus/acquired immune deficiency syndrome. However, some are transmitted via animal-to-human through direct contact or through a vector, which is the actual means of infection transmission to people. Pathogens such as rabies, lyssaviruses, Nipah virus, West Nile virus, Hantavirus, and the agents of Lyme borreliosis, plague, tularemia, leptospirosis, and ehrlichiosis are examples of pathogens having this pattern of transmission. Wildlife zoonosis have impose a substantial burden on healthcare systems, may cause extensive epidemics, and have a likelihood of developing into pandemics. Understanding the epidemiology and risk factors for zoonotic illnesses will assist in the development of effective preventative techniques such as monitoring, early diagnosis, rapid treatment, and vaccinations. This information is vital for taking early preventive measures to safeguard human populations, economic resources and reduce the effect of any possible future disease outbreaks.

Keywords: Wildlife, zoonosis, pathogenic agent, anthropogenic activities, one health, future perspective of zoonosis

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1. INTRODUCTION

Zoonotic diseases, also known as zoonosis, are infectious diseases caused by pathogens such as bacteria, viruses, fungi, or parasites that can be transmitted between animals and humans. Emerging zoonosis includes infectious diseases that have recently been identified and evolved, whereas reemerging zoonosis have previously occurred but have recently exhibited an increase in incidence or extension into a new geographic, host, or vector range (Bengis et al. 2004). There are approximately 1500 known human disease-causing agents, and 65-75% of them are associated with zoonotic organisms (Chhabra and Muraleedharan 2016).

Zoonotic diseases often serve as indicators of ecological disruptions and environmental changes. The occurrence of these diseases can reflect alterations in natural habitats, biodiversity loss, climate change impacts, and human activities such as deforestation or wildlife trade.

Zoonotic diseases highlight the interconnectedness of human, animal, and environmental health. They pose a significant burden on healthcare systems, can cause widespread outbreaks, and have the potential to lead to pandemics. Understanding the epidemiology and risk factors associated with zoonotic diseases helps in developing effective prevention strategies, including surveillance, early detection, rapid response, and vaccination programs (Maher et al. 2023). This knowledge is crucial for protecting human populations and minimizing the impact of future disease outbreaks as displayed in Fig. 1.

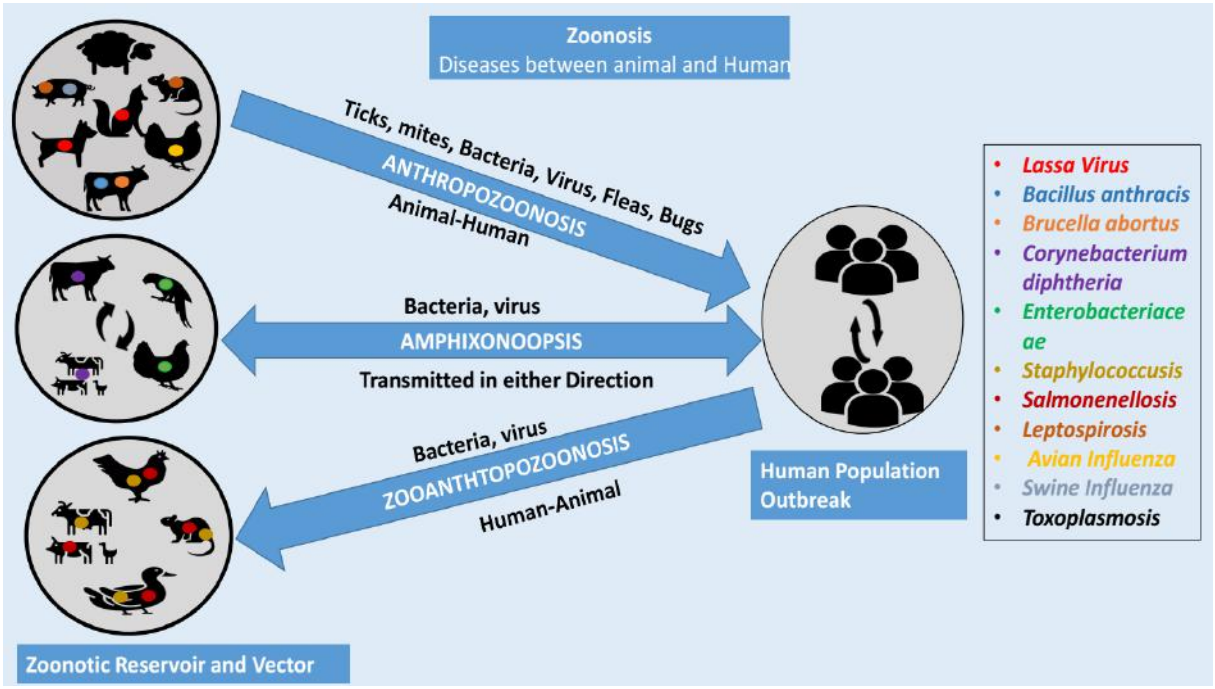

Fig. 1: Wildlife Zoonosis; Zoonosis is always a two-way process i.e., humans to animals and animals to humans, however some may be unidirectional. This figure is showing examples of pathogens (indicated with dots of various colors) along with their reservoir hosts and vectors.

2. Examples of Emerging and Reemerging Zoonotic Diseases

Emerging and re-emerging illnesses have far-reaching consequences not only for public health but also for socioeconomic challenges around the world. There are 132 emerging zoonotic illnesses among the 175

recognized emerging diseases. According to another analysis, zoonosis account for around 60.3% of new diseases. 71.8% of them were derived from wildlife (Jones et al. 2008; Rahman et al. 2020). Table 1 enlists the emerging and re-emerging zoonotic diseases.

Table 1: List of emerging and re-emerging zoonotic diseases

Emerging zoonotic diseases	Re-emerging zoonotic diseases
Ebola	Rabies
Feline Cowpox	Malaria
Avian Influenza	Dengue
West Nile Fever	Brucellosis
MRSA Infection	*Japanese Encephalitis*
Rotavirus Infection	*Schistosoma Japonica*
Hantavirus Infection	Tuberculosis (*M. Bovis*)
Canine Leptospirosis	
Coronavirus Disease 2019 (Covid-19)	
Severe Acute Respiratory Syndrome (SARS)	
Middle East Respiratory Syndrome (MERS)	
Bovine Spongiform Encephalopathy (BSE)	

3. HUMAN AND WILDLIFE COEXISTENCE

Wildlife is crucial for biodiversity, ecosystem services, scientific and medical research, cultural significance, economic benefits, and environmental health (Maher et al. 2023). It supports processes like pollination, seed dispersal, and nutrient cycling, provides essential services like carbon sequestration, water purification, and soil stabilization, and enhances our understanding of biology, behavior, and ecological processes. Wildlife also inspires art, literature, and spiritual beliefs, and generates economic benefits through ecotourism and conservation. Additionally, wildlife serves as an indicator of environmental health, helping us identify and address ecological issues (Burger et al. 2022).

4. HUMAN AND WILDLIFE CONFLICTS

Human-wildlife conflicts arise from competition or negative interactions between humans and wildlife, resulting in crop damage, livestock predation, human safety concerns, resource competition, disease transmission, and illegal wildlife trade (Pozo et al. 2021). These conflicts can lead to economic losses for farmers and herders, as well as human safety concerns. Wildlife also plays a crucial role in zoonotic disease emergence and reemergence, acting as reservoirs for disease transmission (Cupertino et al. 2020). Public health concerns arise from close contact with wildlife, bush meat consumption, or exposure to their habitats can increase the risk of disease transmission, leading to conflicts over public health concerns (van Vliet et al. 2022).

5. FACTOR CONTRIBUTING TO THE EMERGENCE AND REEMERGENCE OF ZOONOTIC DISEASES

The emergence and reemergence of zoonotic diseases can be attributed to various factors. Some of those factors are described as follows:

- Deforestation and animals' habitat destruction for the purpose of expanding agriculture, logging or urbanization has increased the contact between humans, domestic animals, and wildlife, thus, facilitating disease transmission (Goldstein et al. 2022).

- Wildlife trade, especially the illegal trade of exotic animals, can introduce unknown pathogens to humans (Hughes 2021).
- Intensive farming practices, such as factory farming create crowded and stressful conditions for animals, promoting disease spread (Marchese and Hovorka 2022).
- Climate change can alter the distribution and behavior of animals, insects, and vectors that carry diseases. It can also affect the survival and reproduction of pathogens, leading to changes in the prevalence and geographic range of zoonotic diseases (Bartlow et al. 2019).
- Changes in agricultural practices and global travel/trade also contribute to disease spread (Hughes 2021).
- Modifications to the microorganisms themselves or their host range (passing species barriers) also plays an important role in emergence and reemergence of zoonotic diseases (Rehman et al. 2020).
- Improved technological diagnostic and epidemiological methods that recently led to the discovery of a previously unknown or existing disease agent (Morse et al. 2012).
- Furthermore, both human and animal antibiotic abuse and misuse can contribute to the evolution of antibiotic-resistant microorganisms, making it more difficult to treat zoonotic diseases (Williams et al. 2002; Cutler et al. 2010.

6. WILDLIFE CONNECTION WITH ZOONOTIC DISEASES

History told us that human health has always been affected by zoonotic diseases and wildlife played a significant role in those illnesses (Cleaveland et al. 2007). The connection between wildlife and emerging and reemerging zoonotic diseases is increasingly being recognized. Following factors has been found to have an important role:

- Many of the wild animal species act as “reservoirs” for zoonosis, which make them capable of harboring virulent strains of disease without becoming ill themselves and thereby allowing contaminated particles to circulate for long periods before being detected in humans or domesticated animals (Aguirre 2017).
- The high degree of mobility associated with some wildlife species makes them efficient vectors/carriers for infectious agents –many wild birds migrate far distances across continents each year–potentially spreading transmission over large geographical areas quickly (especially if there has been recent contact with animal products like raw meat) (Akter et al. 2020).
- Changes in wildlife habitats caused by human activity have increased the contact between wild species and domestic animals, which has increased the likelihood of disease transmission from one species to another (and sometimes from one species to humans) (Thompson 2013).

7. ANTHROPOGENIC ACTIVITIES AND WILDLIFE ZOONOSIS

7.1. HUMAN Activity and Demographic Factors

Human activity and demographic factors impact the epidemiology of zoonosis having wildlife reservoirs. Activities like hiking, camping, and hunting increase the risk of tick-borne zoonosis and tularemia. Eating habits, such as consuming meat from unusual animals, such as bear, also increase the probability of developing trichinellosis (Gao et al. 1999).

7.2. GLOBAL WARMING

Global warming damage increases pathogen exchange between wild species and domesticated ones (like pigs), leading to public health threats like bird flu strains H7N9. This "pathogen bridge", which occurs from

ducks to poultry farms, then subsequently reach local populations through direct consumption (Reperant et al. 2016).

7.3. MICROBIAL ALTERATIONS OR ADAPTABILITY

The epidemiology of zoonosis with a wildlife reservoir is also influenced by microbial alterations or adaptability. Mutations, such as genetic drift in viruses, gene activation and silencing, genetic recombination, conjugation, transformation, and transduction in bacteria are examples of these alterations (Bengis et al. 2004).

7.4. NATURAL SELECTION AND EVOLUTION

Natural selection and evolution are also key factors and there are numerous routes for adaptive or genetically changed microorganisms to get from wildlife to humans, either directly or indirectly through domestic animals. A worldwide wildlife trade, which is frequently illegal and involves the placement of wild animals in live-animal markets, restaurants, and farms, is crucial in this regard because these activities foster more compact relationships between wildlife, domestic animals, and people (Bell et al. 2004).

8. ROUTES OF TRANSMISSION

8.1. DIRECT TRANSMISSION

Zoonotic diseases can be transmitted from wildlife to humans through direct contact; the primary route of most infections, that involves direct handling of infected wildlife animals or their products for consumption. This includes activities like petting zoo visits, holding and feeding wild mammals, handling amphibians or reptiles, participating in hunting trips, slaughtering diseased animals found on game farms (i.e., fowl cholangio-hepaticosis) etc. Additionally, some virus particles may be resistant to cold temperatures, making it possible for them to remain viable at surfaces likely to cause human infection if they are previously exposed to another infected person. Francisella tularensis, the causative agent of tularemia, is one example of a zoonotic pathogen that can be directly transmitted from wildlife to humans through skin contact with an infected, sick, or dead hare or rodent. Rabies virus, on the other hand, is transmitted through a rabid animal's bite (saliva). Aerosols in dust from rodent excreta transfer Hantaviruses from rats to humans (Kruse et al. 2004).

8.2. INDIRECT TRANSMISSION

Indirect transmission route involves encountering materials that have become contaminated by these animal hosts - either directly due to open bleeding wounds while killing the animal host or externally due veterinary examination techniques (vaccination), medical procedures (needle prick injury during drawing blood sample) etc. Indirect disease transmission occurs also through vectors like ticks and mosquitoes, airborne exposure (e.g., inhalation of aerosolized particles containing zoonotic agents released by coughing or sneezing near an infected animal or human host), fecal-oral contamination, consumption contaminated water or food sources, injury due to bites or scratches from an infected animal/host

species. For instance, mosquitoes are well-known carriers of several zoonotic diseases, such as Rift Valley sickness, equine encephalitis, and Japanese encephalitis. Fleas can transfer Yersinia pestis, flies can spread Bacillus anthracis spores, and sandflies can disseminate Leishmania, whilst ticks are vital in the spread of Borrelia burgdorferi and Ehrlichia/Anaplasma (Kruse et al. 2004).

Numerous elements, such as the host's susceptibility, potential transmission pathways, the number of microbes an animal sheds, the severity of infection, and the pathogenic agent's ability to cross species barriers, might affect the likelihood of transmitting and developing a zoonosis (Bengis et al. 2004).

Zoonotic diseases can be transmitted from the mother to fetus during gestation through transfusion or organ transplantation. Organ transplants can contain various agents, including encysted parasites and latent viruses, which can be reactivated in immunocompromised recipients. The bovine spongiform encephalopathy agent, for example, is normally transmitted solely through tissue ingestion; however, it can be acquired through transfused blood (Bengis et al. 2004). Various routes of transmission of zoonotic diseases are shown in Fig. 2.

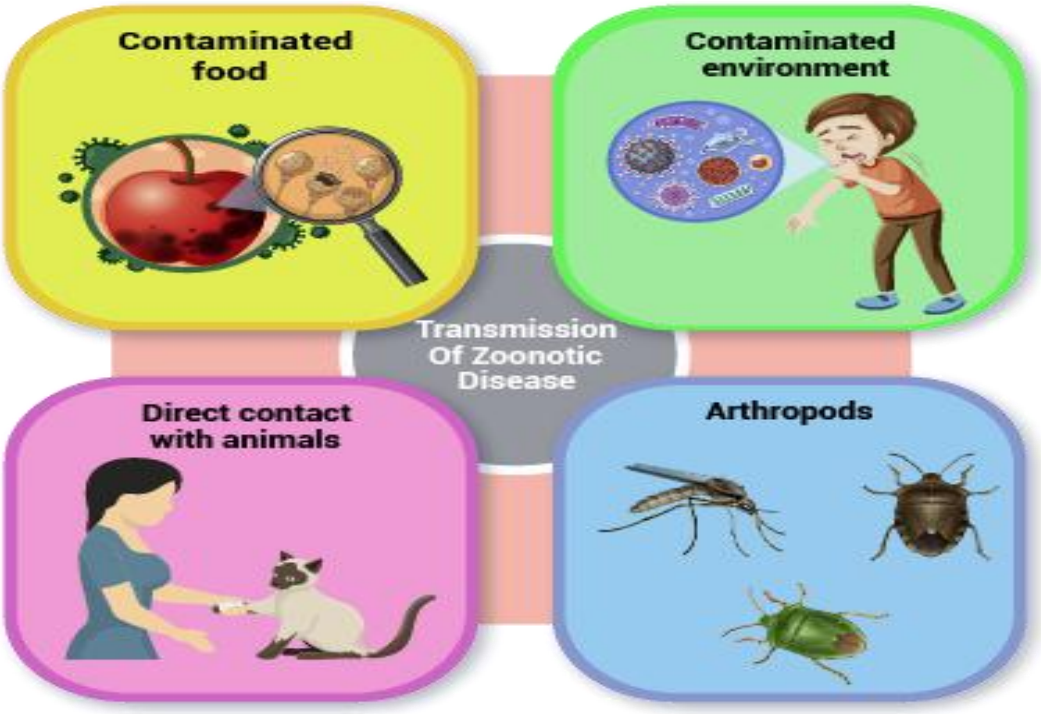

Fig 2: Various routes of zoonotic disease transmission

9. EXAMPLES OF WILDLIFE-TO HUMAN DISEASE TRANSMISSION (FROM PAST AND PRESENT

Zoonotic diseases have been a part of human history for thousands of years. Throughout history, zoonotic diseases have caused devastating epidemics. For example, the bubonic plague, often known as the Black Death, was caused by the bacteria *Yersinia pestis* and transmitted by fleas that infested rats. This 14th-century pandemic killed millions of people in Asia, Africa, and Europe. The outbreak, which began in the Far East, killed almost one-third of Europe's population. However, bubonic plague still exists throughout Asia, Africa, and the Americas, with the World Health Organization reporting 1,000-3,000 cases each year (Perry and Fetherston 1997).

According to ancient stories and current speculations, Alexander the Great died in Babylon in 323 BC of Encephalitis caused by the West Nile virus, a virus that inhabits wild birds. In 1999, the West Nile virus was introduced into the United States, resulting in a recurrent bird epidemic with infections expanding to humans and horses (Marr and Calisher 2003).

Lyme borreliosis, caused by *B. burgdorferi*, is a spirochete found in rodents and *Ixodes* species. Initially identified in 1975, the disease has spread globally. Reforestation in the northeastern US has increased disease transmission through white-tailed deer and deer mice, and the abundance of *Ixodes scapularis* tick vector (Barbour and Fish 1993).

Another zoonosis influenced by both natural and manmade animal migration is bovine tuberculosis caused by *Mycobacterium bovis*. During the colonial era, imported cattle are most likely initially brought bovine tuberculosis to Africa, where it later expanded to and became endemic in animals. (Cosivi et al. 1995).

Human tickborne ehrlichiosis has been recognized and spread recently, commencing with human monocytic ehrlichiosis and human *Granulocytic ehrlichiosis*, which were initially documented in the United States in 1987 and 1994, respectively. The pathogens, *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum*, are intracellular bacteria that survive in zoonotic cycles involving sick deer and rats (Dumler and Walker 2001).

In 1999, *E. multilocularis* was found for the first time in Norway. Due to the parasite's primary host, the Arctic fox, which is naturally mobile, the parasite most likely originated in Russia. Moreover, the sibling vole, the intermediary host, had previously been transported to Norway, probably via imported animal feed. The parasite was able to establish itself. *E. multilocularis* was discovered in a traffic-killed red fox in Copenhagen, Denmark, in 2000. According to the notion, the fox traveled by rail from Central Europe, where infectious disease become prevalent.

A poxvirus that is largely found in Africa is the source of the uncommon zoonosis known as monkeypox. It spreads to rodents and was initially identified in 1958 in monkeys; the African squirrel is its natural host (Reed et al. 2003). In 2003, the virus was introduced to prairie dogs in the US by imported African mice from Ghana and the outcome was an outbreak in the USA resulted in 37 confirmed human cases. By introducing a disease into native animal and human populations, this spread is an example of how non-native animal species can seriously harm public health. Consequently, the likelihood of zoonosis spreading can be increased by animal transportation, commerce, or distribution and by releasing animals into the environment **(**Kruse et al. 2004).

Three zoonotic paramyxoviruses, Hendra, Menangle, and Nipah, were discovered between 1994 and 2004 in wildlife. These viruses have a fruit bat reservoir and can cause human infection when close contact with diseased pigs or horses. Infection with the hendra virus in Australia in1994 led to lethal respiratory illness in horses and humans. The Menangle virus caused influenza-like illness and reproductive issues in pigs in 1996 in Australia, while the Nipah virus in 1998 in Malaysia caused encephalitis in Malaysia, killing 40% of humans and causing severe illness in pigs (Brown 2003).

The present-day example of potential microbial transformation is severe acute respiratory syndrome (SARS). This viral respiratory infection, caused by SARS-associated coronavirus, is thought to have first appeared in November 2002 in Guangdong, China. SARS was initially identified in Asia in February 2003, and the virus quickly expanded to a global epidemic before being halted. Although the reservoir of the virus is unknown, wildlife is a likely source of infection. Animals local to the region where SARS is assumed to have originated, including raccoon dogs, rats, and palm civet cats, have shown signs of natural infection (Guan et al. 2003).

Table 2: Specific Zoonotic Diseases Associated with Wild life Species.

Sr. No	Disease	Reservoir	Agent	Transmission/Vector	Complications	Distribution	Mortality Rate	References
				Viral Agent				
1.	SARS-Cov-1	Bats	SARS-coronavirus	Aerosol dissemination	Respiratory track	Worldwide	9.6%	(Wang and Crameri, 2014)
2.	SARS-CoV-2	Bats	SARS-coronavirus	Aerosol dissemination	Respiratory and intestinal infection	Worldwide	2%	(Wang and Crameri, 2014)
3.	MERS	Camel	MERS-Coronavirus	Aerosol dissemination	Pneumonia	Middle East, Saudi Arabia, worldwide	34%	(Wang and Crameri 2014),
4.	Dengue Fever	Monkey	Dengue Virus	Bites of *Aedes aegypti*	Internal Bleeding, Organ Damage	Africa, Southeast Asia, America, Caribbean, Pacific	<1-20%	(Kularatne 2015).
5.	Highly Pathogenic Avian Influenza (H5N1)	Birds	Influenza viruses	Direct contact with feces, saliva, or mucosa of infected bird	Respiratory track	China, Hong Kong Europe, Africa, China, Russia, Kazakhstan	50%	(Van Kerkhove et al., 2011)
6.	Swine Flu Influenza (H1N1)	Swine	Swine Flu Influenza virus	Aerosol dissemination	Respiratory track	Uk, Mexico	0.001%-0.007%	(Klemm et al. 2016)
7.	Ebola Hemorrhagic Fever	Bats/Apes and Monkey	Ebola virus	Direct contact	multiple organ systems of the body are affected+ extensive internal breeding	Democratic Republic of Congo, Sudan, Uganda, Gabon	50%	(Wang and Crameri 2014)
8.	Hantavirus p Pulmonary Syndrome	Rodents	Hanta virus	Contact with rodent's. Feces	Hemorrhagic Fever Renal syndrome (HFRS)	America, Asia, Europe	38%	(Wang and Crameri, 2014)

9.	Zika Fever	Monkey	Zika virus	Bite of *Aedes* mosquito hemotransfusion, organ transfusion, sexual contact, vertical transmission	Microcephaly, congenital malformations, Guillain-Barre syndrome, neuropathy, myelitis	Africa, America, Southern Asia, Western Pacific	>50%	(Wang, et al. 2016).
10.	Nipah Virus Diseases	Pigs, Bats	Paramyxo-virus	Direct contact or consuming contaminated food products	neurological disorder Systemic vasculitis, thrombosis and parenchymal necrosis	Malaysia, Singapore, India, Bangladesh	40-75%	(Wang and Crameri 2014)
11.	Rabies	Raccoons, Skunks, Bat, Foxes	Lyssa viruses	Direct contact (skin, mucous. tissues)/bite of rabid animal	Cerebral Dysfunction, anxiety, agitation	All Continents Except Antarctica	100%	(Wang et al. 2016).
12.	Rift Vally Fever	Cattle, Buffalo, Sheep Goat, Camel	Rift Valley Fever Virus	Direct contact or bite of infected mosquitos	Inflammation of retina	African Madagascar, Saudi Arabia, Yemen	1-10% Vision loss	(Jelinek, 2016).
13.	Japanese Encephalitis	Pigs And Water Birds	Japanese encephalitis virus	Bite of *Culex tritaenniorhynchus*	Encephalitis syndrome	Asia. North And South Korea, Japan	20-30%	(Gerdes, 2004).
				Bacterial Agent				
1.	Septicemia Plague	Rodents	*Yersinia pestis*	Flea Bites or via skin Lesion	Gangrene and organ Failure	Hong Kong Africa, Asia, South America	40%	(Higgins 2004)
2.	Pneumonic Plague	Rodents. Rabbits, And Large Animal	*Yersinia pestis*	Aerosol Dissemination	Lung infection	Manchuria, Congo, Madagascar, Peru	100%	(Higgin, 2004)
3.	Bubonic Plague (Black death)	Rodents	*Yersinia pestis*	Flea bites	Infect Lymph nodes	Europe Africa, Asia, South America	30-60%	(Higgins 2004)
4.	Leptospirosis	Rodents, Dogs	*Leptosporria interogance*	Direct Contact with infected animal feces/or contaminated soil or water.	Weil's syndrome	Germany, Cosmopolitan Distribution (Tropical and Subtropical Climate)	5-15%	(Ellis 2015)
5.	Anthrax	Cattle, Sheep, Goats, Horses and Swine.	*Bacillus anthracis*	Inhaling /ingesting food contaminated with spores	Cutaneous, gastrointestinal and respiratory tract infection, meningoencephalitis	Asia, Europe, Africa, Australia.	20-50%	(Doron and Gorbach 2008).

6.	Campylo-bacteriosis	Poultry, Cattle, Pigs, Sheep, Cats, Dogs	*Campylobacter* spp.	International travel, eating uncooked/raw meat, dinking unpasteurized milk, etc.	Arthritis, Reiter's Syndrome, Conjunctivitis	Worldwide	<1%or rarely	(Doron and Gorbach, 2008).
7.	Cowpox	Rodents, Cats	Orthropox virus	Direct contact with infected animal	Keratitis, Corneal Erosion	Europe, Russia	1-3%	(Vorou et al. 2008)
8.	Q Fever	Goat, Cattle, Sheep	*Coxiella burnetii*	Contact with urine, blood, milk of infected animal	Organ dysfunctioning, Aortic aneurism, spondylitis	Worldwide Distribution Except New Zealand	1-2%	(Doron and Gorbach 2008).
9.	Tularemia (Rabbit fever)	Hares, Rodents,Ticks	*Francisella tularensis*	Hunting, skinning infected rabbits, ingestion of contaminated food/water	Meningitis, endocarditis, hepatitis	Europe, Asia	30-60%	(Gilland and Cunha 1997)
				Parasitic Agent				
1.	Malaria	Monkey	Plasmodium	Bite of female Anopheles mosquito	Acidosis, hypoglycemia	Worldwide	0.05-0.0-8%	(Youssef and Uga 2014)
2.	Toxoplasmosis	Cats, Beef, Lamb or Pork	*Toxoplasma gondii*	Ingestion of oocytes from soil, water, milk, or vegetables	encephalitis or retinochoroiditis	All Continents Except South America	35%	(Youssef and Uga 2014)
3.	Chagas Disease	Dogs, Cats and Opossum	*Trypanosoma cruzi*	Triatomine bugs	Sleeping sickness	Africa, America and Asia	5-10%	(Rassi and Marin-Neto 2010)
4.	Taeniasis and Cysticercosis	Beef, Pork, Pigs	*Taenia solium*	Direct contact/ ingesting contaminated food/water	Intestinal infection, tissue infection	Africa, Asia, Latin America	1.4%	(Youssef and Uga 2014)
5.	Alveolar Echinococcosis	Sheep, Cattle, Camel, Pig, Moose, Rodents, Dogs	Echinococcus spp.	Ingesting/ Inhaling contaminated food/ water	Rupturing of peritoneal cavity and pleural cavity	Worldwide	50-75%	(Kern 2010)
6.	Fascioliasis	Horses, Pigs	*Fasciola hepatica, F. gigantica*	Drinking contaminated water	Infection of bile duct and liver	America, Asia, Africa	Seldom fatal	(Mas-Coma et al. 2014)
				Fungal Agent				

1.	Sporotrichosis	Cats,	Sporothrix	Cutaneous skin infection/direct contact with spores	Respiratory tract infection, arthritis, Nervous system infection	South America, Asia, Europe	40%	(Mahajan 2014)
2.	Dermatophytosis	Cats, Dogs Cows, Horses	Dermatophytes	Inhalation, direct contact with infected animal	Hair loss, scaring	Worldwide	7.9%	(Mahajan 2014)
3.	Creutzfeldt-Jakob disease (CJD)/ Bovine Spongiform Encephalopathy	Cattle	Prion	Consuming contaminated beef	Fatal neurodegenerative disease	United Kingdom	100%	(Iwasaki 2017)

The era of exploration and trade in the 15th to 18th centuries facilitated the global spread of zoonotic diseases. European explorers and colonizers unknowingly introduced diseases like smallpox, measles, and influenza to indigenous populations in the Americas, resulting in devastating consequences (Kruse et al. 2004).

10. ZOONOSIS CLASSIFICATION

Numerous microorganisms can cause zoonotic illnesses. Zoonosis is divided into bacterial, viral, parasitic, fungal, and protozoa zoonosis types based on the etiology (Schaechter 2009). The primary zoonotic illnesses are included in Table 2, together with information about their etiological agents, animal hosts, key symptoms, geographic distribution, and fatality rates.

11. IMPACT OF ZOONOSIS ON HUMAN AND ANIMAL HEALTH

Zoonosis significantly impact human and animal health. They negatively affect human livelihoods and well-being, particularly in developing countries. Individuals may face obstacles in work performance and family support, and may become isolated, increasing their vulnerability to mental health issues. Similarly, Zoonotic diseases cause animal deaths, leading to significant economic losses in the livestock sector. This can negatively impact animal health and productivity, leading to a 70% drop in livestock products (Hashem et al. 2020).

Zoonotic diseases that impact animal goods and byproducts, such as BSE, avian influenza, and anthrax, cause disruptions in global trade and the economy. Zoonotic epidemics had an overall economic impact of more than 120 billion USD between 1995 and 2008 (Bernstein et al. 2022). The value of Australia's livestock decreased by 16% because of epidemics affecting sheep and cattle (Ijaz et al. 2021).

The SARS outbreak severely affected the global economy, including the tourism sector. Singapore, China, Hong Kong, and Taiwan experienced severe economic effects. Mexico, India, Chile, and the European

Union also suffered economic losses because of restricted tourism and poultry export markets (Rahman et al. 2020).

12. CONTROL OF WILDLIFE ZOONOSIS

Surveillance is crucial for the purpose of preventing and controlling zoonotic illnesses, early infection detection, identifying infected individuals and animals, reservoirs, vectors, and endemic areas. It aids in the proper management of disease, the improvement of human health, and the reduction of morbidity and death. Controlling zoonosis requires integrated monitoring systems strategies at the local, provincial, national, and global levels. In order to perform surveillance effectively, it is necessary to have sufficient diagnostic resources, competent labor, and financing (Giessen et al. 2010).

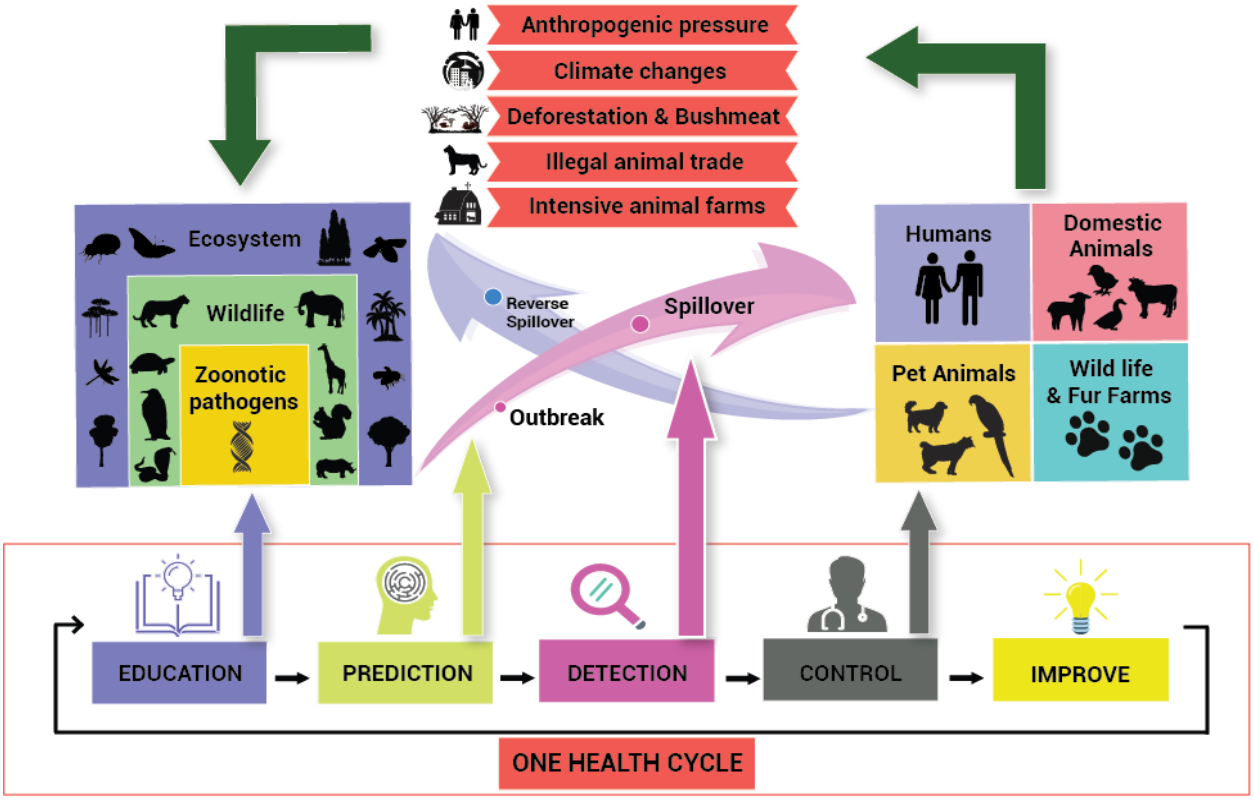

Fig. 3: Control of Wild Zoonosis and One Health.

Zoonosis can also be controlled through general principles of disease control like treating sick people, immunizing healthy people and animals, limiting animal movement, managing animal populations, performing tests, and culling (selective slaughtering). Pest and vector control are also necessary for several parasitic and bacterial zoonoses that are transmitted by insects including ticks, lice, and mosquitoes. Successful vector control strategies should employ physical, biological, and/or mechanical techniques, such as integrated pest management and integrated vector management systems (Rahman et al. 2020). Further zoonosis management measures include the adoption of rules and regulations governing isolation and quarantine, the development of reliable disease reporting (notification) systems, agricultural biosecurity, mass immunization, test and slaughter, public awareness, and health education. Public awareness of zoonosis

can be increased through the use of mass media, electronic information systems, social networking sites, text messages, and other forms of communication (Artois et al. 2011). Fig. 3 illustrates various causes of wildlife zoonosis and ways to control them.

13. ZOONOSIS AND ONE HEALTH

The "One Health Approach" was established to adequately address global health concerns, and it has widespread consequences on poverty, food security, and health security, mostly in poor nations, through zoonosis prevention and control. It is essential in combating newly emerging and re-emerging zoonoses, managing the effects of zoonotic diseases on people, animals, and the environment, and eliminating threats from zoonotic diseases (Rahman et al. 2020).

14. CONCLUSION

A significant number of human infectious diseases are derived from animals, posing a substantial threat to human health. Changes in food trend, climatic pattern, and environmentally unfriendly human operations all have a direct effect on the emergence and reemergence of zoonotic illnesses. The COVID-19 pandemic illustrates the human population's vulnerability to zoonosis. Prioritizing research on one health approach is vital for identifying urgent preventative steps and implementing strong active monitoring for zoonosis detection and management.

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Coronaviruses and their Host Range: Implications for Zoonotic Transmission

21

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ABSTRACT

Coronaviruses cause infections in various species, including mammals, birds, and humans. Their zoonotic potential has surfaced with the occurrences of severe acute respiratory syndrome (SARS), Middle Eastern respiratory syndrome (MERS), and Coronavirus disease 2019 (COVID-19). Additionally, the natural and intermediate hosts for other known coronaviruses to infect humans also originate from the animals. The ability of coronaviruses to infect a wide range of hosts can be attributed to factors such as genetic variability, utilization of different receptors, host immune response, and environmental conditions. Consequently, these viruses can undergo spillover events by adapting to new hosts through amplification hosts. Several factors contribute to the facilitation of spillover events. Pro-zoonotic elements such as interaction with infected animals, the existence of live animal markets, uncontrolled deforestation, and the impact of climate change all play a role in promoting these events. In the absence of proper surveillance, regulation of animal trade, misconceptions surrounding the "one health" approach, and inadequate public health interventions, the likelihood of future spillover events is heightened. This chapter focuses on the critical association between the host range of coronaviruses and their ability to be transferred from animals to humans. It also reviews the current knowledge on the epidemiology of zoonotic coronaviruses and the factors associated with their spread, thus highlighting the gaps and challenges that need to be addressed for better preparedness and response. By understanding this relationship, this chapter stresses the risks associated with zoonotic transmission of coronaviruses, which is crucial to devise prevention and mitigation strategies against them.

Keywords: Coronaviruses; zoonosis; host range; spillover event; one health

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1. INTRODUCTION

Coronaviruses (family: Coronaviridae; order: Nidovirale) are common pathogens for vertebrates, including humans (Zhou et al. 2021). Nidoviruses are divided into four subfamilies based on the structure of genome and phylogenetic relationships: *Alphacoronaviruses*, *Betacoronaviruses*, *Gammacoronaviruses* and *Deltacoronaviruses*. The *Alpha*- and *Betacoronaviruses* produce infections in mammals only. The *Gamma*-and *Deltacoronaviruses* infect mainly birds, but a few can also produce infection in mammals (Woo et al. 2012). *Alphacoronaviruses* and *Betacoronavirses* are correlated with respiratory ailments in humans. However, in animals, they predominately cause gastroenteritis (Su et al. 2016).

Recently, the reputation of coronaviruses in terms of zoonosis peaked, especially after the COVID-19 pandemic (Smith et al. 2022). The current phylogenetic analysis shows that all human coronaviruses have originated from animal-origin coronaviruses. Domestic animals usually act as intermediate hosts between natural hosts of coronaviruses (usually bats) and humans (Woo et al. 2012; Zhou et al. 2018). Due to evolution, genetic recombination and a variety of host range in the Coronaviridae family, these viruses can modify host range and tissue tropism, making their adaptation to new environments effective (Rohaim et al. 2020). Coronavirus replication in different host cells depends upon the presence of specific receptors with varying expression among species (Tai et al. 2020). This chapter outlines the host range of existent coronaviruses, emphasizing its importance in the zoonotic implications of these viruses. The factors affecting the zoonotic spillover are also discussed.

1.1. STRUCTURE OF CORONAVIRUS

Coronavirus genome is made up of a large, positive sense, non-segmented single-stranded RNA, 26-31 kbps in size (Mousavizadeh and Ghasemi 2021). The organization of the genome is 5’-Untranslated Region (UTR)-leader followed by two ORFs (open reading frames; ORF1a, ORF1b, highly variable among strains) that produce replicase/transcriptase further followed by Spike (S), Envelope (E), Membrane (M), Nucleocapsid (N) and ends with 3' UTR- poly A tail (Yang and Leibowitz 2015). The virus exhibits pleomorphism in its size (80-120nm) (Bárcena et al. 2009). Structurally, S protein is highly variable among coronaviruses that harbors a receptor-binding domain (S1; RBD) and membrane-fusion domain (S2; MFD), helping the virus in adsorption and entry into the host cell. This protein also contributes to the host specificity of the virus (Nao et al. 2017). SARS-like viruses have polybasic cleavage sites, which enhance the cell-cell fusion without viral entry being affected (Follis et al. 2006), ultimately helping in the spillover from bats to humans (Menachery et al. 2020). Some coronaviruses also express hemagglutinin protein that exhibits acetyl-esterase activity, which aids in viral entry and progression of the viral pathogenesis (Ashour et al. 2020).

1.2. HISTORICAL BACKGROUND OF CORONAVIRUSES

Coronaviruses first surfaced in the 1930s, when the first coronavirus was reported in chickens with upper respiratory tract infection symptoms in the United States (US). This virus was initially called as infectious bronchitis virus (IBV), later called the Avian coronavirus (Lalchhandama 2020). In mammals, it was first reported in 1946, also in the US, when gastroenteritis in pigs with high mortality led to the discovery of porcine transmissible gastroenteritis virus (TGEV) (Chen et al. 2023). Between 1947 and 1950, 2 murine coronaviruses were discovered: JHM and mouse hepatitis virus (Grabherr et al. 2021). In cats, a new inflammatory intestinal disease reported in 1966 was linked to feline infectious peritonitis virus (FIPV) (Decaro et al. 2021). Later, canine coronavirus was reported in US military dogs in 1974 (Pratelli et al. 2022).

In humans, two coronaviruses were reported in the 1960s with common cold symptoms in England and Chicago and designated as B814 and 299E, respectively (Poutanen 2018). Later, viruses like Human Coronavirus-229E, HCoV-HKU1 and HCoV-NL63 were discovered, causing self-limiting respiratory and digestive tract symptoms (van der Hoek et al. 2004). Human coronaviruses were considered of less importance amid mild infection till the outbreak of SARS caused by SARS-CoV in 2003 (Zhong et al. 2003). The gradual genetic evolution in coronaviruses demonstrated the unstable nature of the coronavirus genome and its adaptability to become more virulent, even fatal, to humans. In 2012, a more lethal form of SARS originated in Saudi Arabia, caused by MERS coronavirus (MERS-CoV) through dromedary camels as intermediate hosts (Zaki et al. 2012). In 2019, coronaviruses' evolutionary and zoonotic potential was etched in history with the pandemic caused by SARS-CoV2. These coronavirus cases were reported worldwide, making SARS-CoV2 a natural catastrophe (Zhou et al. 2021).

2. HOST RANGE OF CORONAVIRUSES

Due to the large single-stranded RNA genome, Coronaviruses undergo rapid genetic recombination and mutations, resulting in several new strains for each virus and the ability to cross host species barriers (Millet et al. 2020). Many human coronaviruses like HCoV-229E, HcoV-NL63, MERS-CoV, SARS-CoV, and SARS-CoV-2 can eventually originate back to bat viruses (Cui et al. 2019). It is interesting to see the host range of known coronaviruses in domestic, wild and companion animals (Table 1-4, adapted from Zhou et al. 2021).

2.1. FACTORS AFFECTING HOST RANGE

Coronaviruses have this broad host range due to the following factors:

2.1.1. GENETIC VARIABILITY

A two-pronged genetic variability from coronaviruses and their hosts is a critical factor in the broad host range for these viruses. Studies have shown that genes involved in the immunity of hosts, including humans, exhibit a strong selection pattern, exerting a selection pressure for genes and pathways key to the host defense, leading to inter-species heterogeneity. Similarly, due to the extremely high mutation rate in the coronavirus genome, new phenotypes can pertain ability to infect new hosts (Quintana-Murci 2019).

2.1.2. RECEPTOR USAGE

A correlation between the host range and these hosts' phylogenetic conservation of coronavirus receptors is critical. The RBD and MFD in the spike protein of different coronaviruses are highly diverse and lead to variability in receptor specificity. Sequence length in the S1 subunit has a low conservation threshold, resulting in variability in sequence length ranging from 544 (IBV) to 944 (229-related bat coronaviruses) (Hulswit et al. 2016). Expression and location of proteinaceous ectopeptidase receptors (APN, ACE2, and DPP4) in different species offer room to cross the host species barrier (Bosch et al. 2014).

2.1.3. INNATE IMMUNE RESPONSE

Most viral infections in mammals are mediated by Toll-like receptors (TLRs) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs). Variation in these mediators in terms of expression, recognition, and activation, coupled with immune evasion strategies of coronaviruses like protein translation blocking by coronaviral non-structural protein 1 (nsp1), can also affect the host range (Kasuga et al. 2021).

Table 1: Host range of known *Alphacoronaviruses* in domestic, wild and companion animals

Host	Virus	Year
Human	HcoV-229	1967
	EHCoV-NL63	2004
Bat	BtCoV/512	2006
	Bat-CoV HKU2	
	HKU10	2012
	HuB-2013	
	Sax-2011	2016
	SC-2013	
	3398	
	CDPHE15	2017
	Tr-BatCoV HKU33	2019
Pig	TGEV	1946
	PEDV	1978
	PRCV	1986
	SeACoV	2018
Cat	FcoV/FIPV	1963
Mink	McoV	1990
Dog	CcoV	2003
Ferret	FRSCV	2006
	FRECV	2010
Rat	RatCoV LRNV	2015
Camel	DcCoV-229E	2016
Shrew	Shrew-CoV/Tibet2014	2017
	WESV	2018
Rabbit	L232	2019

Table 2: Host range of known *Betacoronaviruses* in domestic, wild and companion animals

Host	Virus	Year
Human	HcoV-OC43	1966
	SARS-CoV	2003
	HcoV-HKU1	2005
	MERS-CoV	2012
	SARS-CoV2	2020
Bat	HKU4	2006
	HKU5	
	HKU9	2007
	BtHp-BetaCoV/ZJ2013	2016
	Ro-BatCoV GCCDC1	2016
	CMR704	2018
Pig	PHEV	1962
Mouse	MHV	1964
Bovine	BcoV	1973
Equine	EcoV	2000
Dog	CRCoV	2003
Alpaca	BcoV	2007
Giraffe	GiCoV	2007
Sable antelope	SACoV	2008
Camel	DcCoV-HKU23	2014
Hedgehog	Hedgehog coronavirus 1	2014
Rat	HKU24	2015
	RtMruf-CoV-2/JL2014	2018

Table 3: Host range of known *Gammacoronaviruses* in domestic and wild animals

Host	Virus	Year
Poultry	IBV	1931
	Avian coronavirus 9203	2022
Turkey	TcoV	1951
Beluga Whale	BWCoV SW1	2008
Duck	Duck coronavirus 2714	2013
Bottleneck Dolphin	BdCoV HKU22	2014
Goose	Goose coronavirus CB17	2019

Table 4: Host range of known *Deltacoronaviruses* in domestic, wild and companion animals

Host	Virus	Year
Asian Leopard Cat	ALC/GX/F230/06	
Chinese ferret badger	CFB/GX/F247/06	2007
	CFB/GX/F250/06	
Bulbul	BuDCoV HKU11	
Thrush	ThDCoV HKU12	2009
Munia	MunDCoV HKU13	
Pig	PDCoV HKU15	
White-eye	WEDCoV HKU16	
Sparrow	SpDCoV HKU17	
Magpie robin	MRDCoV HKU18	2012
Night heron	NHDCoV HKU19	
Wigeon	WiDCoV HKU20	
Common moorhen	CMDCoV HKU21	
Falcon	FalDCoV UAE-HKU27	
Houbara bustard	HouDCoV UAE-HKU28	2018
Pigeon	PiDCoV UAE-HKU29	
Quail	QuaDCoV UAE-HKU30	
Common magpie	HNU1-1, HNU1-2, HNU2 and HNU3	2022

2.1.4. ENVIRONMENTAL FACTORS

Deforestation is directly linked to the emergence of Ebola, SARS and other bat-borne viruses due to the human-related selectivity of environments suitable for wild animals like bats, leading to increased chances of transmission of viruses (Afelt et al. 2018). Population growth and globalization are other essential factors linked to the spread of zoonotic viruses like SARS-CoV and SARS-CoV2 (Colson et al. 2022). Climate changes can also cause a revival of viral replication under stress, resulting in more spillover events (Bhattacharya et al. 2020a).

2.2. CROSS-SPECIES SPREAD OF CORONAVIRUSES

Coronaviruses jump between species courtesy of their reservoir hosts; bats in the case of most *Alpha*- and *Betacoronaviruses*, while wild birds for *Gamma*- and *Deltacoronaviruses* (Woo et al. 2012). The following points highlight the potential for cross-species transmission of coronaviruses:

2.2.1. SPILLOVER EVENTS

Throughout history, coronaviruses have crossed the species barrier on multiple occasions. Molecular epidemiological studies on SARS-CoV show that the primary human cases of the disease likely contracted

the virus through masked palm civets as intermediate hosts (Wang et al. 2018), while horseshoe bats were identified as reservoir hosts for the virus (Li et al. 2005). SARS-CoV also shows infection in many lab and companion animals under experimental conditions (Ruiz-Aravena et al. 2022). For MERS, bats are established as putative reservoirs, while dromedary camels are intermediate hosts. Although rare, direct transmission from camels to humans is also documented (Azhar et al. 2014). SARS-CoV2 is probably the most important in this aspect as it caused a pandemic. Although its primary reservoir host has not been established yet, horseshoe bats, pangolins, and minks are probable candidates based on molecular docking studies (Ruiz-Aravena et al. 2022). Apart from coronaviruses of public health importance, many viruses infecting domestic animals also spilled over from wild animals. Bovine coronaviruses (BCoVs) emerged from rodents over 600 years ago (Lau et al. 2015). Canine coronaviruses like Canine Respiratory CoV (CRCoV) originated from BCoVs due to a host species shift (Erles et al. 2007). Feline Coronavirus-I (FCoV-I) has a genetic resemblance to CCoV-I, and FCoV-II is a product of recombination between FCoV-I and CCoV-II (Pratelli et al. 2003). Porcine coronaviruses like TGEV, Porcine Hemagglutinating and Encephalomyelitis Virus (PHEV) and Porcine Deltacoronavirus (PDCoV) originated from canines, bovines and wild birds, respectively (Decaro and Lorusso 2020). These events suggest that coronaviruses show high diversity among host species and are not shy to cross the host barrier, hinting towards more zoonotic spillover events in the future.

2.2.2. AMPLIFICATION HOSTS

Domestic animals are in direct contact with human populations and are indirectly linked to wild animals, thus facilitating the virus amplification in these populations (Johnson et al. 2015). Animals like civets (Guan et al. 2003), horseshoe bats (Li et al. 2005), camels (Reusken et al. 2013), and pigs (McLean and Graham 2022) have all been established as amplifying hosts for a variety of coronaviruses of zoonotic importance.

2.2.3. ADAPTATION TO NEW HOSTS

Coronaviruses owe their adaptation to novel hosts and environmental niches to their high recombination and mutation rates (Latif and Mukaratirwa 2020). For example, the process of adaptation of SARS-CoV-2 to humans likely started years ago, when its antecedent strayed from the bat coronavirus (Burki 2020). Coronaviruses use strategies like overcoming the host defense barriers, replicating, and shedding out of the host cells. These are coupled with virus-induced modification of physiological responses like weakening of interferon production, cuffing immunogenic motifs, evading viral RNA detection, exploiting cell autophagy, activating host cell apoptosis, bringing lymphocyte enervation and diminution, and finally, mutation and evasion from immunity (Kasuga et al. 2021). These strategies help coronaviruses evade existing hosts and adapt to new hosts, causing more spillover events.

3. ZOONOTIC TRANSMISSION OF CORONAVIRUSES

The term "spillover" or "evolutionary jump" describes the event in which a virus spreads from a natural host to a new host, infecting the latter. This could happen by accident, through a first-time exposure, repeatedly, or by a crucial genetic mutation that allows the pathogenic infection of the new host (Plowright et al. 2017). This infection can lead to a dead end or spread to conspecifics by resultant epidemiological cycling or even zooanthroponotic transmission, evident from COVID-19 (Zhu et al. 2020). Spillover is a chance occurrence instead of a typical organism's infection cycle component. In common parlance, cross-species spillover is described as a pathogen jump from animals to humans, where it gets established (Plowright et al. 2017).

3.1. DEFINITION AND TYPES OF ZOONOTIC TRANSMISSION

The World Health Organization describes zoonosis as "any infection that is naturally transmissible from vertebrate animals to humans" (WHO 2022). This is strengthened by the fact that the virus is kept alive in a population of animals (a reservoir), making it a constant source of infection for people (WHO 2020). There are many different types of viruses in the coronavirus family, and some of them have the capacity to infect humans from other species. The most egregious instance is the zoonotic spread of SARS-CoV-2, which caused the COVID-19 epidemic (Andersen et al. 2020; Lam et al. 2020; Xiao et al. 2020).

3.1.1. DIRECT ZOONOTIC TRANSMISSION

When a virus spreads from an infected animal to a human, it is said to have a direct zoonotic transmission. Close contact with infected animals, such as handling or eating them or exposure to their body fluids, can cause this. For instance, the SARS-CoV-2 virus is thought to have originated in a seafood market in Wuhan, China, where live animals, including wildlife species, were offered for sale (Zhou et al. 2020).

3.1.2. INDIRECT ZOONOTIC TRANSMISSION

Indirect transmission is the process by which a virus is transferred from an animal to a human. The virus first spreads from animals to an intermediate host, and then human contact with the intermediate host results in human exposure. The intermediate host acts as a link between the animal reservoir and the people. Regarding SARS-CoV-2, it is believed that an intermediate animal host, such as a wild animal possibly a pangolin, might have played a role in the transmission to humans (Zhang et al. 2020).

3.1.3. ENVIRONMENTAL ZOONOTIC TRANSMISSION

Environmental transmission occurs when humans encounter a contaminated environment that contains the virus. Humans may contract the virus from infected animals when they touch certain surfaces or objects. While less common, environmental transmission has been reported for certain coronaviruses, although the specific mechanisms and risks can vary (Wang et al. 2018).
Fig. 1 schematically shows the common types of zoonoses. Note that all the zoonotic coronaviruses described so far involve an intermediate host. Rabies is a classic example of direct viral zoonosis, while animal trade markets played a crucial role in the spread of COVID-19, making it a substantiated example of environmental zoonosis.

3.2. TRANSMISSION OF CORONAVIRUSES

A basic summary of coronaviruses and their transmission, including zoonotic transmission, is provided by the WHO, which explains how several coronaviruses, including SARS-CoV (from civet cats) and MERS-CoV (from dromedary camels), have been transmitted from animals to people (WHO 2020). SARS-CoV2 was the reason for the most recent COVID-19 outbreak in 2019, which significantly impacted people's health, standard of living, and economy. Given the recent outbreak, there are numerous knowledge gaps regarding this novel virus's comparative and zoonotic features. A correlation between the known natural and intermediate hosts of human coronaviruses and the factors contributing to this zoonotic

relationship is important. Fig. 2 represents the natural and intermediate hosts of seven known human coronaviruses. Bats are the natural hosts for 5 out of 7 known human coronaviruses; as discussed, they all involve intermediate mammalian hosts. Farm animals like cows and camels are prone to coronaviruses and spread infections to humans. Hence, this figure highlights the need for active surveillance of coronaviruses circulating in these animals and the pursuit of uncovering other unknown intermediated hosts.

3.3. FACTORS CONTRIBUTING TO ZOONOTIC TRANSMISSION

Zoonotic transmission is a multipronged phenomenon and can involve a variety of factors, some of which are discussed below:

3.3.1. CONTACT WITH INFECTED AND DISEASED ANIMALS

The zoonotic transmission of coronaviruses is significantly influenced by contact with infected animals. However, they spread more easily through direct contact with diseased animals or bodily fluids. Activities like handling, butchering, or eating diseased animals might cause this. For instance, in the case of SARS-CoV, it is thought that people contracted the disease by touching infected civets (Guan et al. 2003).

3.3.2. OCCUPATIONAL EXPOSURE TO ANIMALS

Some activities, like those involving animal farming, veterinary care, and wildlife research, increase the risk of zoonotic transmission. Animal-related jobs can expose people to coronaviruses through direct contact, bites, scratches, or inhaling contaminated particles, especially in settings with high viral loads (Johnson et al. 2020).

3.3.3. VETERINARY AND ANIMAL CARE PRACTICES

Zoonotic disease transmission can occur due to inadequate infection control procedures and poor handling of affected animals in veterinary offices, animal shelters, or wildlife rehabilitation facilities. These environments present chances for the spread of coronaviruses to veterinary staff, careers, and visitors (Smith et al. 2022).

3.3.4. EXPOSURE TO ANIMAL WASTE

In areas with infected animals, contact with animal waste, polluted surfaces, or contaminated soil can increase the risk of zoonotic transmission. Animal excrement or respiratory secretions can carry viruses that might linger in the environment and potentially infect people who encounter contaminated objects (Decaro et al. 2021).

3.3.5. CONSUMPTION OF INFECTED ANIMALS

The consumption of diseased animals has the potential to spread coronaviruses to people. Consumption of civets in China during the SARS-CoV pandemic in 2002–2003 has been connected to the disease (Guan et al. 2003). Consuming raw camel meat or milk has been linked to MERS-CoV (Azhar et al. 2014). Eating exotic animals in Wuhan's live animal markets is linked to SARS-CoV2 (Wu et al. 2020).

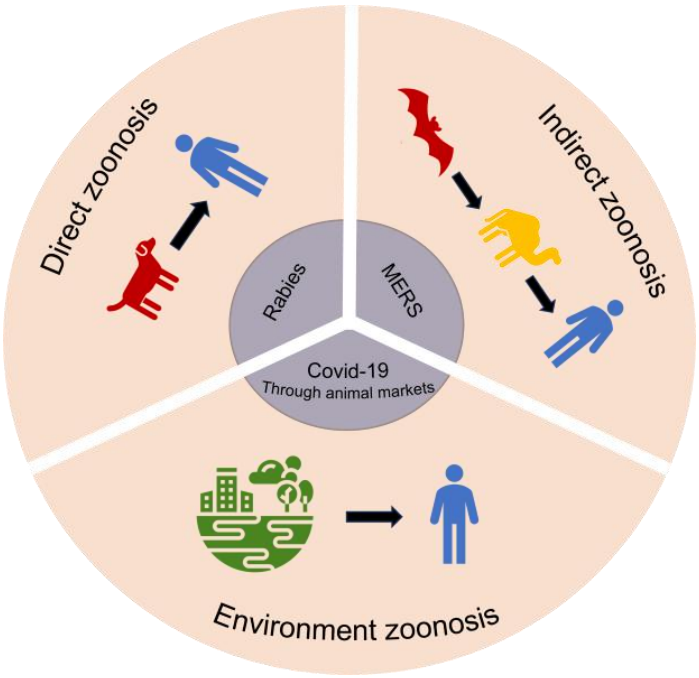

Fig. 1: Common types of zoonotic transmission. Red represents natural hosts, yellow represents intermediate hosts, and blue represents humans.

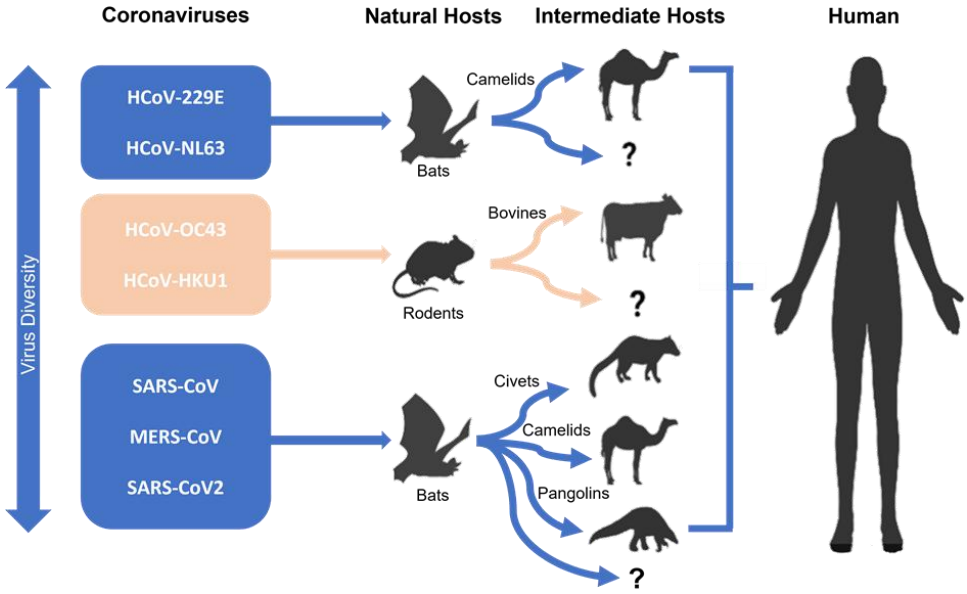

Fig. 2: Schematic representation of natural and intermediate hosts of seven known human coronaviruses. Possible unknown intermediate hosts (represented by **?**) provide major knowledge gaps in studying these viruses.

3.3.6. ENVIRONMENTAL FACTORS

Environmental factors such as deforestation and ecological disruption may force bats and other species to seek new habitats close to human habitations (Daszak et al. 2013). Global warming and climate change also affect the ability of the virus to survive and spread, potentially changing the probability of zoonotic spread to humans. Human encroaching in wildlife habitats increases the interactions with animal species that are coronavirus carriers, making it easier for infections to spread to people (Olival et al. 2017). Globalization and cross-border travel also have the potential to spread the virus quickly. Traveling infected people can spread the virus to new locations and populations, causing small-scale outbreaks and even sparking larger-scale epidemics or pandemics (Bogoch et al. 2015).

4. IMPLICATIONS AND CHALLENGES FOR PREVENTING ZOONOTIC TRANSMISSION OF CORONAVIRUSES

Control and preventive measures for coronavirus-related zoonosis depend on the type and strain of the virus, the seeming or known risk of transmitting a particular virus to humans, and the country/place of the disease spread. Monetary resources available for control programs and the structure and capacity of one health further impact control and preventive measures (Gebreyes et al. 2014). The following points can explain the challenges involved in preventing coronavirus zoonosis:

4.1. SURVEILLANCE AND EARLY DETECTION

Resources and training for thorough surveillance and early virus detection are significant limitations, particularly in the developing world. Problems like under-detection and, inadequate reporting, untimed and incomplete surveillance data further delay the prevention measures (Ibrahim 2020).

4.2. REGULATION OF ANIMAL MARKETS AND TRADE

Even in the 21st century, effective lawmaking on regulating animal markets, particularly the wildlife trade, is not well established in developing countries. Policies on the protection of habitats for animals like Bats have caused them to adapt to the same environment inhabited by humans, increasing the probability of interaction and disease spread. Wildlife trade also increases the chances of direct contact between people and animal species (Bhattacharya et al. 2020b).

4.3. ONE HEALTH APPROACH

One Health approach depends on the smooth interplay between sectoral power relations and the priorities of public health institutes. Competing interests between livestock and human authorities, lack of understanding of a combined One Health surveillance system, and poor coordination and active collaboration between responsible authorities are key hurdles that must be conquered to enforce the One Health policies effectively (Ruckert et al. 2020).

4.4. PUBLIC HEALTH INTERVENTIONS

Due to the highly variable genome structure for most coronaviruses, the vaccine and therapeutic cover are usually inept. To cover this, public health policymakers must primarily rely on non-therapeutic interventions to minimize the disease burden (Peak et al. 2017). Implementing them is not always easy and depends on the role of the government, media, healthcare providers, and eventually, the people, which makes the zoonotic risk even more challenging to face.

5. FUTURE PERSPECTIVES

This chapter has outlined the importance of understanding the host range of coronaviruses concerning their zoonotic potential on multiple fronts. Without urgently addressing these factors at the local and international level, coronavirus epidemics will emerge and persist for the foreseeable future. The following points highlight some of these nuisances:

5.1. INCREASED RISK OF FUTURE SPILLOVER EVENTS

As discussed earlier, without progressed surveillance and regulation of animal trade, the hazard of zoonotic spillover events from animals to humans remains high (Bhattacharya et al. 2020b). A recent example is the replication of Simian Hemorrhagic Fever Virus (SHFV) in human monocytes and its similarity with the Human Immunodeficiency Virus (HIV) in evading host immune response, calling for human serological surveillance (Warren et al. 2022). This further accentuates the continuous surveillance of these red flags to avoid future spillover events and the emergence of new infectious diseases.

5.2. GLOBAL HEALTH VULNERABILITY

Without proper preparedness, implementation of public health policies and international collaboration, countries become vulnerable to swift disease spread. Apart from developing countries, where millions live in high-density communities, the developed world is also at risk of harboring vulnerable groups and health inequalities (Sam 2020). Lack of capital in healthcare framework and research can pressure healthcare systems during such outbreaks.

5.3. ECOLOGICAL IMBALANCE

Wildlife obliteration and habitat destruction can unsettle ecosystems and force species like bats to adapt to habitats closer to human settlements, increasing the likelihood of disease transmission. A comprehensive 25-year study on bat population dynamics concerning changing ecology has shown the change in land use by bats and their persistence in agricultural areas previously uninhabited by them (Eby et al. 2023). Ignoring the environmental impact of climate change can further exacerbate these issues.

5.4. SOCIOECONOMIC COSTS

Epidemics and pandemics can have overwhelming socioeconomic consequences, including loss of life, economic downturns, and social upheaval. Even in a developed country like the United States, huge socioeconomic disparities emerged at the beginning of the spread of COVID-19 (Banerjee 2022). Failure to learn from previous outbreaks can lead to repetitive economic and societal commotions.

6. CONCLUSIONS

This chapter underscores the grave importance of comprehending the host range of coronaviruses and their zoonotic potential. The evidence presented strongly highlights that most human coronaviruses originate from animals, thus accentuating the need for keen vigilance and regulation of animal trade. A complex interplay of genetic variability, receptor usage, host immune response, and environmental influences also causes the coronaviruses to infect diverse hosts, contributing to spillover events and viral adaptation in new host species. As human populations continue to intrude into wildlife habitats, our interactions with potential intermediate hosts of coronaviruses become more frequent. Due to these epidemics and pandemics, the straining healthcare systems demand an urgent and collective response. Wildlife habitat destruction and climate change intensify the probability of future spillover events, demanding swift conservation and environmental restoration efforts. Furthermore, the socioeconomic status of particularly marginalized communities is national and international cooperation. Understanding this intricate relationship between coronavirus host range and zoonotic potential is imperious to craft effective strategies to prevent and mitigate future outbreaks.

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Zoonotic and Reverse Zoonotic Transmission of SARS-CoV-2 Virus: A Perspective on Human-animal Interface

22

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ABSTRACT

The emergence of SARS-CoV-2 has underscored the crucial interaction between humans and animals, offering a unique perspective on the dynamics of zoonotic and reverse zoonotic transmission. This chapter aims to consolidate current knowledge on the two-way transmission of SARS-CoV-2 across the human-animal interface. We delve into the zoonotic origins of the virus, exploring potential reservoir hosts and intermediary species. Additionally, we summarize various events of reverse zoonosis, where humans have transmitted the virus to animals, raising concerns about the establishment of viral reservoirs in diverse species. This bidirectional transmission has significant implications for public health, necessitating a holistic approach to disease surveillance, wildlife conservation, and one health strategies. The evidence of zoonosis and reverse zoonosis sheds light on the expansive spectrum of potential hosts susceptible to SARS-CoV-2 infection, emphasizing the dynamic interplay within the host landscape. These phenomena not only underscore the intricate host dynamics of the virus but also emphasize the ability of various species to act as reservoirs, transmitters, or carriers, potentially contributing to pandemics among humans. By comprehensively understanding the intricacies of SARS-CoV-2 transmission dynamics at the human-animal interface, we can enhance our preparedness to mitigate future zoonotic events and safeguard both human and animal health.

Keywords: SARS-CoV-2, Zoonosis, Reverse zoonosis, Human-animal interface, Host dynamics

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1. INTRODUCTION

Zoonotic pathogens, originating from wildlife, have a significant impact on both public and animal health leading to epidemics and pandemics (Bengis et al. 2004). The emergence and re-emergence of viral pathogens have resulted in a global burden of infectious diseases, billions of cases and millions of fatalities. Before becoming a zoonotic pathogen, a virus of wildlife origin must overcome various hurdles, including ecological, behavioral, interspecies and immunological barriers (Plowright et al. 2017). Some animals can act as epidemiological bridges and serve as intermediate hosts in transmitting viruses from animals to humans.

Practices like intensive animal husbandry, close contact between animals and humans, and urbanization can create opportunities for the spillover of zoonotic viruses at the human-livestock interface (Magouras et al. 2020). Conversely, humans in close contact can also transmit viruses to animals, particularly domestic and companion animals, leading to reverse zoonosis (Messenger et al. 2014). These zoonotic and reverse zoonotic events raise concerns about infected hosts becoming ill, shedding viruses into the environment, and potentially reintroducing viruses among susceptible hosts (Goraichuk et al. 2021).

Recently, a novel respiratory illness known as COVID-19 appeared in China, in late 2019 and become a major global health challenge. This pandemic occurred due to infection in humans with SARS-CoV-2. Following previous outbreaks of other coronaviruses, the SARS-CoV-2 virus is more contagious and poses a significant threat to human health with substantial economic losses (Adil et al. 2021). Initially, the origin and spread of this virus was a subject of controversy and therefore, numerous studies have investigated its zoonotic potential by examining its ability to infect various animal species (Sit et al. 2020; Bessière et al. 2021; Gortazar et al. 2021; Grome et al. 2022; Purves et al. 2023). Conversely, the virus has also shown the ability to transmit from humans to animals, resulting in varying degrees of infection in different animals. The capability of zoonosis and reverse zoonosis of this virus poses serious threats to animal and public health (Kumar et al. 2020; Olival et al. 2020; Dróżdż et al. 2021; Fischhoff et al. 2021). Despite detailed reports, information on the transmission of the SARS-CoV-2 virus (Fig. 1), particularly focusing on a wide range of susceptible hosts and the propensity for inter and cross-species transmission is scattered. Understanding its transmission is crucial in linking all susceptible hosts and comprehending the larger evolutionary dynamics to develop effective disease control strategies and diagnostic approaches. Therefore, this chapter aims to compile scattered information on zoonotic and reverse zoonotic infections or transmission events of the SARS-CoV-2 virus and draw the global scientific community's attention to its public health concerns.

2. ZOONOTIC ORIGIN AND TRANSMISSION

The SARS-CoV-2 virus is a member of the *Coronavirus* genus within the family *Coronaviridae*, which comprises seven different viruses with the potential to cause zoonotic infections in humans (Hu et al.

2021). The CoVs typically target the respiratory system and cause flu-like infection in humans and have been identified in various animals, including birds, rodents, and domestic animals. Comparative studies suggest that all CoVs likely originated from bats, mice, and cattle before being transmitted to humans (Segars et al. 2020; Dróżdż et al. 2021). Other CoVs are believed to be originated from bats and caused outbreaks in humans through various intermediate hosts including civets and camel. Likewise, the COVID-19 pandemic is believed to have emerged from zoonotic transmission, with the SARS-CoV-2 virus likely to originate in animals before being transmitted to humans (Dróżdż et al. 2021). While the exact origin is still under investigation, bats are widely considered the likely source, with a potential intermediate host involved in the transmission to humans, possibly a pangolin, based on genetic similarities (Ul-Rahman et al. 2020).

Various bat species may harbour a diverse range of CoVs, and their close interaction with humans in certain regions may have facilitated spillover events (Banerjee et al. 2021). The immune system of bats has garnered significant scientific interest due to its potential implications for human health. Bats' ability to control viral infections effectively while minimizing harmful inflammatory responses has drawn attention as it could provide valuable insights into developing strategies for managing viral diseases in humans. By studying the molecular and genetic mechanisms underlying bats' immune adaptations, researchers aim to investigate various interventions and preventive approaches to reduce the impact of viral infections and transmission to humans. Bats may serve as natural models for investigating host-virus interactions and may hold the key to innovative approaches for combating viral diseases in humans (Letko et al. 2020).

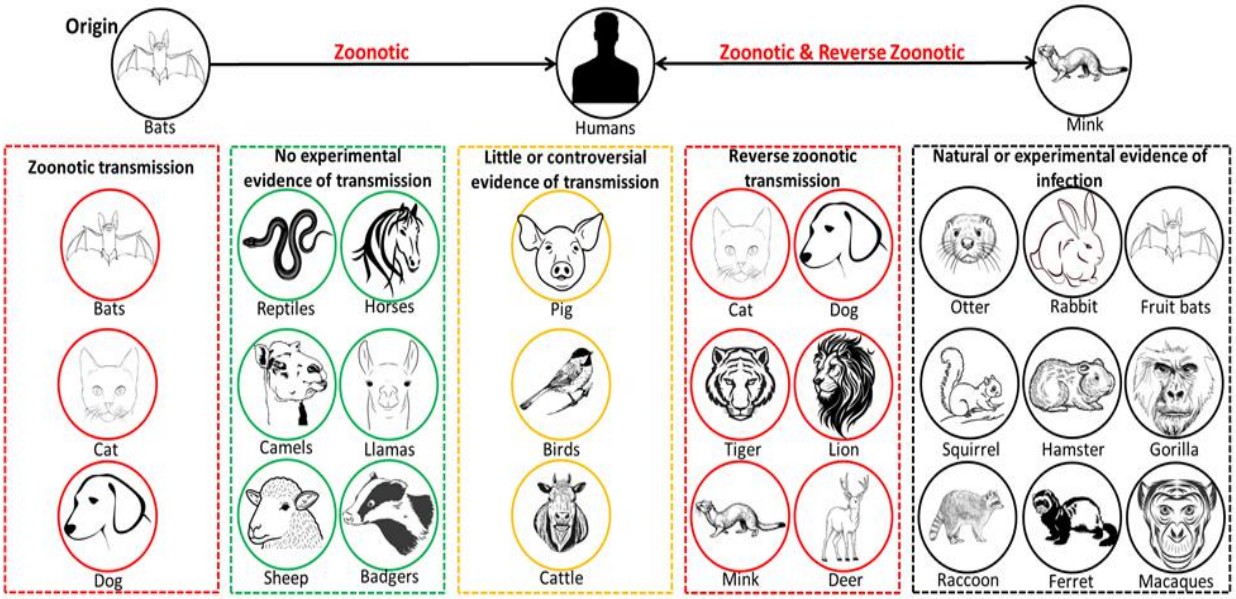

Fig. 1: Susceptibility of a wide range of domestic and wild animals to natural or experimental infection of SARS-CoV-2 virus across the globe.

The spread of the SARS-CoV-2 virus among human and animal populations can occur through diverse mechanisms, which include both direct and indirect routes. Individuals who have close contact with infected bats or handle infected wildlife are at higher risk of contracting zoonotic infections due to the initial spillover of the virus. Additionally, the virus can be spread via respiratory droplets, aerosols, contact with contaminated surfaces, and the consumption of infected animal products (Zhou and Shi

2021). Previous studies have suggested that numerous animals can act as intermediate hosts for the transmission of viruses at animal-to-human, animal-to-animal, human-to-human, and human-to-animal interfaces (Hedman et al. 2021; Brüssow 2023). However, the identification of intermediate hosts that facilitate the transmission of the SARS-CoV-2 virus between susceptible hosts remains an active area of scientific investigation and is still debatable.

3. CROSS- AND INTER-SPECIES TRANSMISSION

The potential of the SARS-CoV-2 virus to transmit between various animals has become a major cause of concern, as it raises significant questions about the virus's infectivity and spread across various hosts. The potential of a virus being transmitted across species barriers is a complex process that is influenced by various factors, including viral attachment, adaptation, and molecular interactions (Dhama et al. 2020). For most viruses, such as the influenza virus and SARS-CoV-2 virus, interactions between donor and recipient hosts play a crucial role in facilitating the transmission to overcome cross species barriers. The behaviour and activities of hosts in shared geography or habitats can play a significant role in either facilitating or hindering virus transmission among a wide range of susceptible hosts. Human activities, particularly those that promote close contact between infected hosts and uninfected hosts, can increase the risk of zoonosis and reverse zoonosis (Ayim-Akonor et al. 2020; Goraichuk et al. 2021).

Numerous cases of species-to-species transmission of the SARS-CoV-2 virus has been documented, offering valuable insights into its adaptability and ability to infect different animal species (Abdel-Moneim and Abdelwhab 2020; Leroy et al. 2020; Salajegheh Tazerji et al. 2020; Oude Munnink et al. 2021). Previous studies also confirmed that the virus has been found to spread rapidly among the mink population and found evidence of human-to-mink transmission and mink-to-human transmission, indicating the bidirectional nature of cross-species transmission (Fenollar et al. 2021; Hammer et al. 2021; Lu et al. 2021; Oude Munnink et al. 2021). The occurrence of transmission within a recipient population depends on intraspecific contacts that play a crucial role in the transmission of the virus. The ability of the virus to cause infection or remain persistent in various hosts is dependent on factors such as population density, mixing patterns between donor and recipient host species, and biological phenomena against a pathogen (Lim et al. 2016). Previous serological studies highlighted that domestic cats residing in proximity to mink farm had specific antibodies for the SARS-CoV-2 virus, suggesting both zoonotic and animal-to-animal transmission (Zhang et al. 2020; Barua et al. 2021; Udom et al. 2022). Airborne transmission of the SARS-CoV-2 virus has also been reported between cats and hamsters (Yen et al. 2022). Additionally, natural infection of the SARS-CoV-2 virus has been reported in captive/domestic ferrets (Giner et al. 2021).

Considering transmissibility, virulence, and the degree of infection in various hosts, the World Organization for Animal Health (WOAH) recognizes the potential implications of such events for public health and the effectiveness of treatment and vaccines. It's worth noting that few hosts, including domestic and companion pets, can develop an infection with or without showing clinical signs and potentially lead to zoonotic and reverse zoonotic transmission by shedding the virus into the environment. Individuals directly associated with animal welfare management, including zoo workers, farmers, veterinarians, and animal lovers, are at high risk of zoonotic infections (EFSA 2023). Moreover, intermediate hosts can play a critical role in inter- and cross-species transmission of the SARS-CoV-2 virus by serving as a bridge between the original reservoir species and the target host species. These intermediate hosts may provide an environment conducive to viral replication and transmission, allowing the virus to adapt to new cellular and immune systems (Zhao et al. 2020). Identifying and studying these intermediate hosts is crucial for understanding the dynamics of inter- and cross-species transmission and implementing preventive measures.

4. MOLECULAR MECHANISM OF CROSS-SPECIES TRANSMISSION

Various biological factors play a crucial role in the ability of a virus to switch species and facilitate cross-species transmission. One important factor is the expression of receptors during cell attachment, which can increase the virus's capability to infect a new host. After virus attachment to the host cell, viral protein, and cellular machinery play a vital role in virus replication and dissemination to another host (Kane et al. 2023). A virus that can replicate at a high level within a host is generally more capable of being transmitted to other hosts. In case of SARS-CoV-2 virus, it has been observed to replicate efficiently in cats and ferrets, leading to transmission to other species. However, the limited replication of the virus in dogs, chickens, and pigs suggest restricted transmission in these species (Hossain et al. 2021). The molecular mechanism by which the SARS-CoV-2 virus targets different species involves the interaction between viral proteins, particularly the spike protein, and cellular receptors on host cells. The spike protein plays a pivotal role in facilitating virus attachment to host cells and determining the host range and tropism of the virus. The primary receptor for SARS-CoV-2 is ACE2 which is present in various human tissues. However, the expression and availability of ACE2 receptors in a wide range of animals can vary and influence host susceptibility to infection (Luan et al. 2020).

The capability of SARS-CoV-2 to infect different species is usually influenced by the presence and structure of ACE2 receptors in the target species. Some animal species may have ACE2 receptors with a higher affinity for the viral spike protein, facilitating efficient viral entry and replication. The spike protein, particularly the receptor-binding domain, plays a crucial role in infecting various hosts by binding to ACE2 receptors (Liu et al. 2021). To successfully infect a new host species, the receptor-binding domain may undergo genetic mutations that enable it to interact with ACE2 receptors in the target species. These genetic mutations may facilitate the attachment potential of the spike protein and host receptor, enhancing the viral entry mechanism into cells of new host species (Liu et al. 2021). Apart from the receptor-binding domain and its interaction with cellular receptors, other cellular factors and host immune responses, including innate and adaptive immune mechanisms, can influence the potential of the virus to infect and replicate in different species (Liu et al. 2021).

5. ZOONOTIC AND REVERSE ZOONOTIC EVENTS IN PET ANIMALS

Distinct coronaviruses of animals, domestic cats and dogs are now considered to have an infection by acquiring and shedding the SARS-CoV-2 virus into the environment (Bosco-Lauth et al. 2020; Patterson et al. 2020). Since the start of the pandemic, sporadic cases of cross- and intra-species transmission of the SARS-CoV-2 virus in domestic cats have been reported from various countries (Table 1). Various experimental studies have highlighted the susceptibility of cats to get infection and spread the virus to other pets and humans through respiratory droplets (Bosco-Lauth et al. 2020; Bao et al. 2021; Decaro et al. 2021). The detection of neutralizing antibodies also indicated the natural infection in cats in China (Deng et al. 2020). Similarly, previous studies observed the existence of anti-SARS-CoV-2 antibodies in domestic cats in Italy and France, where the owner or family members suspected or confirmed COVID-19 cases (Fritz et al. 2020; Patterson et al. 2020).

Notably, a study reported an active infection in cats having a clinical presentation of COVID-19 which was residing in the vicinity of mink farms facing outbreaks (Amman et al. 2022; van Aart et al. 2022). Despite evidence of active infection, the route of spread or source of infection in cats remains uncertain and unclear. Emerging evidence emphasizes that cats may develop non-sterilizing immunity following natural infection and remains susceptible to reinfection to spread disease into the human and cat population. On the other hand, evidence on human-to-cat transmission following the identification of active COVID-19 cases in cat owners in Belgium and Hong Kong highlighted the reverse zoonosis (Barrs et al. 2020; Garigliany et al. 2020). The genome of the virus was detected in cat vomit, faeces, and nasopharyngeal

and rectal swabs in France. The substantial evolutionary analysis highlighted that the isolated SARS-CoV-2 strains originating from cats belonged to a phylogenetic clade that was predominant among French human clinical cases (Sailleau et al. 2020). Similarly, cats from a household in Spain exhibited SARS-CoV-2 infection and were found positive through oropharyngeal swab testing (Segalés et al. 2020).

Experimental studies have indicated that infected dogs typically shed minimal to no virus, suggesting a low risk of contracting and transmitting the virus (AVMA 2020; Van Aart et al. 2022). However, there have been isolated cases of dogs testing positive for SARS-CoV-2 in various countries (Table 1). In these cases, the SARS-CoV-2 virus genome was found in samples collected from dogs having no clinical presentation of COVID-19 infection. On the other hand, numerous studies conducted in American and European countries observed a varying clinical presentation of COVID-19 infection in dogs (AVMA 2020; Sit et al. 2020; Van Aart et al. 2022). However, there is still some disagreement regarding the presence of the virus and its transmission to humans from dogs. Several studies have noted a higher risk of dogs being exposed in households with confirmed COVID-19 cases (Bosco-Lauth et al. 2020; Sit et al. 2020; Decaro et al. 2021). However, definitive evidence of transmission between pets and humans is currently lacking. As a precautionary step, it is advisable to include pets in self-isolation measures. These findings underscore the importance of further research to understand how domestic pets contract the virus and transmit it to other animals or humans.

6. SUSCEPTIBILITY OF MINKS, FERRETS, RABBITS AND PANGOLIN

Mink farms have been at the center of outbreaks due to the ability to transmit the virus from humans to minks and leading to widespread infections among the mink population (Oreshkova et al. 2020; Aguiló-Gisbert et al. 2021; Domańska-Blicharz et al. 2021; Fenollar et al. 2021; Hammer et al. 2021).

These outbreaks have been reported in several American and European countries. It is speculated that the outbreaks among the mink population were associated with active COVID-19 cases of farmers and/or staff members or their family members and the similarity index between SARS-CoV-2 sequences isolated from humans and minks confirmed the transmission from mink to humans (Fenollar et al. 2021). These reports prompted a thorough investigation to understand the potential routes of transmission and assess the associated environmental and occupational hazards, including the risk of transmission from infected mink to humans. The transmission of SARS-CoV-2 to farmed mink has had devastating effects, leading to increased mortality rates and significant economic losses in mink farming. The introduction of the virus in mink farms occurred through infected farm workers who had close contact with the animals (Oude Munnink et al. 2021).

Once the virus was introduced, it spread rapidly among the minks, resulting in a high number of infected animals. To control the outbreaks and prevent further transmission, infected minks on affected farms were euthanized, and strict testing measures were implemented to monitor the situation. During these outbreaks, genetic changes were observed in the virus as it circulated within the mink population. This indicates that the virus can undergo genetic modifications during transmission among minks (Ren et al. 2021). These genetic changes raise concerns about the potential for the virus to evolve and adapt within animal populations, which could have implications for public health and the effectiveness of vaccines and treatments. The researchers found that the viral strain detected in the minks was found to be identical to the strain circulating in humans in Denmark and emphasized the circulation of the same virus strains (Oude Munnink et al. 2021). Furthermore, a pet ferret residing in a household with a confirmed COVID-19 patient case also tested positive for the virus (Račnik et al. 2021).

Thus, it is speculated that minks and ferrets are involved in the transmission of the SARS-CoV-2 virus among human and other animal populations. Initially, there was speculation that pangolins, particularly the Malayan pangolin (*Manis javanica*), may play a pivotal role as intermediate hosts in transmitting the

Table 1: Zoonotic and reverse zoonotic events related to natural and experimental infection of SARS-CoV-2 in a wide range of domestic and wild animals

Host species	Infection	Transmission	Country	References
Cat	Natural	Cat-to-cat	China	Bao et al. 2021
	Natural	Cat-to-human	USA, Netherland, Hong Kong	AVMA 2020
	Natural	Cat-to-cat, cat-to-human	France	Bessière et al. 2021
	Natural	Human-to-cat	Greece, Cyprus, UK, Switzerland, Germany, Chile, Italy	Michelitsch et al. 2020; Chaintoutis et al. 2021; Curukoglu et al. 2021; Hosie et al. 2021; Klaus et al. 2021; Neira et al. 2021; Pagani et al. 2021; Zoccola et al. 2021
	Experimental	Cat-to-cat	USA, Germany	Gaudreault et al. 2022a; Halfmann et al. 2020; Braun et al. 2021
Dog	Natural	Human-to-dog	Hong Kong	Sit et al. 2020
	Natural	Dog-to-human	USA, Spain, Russia, France, Germany	AVMA 2020
Cattle	Experimental	No intraspecies transmission	Germany	Ulrich 2020
Poultry and avian species	Experimental	No intraspecies transmission	China, USA	Shi et al. 2020; Suarez et al. 2020
Pig	Experimental	None	China	Shi et al. 2020
Rabbit	Experimental	None	New Zealand	Mykytyn et al. 2021
Domestic Ferret	Natural	Human-to-ferret	Spain	Gortazar et al. 2021
Syrian Golden Hamster	Experimental	Hamster-to-hamster	China	Chan et al. 2020
Mink	Natural	Human-to-mink, Mink-to-mink, Mink-to-human	Netherland	Oreshkova et al. 2020; Van Aart et al. 2022
Rodents including mouse, wood rat, raccoon, and squirrel	Experimental	No intraspecies transmission	USA	Bosco-Lauth et al. 2021
Otters	Natural	Not reported	USA	APHIS 2021a
Fruit Bats	Experimental	Bat-to-bat	Germany	Schlottau et al. 2020
Tiger	Natural	Human-to-Tiger, Tiger-to-tiger	USA	Grome et al. 2022
Lion	Natural	Human-to-Lion, Tiger-to-Lion, Lion-to-Lion	USA	McAloose et al. 2020
Rhesus Macaques	Experimental	Intraspecies transmission	China, USA	Deng et al. 2020; Munster et al. 2020
Western Lowland Gorilla	Natural	intraspecies transmission	USA	APHIS 2021b
White-Tailed Deer	Natural and experimental	Perinatal transmission, intraspecies transmission	USA	Cool et al. 2022
Fallow Deer	Natural and experimental	Human-wildlife transmission	USA	Purves et al. 2023

SARS-CoV-2 virus. This was due to the discovery and evolutionary trend of SARS-CoV-2-like coronaviruses in confiscated pangolins, as well as the identification of pangolin cell types that might be susceptible to the virus (Liu et al. 2020; Ul-Rahman et al. 2020). The potential role of rabbits as hosts of SARS-CoV-2 has

also been examined, considering their farming for meat and fur (Mykytyn et al. 2021). In a study involving young New Zealand white rabbits, the animals were intentionally infected with the virus and monitored for 21 days. Despite the absence of clinical signs of infection, the rabbits were found to shed the virus in nasal and oropharyngeal secretions and exhibited evidence of seroconversion (Pomorska-Mól et al. 2021; Fritz et al. 2022). Notably, the study's findings may not be representative of infections in rabbits of different ages or breeds, highlighting the need for further research on the potential of rabbits as hosts of the virus. The susceptibility of mink, ferrets, and rabbits to SARS-CoV-2 infection highlights the importance of implementing strict biosecurity measures in animal farming environments to prevent the transmission of viruses from humans to animals and vice versa. Continued surveillance and monitoring of both human and animal populations are crucial to better understand and mitigate the risks associated with reverse zoonotic transmission.

7. SUSCEPTIBILITY OF LIVESTOCK AND WILD ANIMALS

The potential of virus transmission among animals and humans is now considered a serious concern because of the establishment of carriers or reservoirs, especially in regions with frequent human-animal contact and high livestock density. Recently, researchers intentionally infected six cattle with the virus, but found no transmission to other animals residing in close proximity (Ulrich 2020; Bosco-Lauth et al. 2021). Despite the absence of natural transmission, a study claimed a low level of viral shedding from infected cattle into the environment (Ulrich 2020). Similarly, the SARS-CoV-2 virus does not have the potential to infect livestock species, including sheep, camels, and llamas (Bosco-Lauth et al. 2021; Chouchane et al. 2021; Xu et al. 2021; Gaudreault et al. 2022b; Hong et al. 2022). However, previous studies claimed the susceptibility of various wild animals to SARS-CoV-2 infection (Table 1).

After the first case of SARS-CoV-2 infection in Malayan tigers, other tigers, and lions residing at the same zoo were also found to be infected in a Zoo in New York. It is noteworthy that the SARS-CoV-2 sequence isolated from infected tigers was found to have the highest genomic identity with sequences isolated from zoo keepers and clinical cases reported from the same city. However, the substantial analysis of the whole-genome sequences of the SARS-CoV-2 virus highlighted that lions and tigers were affected by distinct SARS-CoV-2 strains and indicated separate transmission events (McAloose et al. 2020). Through genetic and epidemiological analysis, it was determined that transmission from humans to tigers had occurred, specifically from zookeepers. However, the source of infection for the lions remained unclear. This indicated that the infection was likely transmitted from an asymptomatic zookeeper to the tigers (Bartlett et al. 2021). Wild animals exhibited varying SARS-CoV-2 infections showing asymptomatic infection to different clinical presentations. In all cases, staff members at the zoo also found positive for COVID-19, indicating possible transmission of the SARS-CoV-2 virus between humans and wild animals (McAloose et al. 2020; Grome et al. 2022).

8. EXPERIMENTAL INFECTION IN VARIOUS HOSTS

During the COVID-19 pandemic, there is a growing need to identify suitable animal models for studying the pathology of the disease and evaluating potential therapeutics and vaccines. Experimental infections have been conducted to study the susceptibility and transmission potential of SARS-CoV-2 in various wild animal species and provide crucial insight into the susceptibility of a wide range of hosts (Table 1). These studies showed that a large number of animals including rodents are highly susceptible to infection and can play a vital role in the shedding of virus into the environment and subsequent transmission to other animals (Abdel-Moneim and Abdelwhab 2020; Sun et al. 2020).

In the experimental studies, it is observed that the virus can effortlessly replicate in the respiratory and gastrointestinal tract of various animals and elicit immune responses for the synthesis of neutralizing antibodies. Upon re-infection, it was noted that cats cannot shed an adequate virus into the environment that is required for transmission to other cats (Gaudreault et al. 2022a). Similarly, cattle, dogs, and domestic pigs have shown poor viral replication while poultry species are not susceptible to the virus (Meekins et al. 2020; Schlottau et al. 2020). Among rodents, hamsters and ferrets showed susceptibility to acquiring SARS-CoV-2 infection and the ability to shed the virus for further transmission to susceptible hosts. Several non-human primates showed susceptibility to acquiring SARS-CoV-2 infection and have shown clinical presentations similar to those observed in COVID-19 patients. Due to viral replication and severe infection of the SARS-CoV-2 virus, non-human primates are now commonly used as models for biomedical research (Gonçalves et al. 2021).

9. POTENTIAL OF MECHANICAL TRANSMISSION

Arthropods can pose challenges by acting as potential vectors for pathogens that can be transmitted to humans and other animals. Arthropods or pests including rats, mosquitoes, mice, houseflies, ticks, and cockroaches are usually prevalent in various environments, including public places, farms, and healthcare settings (Nekoei et al. 2022). These pests can come into contact with contaminated surfaces, potentially acquiring and transmitting pathogens. Previous research has indicated that arthropods, including ticks, houseflies, mosquitoes, and midge can mechanically transmit the virus (Reuben et al. 2020; Balaraman et al. 2021 a,b). Recent experimental studies demonstrated that houseflies can spread the virus into the environment for up to 24 hours following exposure to the virus (Montes et al. 2020; Balaraman et al. 2021a). Previous studies have shown that houseflies can acquire and carry infectious viral particles for a short period of time after exposure. They can retain the virus in their bodies for up to 24 hours, suggesting the potential for mechanical transmission (Balaraman et al. 2021a). This finding highlights the potential role of houseflies in the transmission and dissemination of the virus, raising concerns about the importance of implementing measures to control insect vectors and prevent further spread of COVID-19. According to recent research, there is evidence suggesting that biting midges and mosquitoes do not facilitate the replication of SARS-CoV-2 and are improbable to act as biological vectors for the virus (Balaraman et al. 2021b).

Passive or mechanical transmission occurs when pests carry the virus on their body parts or mouthparts and transfer it to other hosts, without virus replication or development within the pests themselves (Reuben et al. 2020). Studies have shown that the virus does not replicate in Aedes mosquito cells, and live Aedes mosquitoes collected during the pandemic showed no signs of carrying the virus. Furthermore, injecting mosquitoes with the virus did not result in any viral replication (Huang et al. 2020; Xia et al. 2020). Similarly, experiment with biting midges and certain Culex mosquito species also indicated that they do not support viral replication when feeding on infected blood (Reuben et al. 2020).

10. CONCLUSION

The COVID-19 pandemic has had a profound impact on human lives, the economy, and daily routines. This disease, believed to have originated in bats, has brought attention to the potential for zoonotic transmission, where diseases pass from animals to humans. However, we must also consider the possibility of reverse zoonosis, where the virus can be transmitted from humans back to animals. Cases of SARS-CoV-2 infections have been documented in various animal species, including pets, zoo animals, and certain farm animals. These findings hold significant importance in comprehending the possible

involvement of various animal species in the transmission and dissemination of SARS-CoV-2. Moreover, they aid in formulating appropriate control strategies to manage the spread of the virus effectively. To reduce the risk of zoonotic and reverse zoonotic events, it is crucial to incorporate vulnerable animals into surveillance strategies. This includes monitoring pets, farm, zoo and laboratory animals, and animals used in biotechnology production. By embracing the One Health approach, interdisciplinary collaboration among professionals in human and animal health, environmental science, policymaking, and other relevant fields can protect the health of humans, animals, and the environment, ultimately mitigating the risks of future pandemics.

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The Emergence of Marburg Haemorrhagic Fever as a Public Health Threat Transmitted from Wildlife to Human: A Zoonotic Perspective

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ABSTRACT

Marburg virus, a member of the Filoviridae family, is the causative agent of Marburg virus disease (MVD), a severe and often fatal illness in humans. The virus is believed to originate from fruit bats, acting as natural hosts. Human infection results from direct contact with their bodily fluids or contaminated materials. Diagnosis involves detecting viral RNA or antibodies in blood samples, with advanced molecular techniques like PCR being crucial. Prevention strategies encompass strict hygiene practices, particularly in healthcare settings, and the use of personal protective equipment. Control measures involve isolation of infected individuals and contact tracing. Marburg virus, like Ebola, manifests as a viral hemorrhagic fever, impacting vascular integrity and causing multi-organ failure. The zoonotic nature of Marburg virus emphasizes the importance of understanding and monitoring animal reservoirs to prevent spillover events. The pathophysiology involves viral replication in various organs, leading to systemic inflammation and vascular compromise. Developing effective treatments and vaccines remains a critical focus in managing Marburg virus outbreaks, highlighting the interdisciplinary efforts needed to combat emerging infectious diseases. Constant surveillance, international collaboration, and public health awareness are vital components of the global strategy to mitigate the impact of this highly infectious and lethal virus. Addressing Marburg virus (MARV) outbreaks in Africa requires comprehensive research and proactive measures. Despite its origin, the virus's potential to impact the entire continent necessitates continued studies for effective patient management and vaccine development. Trials on non-human primate models are crucial for understanding pathogenesis and drug effects. A robust surveillance system, ecological studies, and sero-epidemiological surveys in endemic regions are vital for outbreak prevention. Collaborative efforts involving public health experts, scientists, and awareness campaigns are essential. Future epidemic preparedness hinges on community education and strategic planning based on thorough research and understanding of MARV's transmission dynamics.

Keywords: Marburg virus, Filoviridae, Outbreaks, Zoonotic, Surveillance

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1. INTRODUCTION

Marburg virus (MARV) is an emerging pathogen of Family Filoviridae containing the deadliest pathogens of public health concern. This family contains only 2 Genera of viruses named Ebola Virus and MARV. Both are known for causing viral hemorrhagic fever in humans, so they are classically characterized as Filoviral Hemorrhagic Fever (FHF) (Hartman et al. 2010) with a 23-90% case fatality rate (Leffel and Reed 2004). According to NIAID (National Institute of Allergy and Infectious Diseases), MARV is characterized as a category A primary infectious agent (Bente et al. 2009). It can easily be disseminated from one person to another and has a major public health impact. It requires an immediate action plan due to the high mortality rate. Moreover, according to WHO and the CDC, it is also considered as a Biosafety level 4 pathogen (Nakayama and Saijo 2013). It is a viral zoonotic disease that can be spread via direct contact with blood, other body fluids, and aerosol droplets. Bats are the reservoir hosts of MARV that can infect both human and non-human primates (NHPs). This disease is getting a major public health importance due to the disruption of the forest ecosystem and increased exposure of humans to wild animals. MARV has been associated with multiple epidemics with high case fatality rates in humans and NHPs since its detection in 1967 (Gonzalez et al. 2015).

Marburg Hemorrhagic Fever (MHF) is clinically characterized by coagulopathy, hemorrhagic fever, and dysfunction of many organs, including the liver, brain, kidney, and spleen (Van Paassen et al. 2012). In addition to its natural occurrence, Ebola and Marburg were used as subjects for biological warfare. The Soviet Biological warfare program initiated in mid-1920 included MARV and other bio-warfare agents (Roffey et al. 2002). Moreover, currently, there is no effective preventive and post-exposure vaccine or treatment available for humans, although significant efforts have been made over a period of last five years to develop protective vaccines. There is increased research interest in this highly fatal filovirus due to its intentional and unintentional introduction of infection outside of central African endemic areas (Paragas and Geisbert 2006).

So, there is a dire need to focus on this lethal virus in research to develop vaccines and antiviral drugs against this deadly virus. Considering the outbreaks of MARV and increasing prevalence, it is necessary to educate the public about this notable disease.

2. ETIOLOGY

MARV is a member of the family *Filoviridae***,** genus *Marburgvirus* and order *Mononegavirales*. The Marburgvirus genus contains two lineages, i.e., Lake Victoria Virus and Ravn Virus (Feldmann et al. 2013). This order of viruses contains notable pathogenic viruses belonging to *Rhabdoviridae*, *Paramyxoviridae* and *Bornaviridae*. The family *Filoviridae* is considered as highly significant because it contains only two viruses, Ebola and Marburg, with great public health concerns. The genus Marburg virus contains only one specie *Marburg Marburgvirus* (Kuhn et al. 2011). In 1967, an outbreak was investigated in Europe using electron microscopic techniques, revealing a filamentous structure resembling Leptospira bacteria or Rhabdoviridae viruses (Fig. 1). After three months, Gerhard and Muller identified MARV based on inclusion bodies and negative staining of infected plasma of patients and Guinea pigs (Slenczka and Klenk 2007).

3. GENOME AND STRUCTURE OF MARBURG VIRUS

The genome of *Marburg marburgvirus* is negative sense single-stranded RNA that is linear and non-segmented. MARV is pleomorphic, including rod shape, circle, U, six digits, or more commonly filamentous (Bharat et al. 2011). The diameter of the virus virion is 80 nm, with great variation in its length. The average length of this virus is 790 nm (Welsch et al. 2010). The virion surface is shielded with glycoprotein spikes of 5-10 nm length, which are placed at a distance of approximately 10 nm (Feldmann et al. 1991). The genome of MARV is 19.1 kb, and it encodes for its seven structural proteins such as nucleoprotein (NP), large protein (L), viral protein-24 (VP-24), VP-40, VP-30, VP-35, glycoprotein (GP), and large protein (L) (Fig. 2). The viral genome is surrounded by enucleocapsid. Nucleocapsid is comprised of 4 structural proteins, namely NP, VP-35, VP-30 and L, that play a significant role in the development of its tubular helical structure (Becker et al. 1998).

These four structural proteins are important for the transcription and replication of the virus. VP-24 interacts with NP and cellular membranes, involved in the release of virion from cell during its lifecycle and pathogenesis. The inner matrix of MARV is made up of VP-40 (Bamberg et al. 2005). The host-derived membrane surrounding the MARV contains spikes that are made up of GP (Bharat et al. 2011). Table 1 shows the viral proteins of MARV with their functions.

4. EPIDEMIOLOGY AND DISEASE OUTBREAK (EMERGENCE)

In 1967, the first outbreak of MHF was reported in Frankfurt, Marburg (Germany) and Serbia with 31 patients. Out of 31, 25 were primary cases and 6 were secondary cases. All the patients with primary

Table 1: Viral proteins of MARV with their functions (Brauburger et al. 2012; Abir et al. 2022)

Viral Protein	Functions
NP	Formation of nucleocapsid, RNA genome encapsidation, Budding, and Replication and Transcription
VP-35	Formation of nucleocapsid, Cofactor for RNA polymerase, and Interferon antagonist
VP-40	Matrix protein, Budding, and Inhibition of interferon signaling
GP	Virion attachment to target cells, Receptor binding, and Tetherin antagonism for adaptation in host
VP-30	Formation of helical nucleocapsid
VP-24	Budding and Maturation of nucleocapsid, regulation of replication and Cytoprotective genes activation
L	Catalytic domain for RNA dependent RNA polymerase, and Regulation of transcription and replication

infection in Marburg, Frankfurt, and Serbia had direct contact with the cell culture, organs and blood of Green Monkeys *(Cercopithecus aethiops)***.** These monkeys were imported from Lake Victoria Island in Uganda. Identification and characterization of causative agents were done within three months by scientists in Hamburg and Marburg. It was named Marburg because it was first isolated in this city, and the highest number of cases was also reported in this city (Slenczka and Klenk 2007).

In 1975**,** an outbreak was recorded in Johannesburg when an Australian citizen had been hitchhiking and visiting Zimbabwe. He was admitted to the hospital and died after a few days while milder disease appeared in his companion and nurse, and later they recovered. Sero-convalescent studies revealed that the MARV strain was closely related to the virus involved in the 1967 outbreak. Sporadic outbreaks occurred from 1975 to 1985, and most cases were from Eastern Africa except an accidental case reported in a laboratory in Russia (Brauburger et al. 2012).

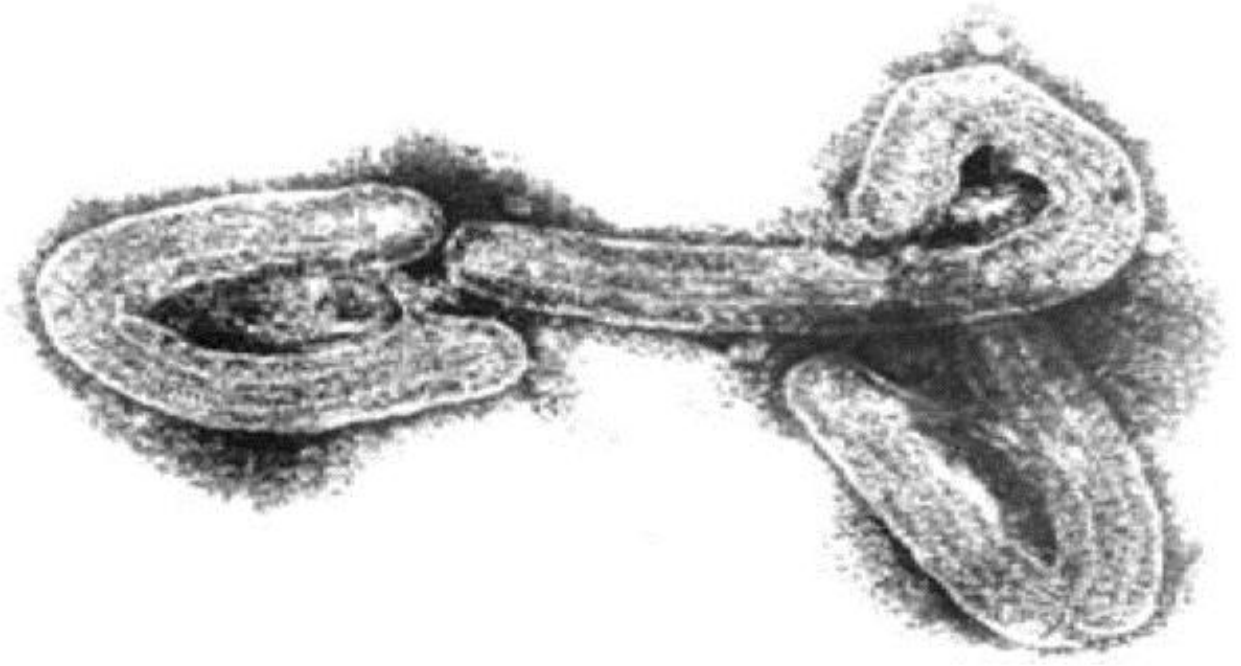

Fig. 1: Electron micrograph of MARV infection By Slenczka and Klenk (2007).

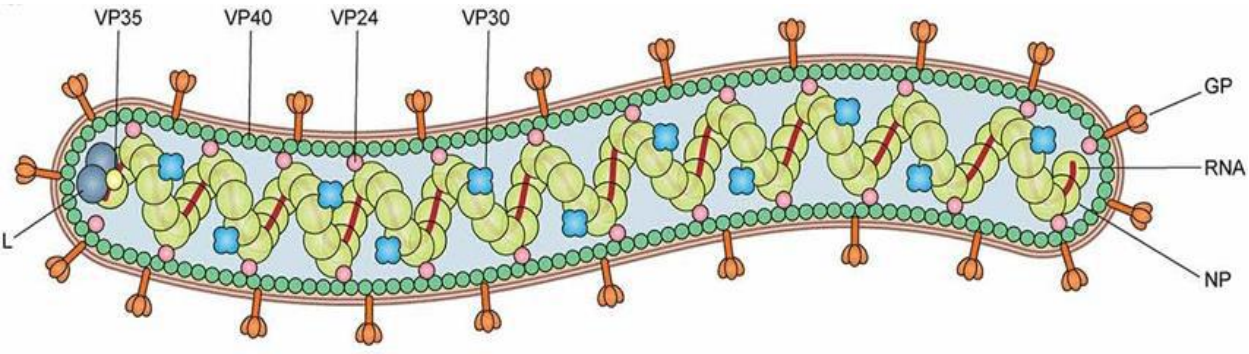

Fig. 2*:* MARV Structure depicting structural proteins*:* Source: https://doi.org/10.1080/21505594.2022.2054760 (Abir et al. 2022).

In 1998-2000, an outbreak occurred in DRC (Democratic Republic of Congo) Durba (Colebunders et al. 2007). In 2004-2005, another outbreak occurred in Angola. Investigations of the Durba outbreak revealed a link between the outbreak and working in a gold mine. In the Durba outbreak, nine different virus variants were identified that were indicative of the exposure of the human population to natural reservoirs in gold mines (Feldmann et al. 2004).

In Kamwenge, a district in Uganda, 4 cases were reported between June and September 2007. The most recent occurrences of MARV infections were in 2008 when two tourists visited Python Cave in Uganda and encountered the virus. One died after returning to the Netherlands, while another developed minor symptoms and recovered. The natural reservoir was frugivorous bats roosting in Africa (Brauburger et al. 2012).

Moreover, Uganda faced another three epidemics from 2012-2017. In 2012, an outbreak occurred in Kabale that affected 15 individuals. In 2014, a health worker was affected and died within a few days in Kampala. The detected MARV strain had similarity with the MARV strain secluded from Egyptian Frugivorous Bats (Nyakarahuka et al. 2017). In the 2017 outbreak, four individuals of the same family were affected in the Kween district of Uganda (Nyakarahuka et al. 2019).

In August 2021**,** one person got infected and died in Guinea, West Africa (WHO 2022). In July 2022, an epidemic of MARV occurred in Ghana, West Africa, where two individuals got infected and died. This epidemic is still under investigation. On February 2023, the Ministry of Health of Equatorial Guinea reported an epidemic with 15 cases confirmed through RT-PCR and 23 probable cases. Moreover, on March 2023, the Ministry of Health of the United Republic of Tanzania reported 8 cases of MHF in northern Tanzania (Deb et al. 2023). The geographical occurences of Marburg virus is highlighted in Fig. 3.

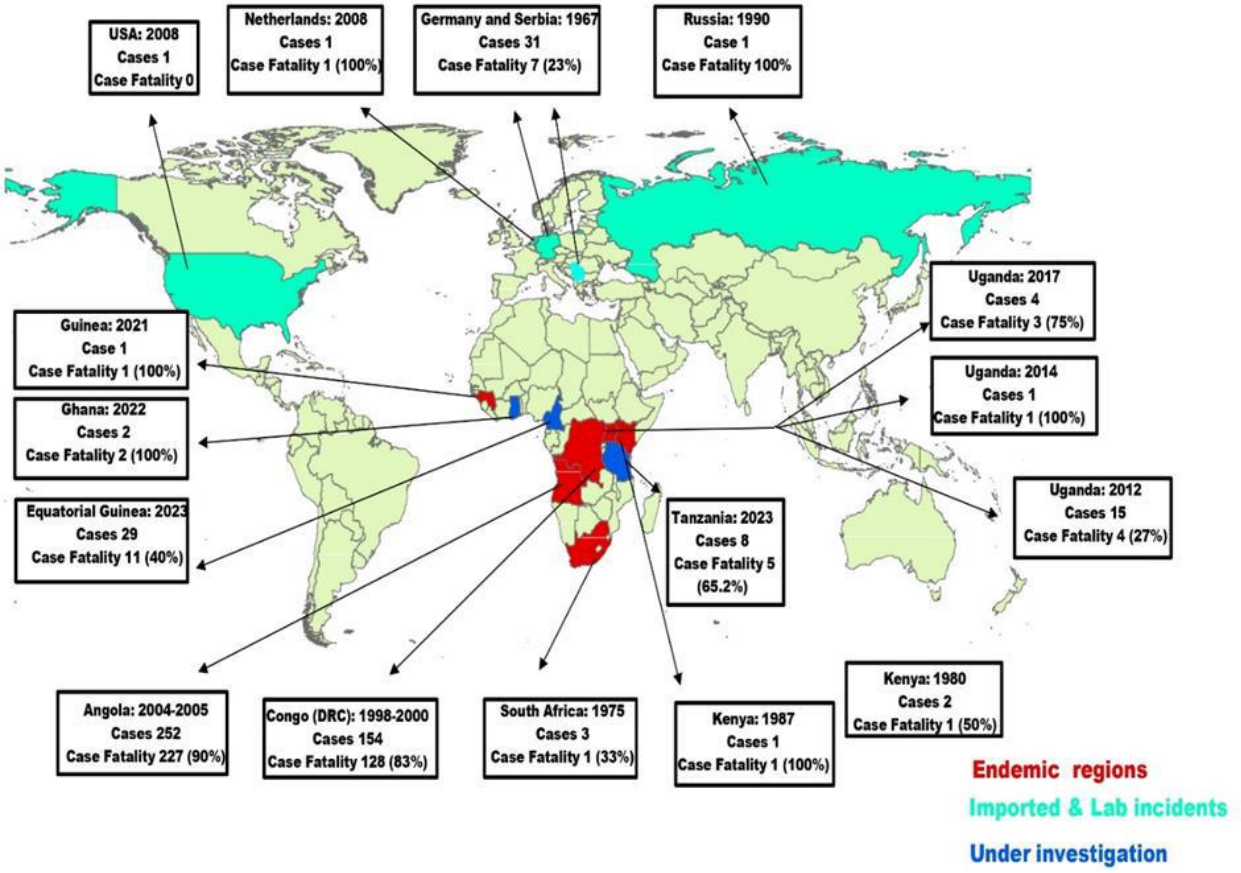

Fig. 3*:* Geographical distribution of MARV Outbreaks (Designed on ArcGIS Desktop 10.5).

So far, 17 outbreaks have been reported around the globe. Due to increased trade and travelling, MARV is considered a major public health concern. On a daily basis, thousands of individuals from African regions come to Guangzhou due to settlement, and similarly, travelling activities happen around the globe. There is a huge risk of MARV importation all over the world. Therefore, there is a need for international cooperation to control MARV (Zhao et al. 2022). Epidemiology and case fatality rate of all MARV outbreaks is enlisted in Table 2.

Table 2: Epidemiology and case fatality rate of all outbreaks related to MARV infection (Zhao et al. 2022; Deb et al. 2023; Kilangisa 2023)

Year	Country	Suspected Origin	Cases	Case Fatality	Notes
2023	Tanzania	Under investigation	8	65.2%	
2023	Equatorial Guinea	Under investigation	29	40%	
2022	Ghana	Under investigation	2	100%	
2021	Guinea	Guinea	1	100%	
2017	Uganda	Uganda	4	75%	
2014	Uganda	Uganda	1	100%	
2012	Uganda	Uganda	15	27%	
2008	Netherlands	Uganda	1	100%	Imported
2008	USA	Uganda	1	0	Imported
2007	Uganda	Uganda	4	75%	
2004-2005	Angola	Angola	252	90%	
1998-2000	Congo (DRC)	Congo	154	83%	
1990	Russia	Russia	1	100%	Laboratory incident
1987	Kenya	Kenya	1	100%	
1980	Kenya	Kenya	2	50%	
1975	South Africa	Zimbabwe	3	33%	Imported
1967	Germany and Serbia	Uganda	31	23%	Imported and Lab leak

5. SOURCES OF MARBURG VIRUS

5.1. RESERVOIR HOST OF MARV

Animals, especially bats are the natural reservoirs of MARV (Swanepoel et al. 2007). Egyptian fruit bat (*Rousettus aegyptiacus*) is the most frequent reservoir host of MARV. Some unidentified Chiroptera and Hipposideros caffer act as minor infection sources (Chakraborty et al. 2022). In 1999, in the DRC, 12 MARV strains were isolated from bats of unclassified species of order Chiroptera (Swanepoel et al. 2007). In 2007, in Uganda, one strain of MARV was isolated from Hipposideros caffer (Towner et al. 2009). *Rousettus aegyptiacus* is the main source of infection from which many MARV strains were isolated, including; 61 from Uganda in 2007-2012, 4 from Gabon in 2005-2009, 11 from Sierra Leone in 2017-2018, 1 from Kenya, two from Zambia in 2018 and 2 from South Africa in 2013-2017 (Abir et al. 2022).

5.2. INTERMEDIATE HOSTS AND AMPLIFIER HOST OF MARV

The main source of virus shedding is saliva, urine, and excrement of the bat. The intermediate hosts, including animals hunted for bush meat and NHPs, are the primary vectors (Abir et al. 2022). The potential amplifier hosts of the zoonotic Marburg Virus Disease (MVD) are Pigs and African green monkeys (Dhama et al. 2022).

6. TRANSMISSION OF MARBURG VIRUS

6.1. BAT-TO-BAT TRANSMISSION

In bats, it is hypothesized that biting, sexual interactions, and hematophagous arthropods are the possible routes of MARV transmission (Dhama et al. 2022). A study in the recent past on MARV-inoculated bats

detected the virus shedding in oral, urine and rectal samples of MARV-inoculated bats and in the blood and oral samples of in-contact bats. This study proves the horizontal transmission of MARV (Schuh et al. 2017). The detection of MARV in the intestine, salivary gland, kidneys, bladder, lungs, and tissue of the female reproductive tract of MARV-inoculated bats shows that MARV may spread either by vertical or horizontal route inside the reservoirs (Paweska et al. 2012).

6.2. BAT TO HUMANS & NHPS TRANSMISSION

MARV is mostly transmitted by bats to humans and NHPs through faeces, saliva, and partially consumed MARV-contaminated fruit (Schuh et al. 2017; Amman et al. 2021). The partially chewed MARV-contaminated fruits are frequently dumped on the ground by the reservoir bats during feeding on ripe fruits. These MARV-contaminated fruits can be consumed by susceptible humans or animals (Brainard et al. 2016; Amman et al. 2021). The direct contact with bodily fluids of infected bats and inhalation of MARV-contaminated excreta of bats spread the MARV to humans. The virus is also transmitted through contact with dead or infected animals, such as forest antelopes, monkeys, bats, and chimpanzees (Dhama et al. 2022). The infected intermediate animals may transmit the MARV to humans in the early phase. The MARV-containing bushmeat-hunting animals are common causes of transmission to humans and NHPs (Abir et al. 2022).

6.3. HUMAN-TO-HUMAN TRANSMISSION

MARV transmission occurs directly from human to human through contact via broken skin in various ways. The key factors in the spread of MARV are contaminated surfaces and items, bodily fluids, and nosocomial transmission. Sexual transmission of MARV also occurs due to its presence in the semen of infected males (Kortepeter et al. 2020). Following clinical recovery, the transmission of MARV through infected semen for up to seven weeks has been documented (Kassa 2019). Iatrogenic transmission of MARV has also been reported in humans (Lawrence et al. 2022). Transmission of the MARV occurs via parenteral introduction, mucosal surfaces, and skin damage. Parenteral exposure is the most fatal route of infection, while in an outbreak, the most persistent source of infection is direct contact with infected humans or animals (Fig. 4) (Kassa 2019). The risk of getting a disease is higher in healthcare workers, corpse handlers, spelunkers, and mine workers (Bausch et al. 2003; Mohapatra et al. 2022).

6.4. NHP-TO-NHP AND HUMAN-TO-HUMAN TRANSMISSION

Aerosols are the route of MARV transmission from human to human and NHP-to-NHP (Zhao et al. 2022). During an outbreak, transmission has also occurred through the air, as MARV may remain in the aerosols (Johnston et al. 2015). MARV fomite transmission can play a significant role in spreading the virus from both human to human and NHP-to-NHP (Fig. 4). It can survive at low temperatures for more than three weeks on solid surfaces (glasses and plastics) (Piercy et al. 2010).

7. CLINICAL FINDINGS AND SYMPTOMS

The clinical findings in a MARV-infected patient might change depending on different factors, such as the virulence of the strain, the immune status of the host, and medical maintenance. According to reports, in humans, the incubation period varies from two to twenty-one days, with an average value of five to nine days (Slenczka 1999; Kassa 2019). According to the disease course, MHF can be divided into three separate phases based on disease outcomes: the initial generalization phase, an early organ phase, and the late organ phase or convalescence phase (Kassa 2019). Each phase, along with clinical findings, is elaborated in Fig. 5.

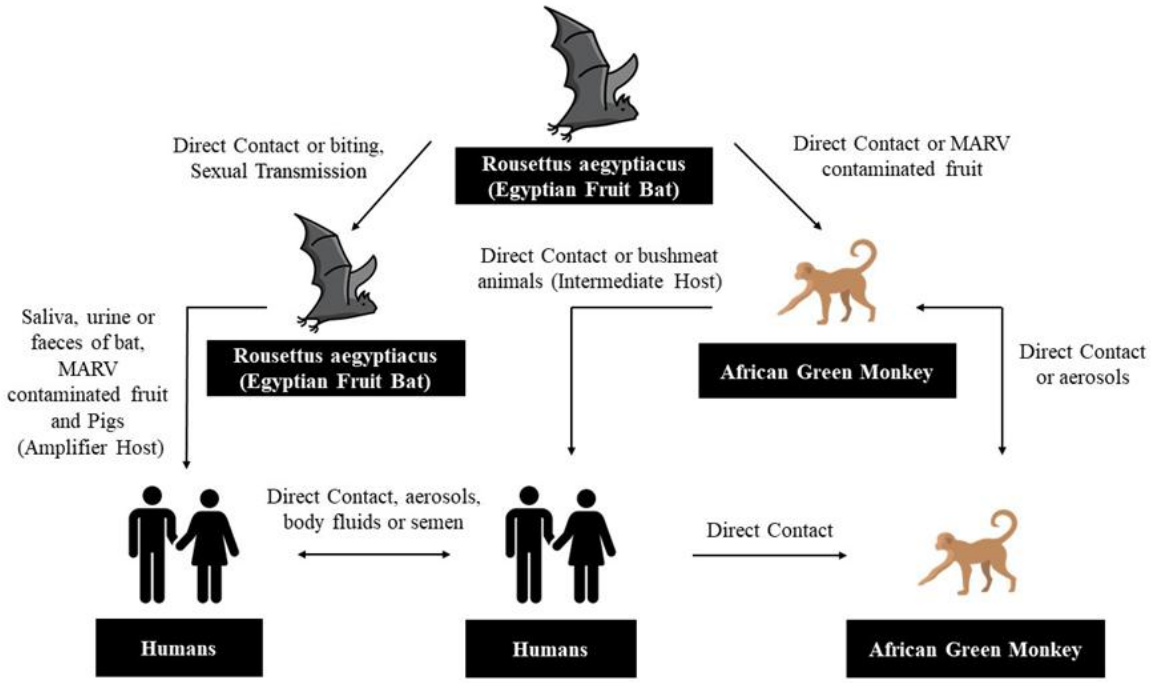

Fig. 4: Transmission of MARV.

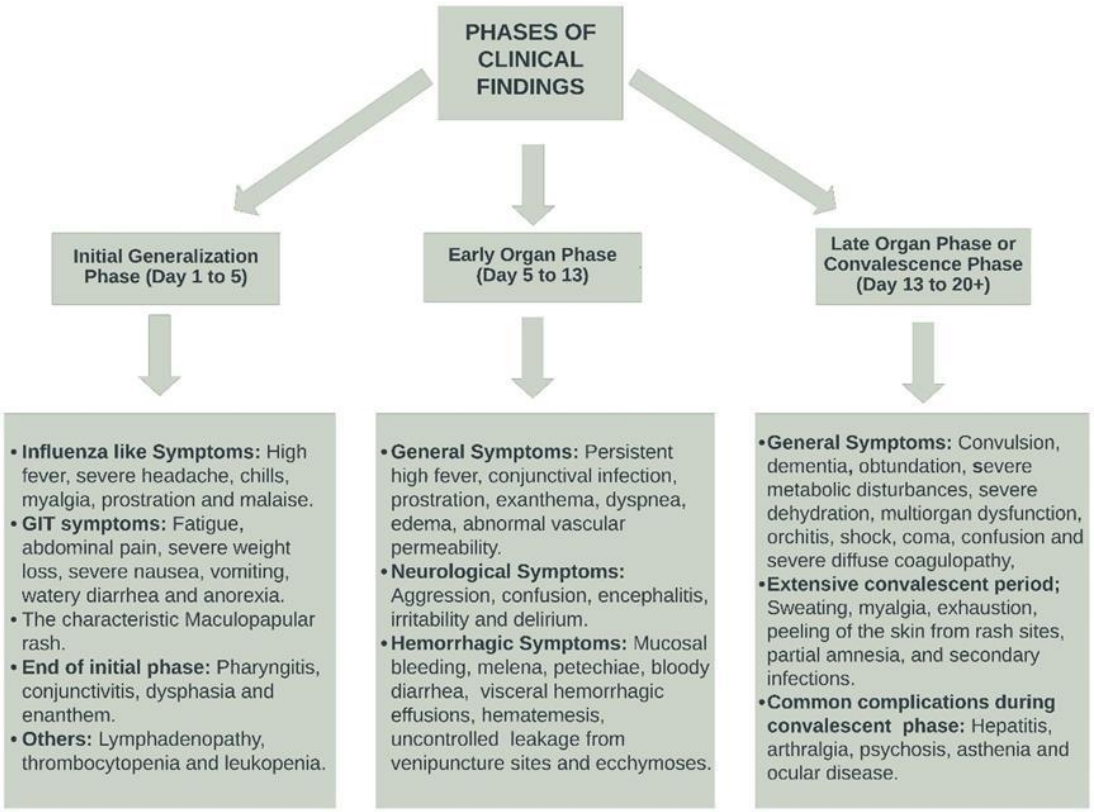

Fig. 5*:* Clinical findings and symptoms of MARV.

7.1. PHASE 1: INITIAL GENERALIZATION PHASE

The initial generalization phase lasts for five days after the disease onset, followed by rapid debilitation, high fever (~40°C), chills, myalgia, severe headache, pharyngitis, conjunctivitis, enanthem, malaise, anorexia, vomiting, and severe watery diarrhea (Kassa 2019; Abir et al. 2022). Middle to late stage is characterized by an erythematous, non-pruritic, and maculopapular rash on the face, trunk, and extremities. This maculopapular rash is a typical symptom of early MARV infection that can begin focally and then spread from its focal point (Colebunders et al. 2007; Kortepeter et al. 2020).

7.2. PHASE 2: AN EARLY ORGAN PHASE

This phase lasts between five to thirteen days and is characterized by exanthema, dyspnea, prostration, abnormal vascular permeability, and edema (Feldmann et al. 2013; Kassa 2019). Rapidly it develops into a febrile illness that leads to shock and multi-organ dysfunction (specifically pancreas, liver and kidney) (Kuhn 2008; Lawrence et al. 2022). Hemorrhagic manifestations may develop in the later stages, including mucosal bleeding, petechiae, unrestricted leakage from venipuncture sites, melena, dysentery, visceral hemorrhagic effusions, ecchymoses and hematemesis (Kassa 2019). The hemorrhagic manifestations are experienced by only one-third of patients at the peak of MARV infection (Rougeron et al. 2015). Many patients may die within a few days after the onset of this phase (Miraglia 2019). Nervous signs such as encephalitis, disorientation, irritability, and aggressiveness appear at the end of this phase (Mehedi et al. 2011).

7.3. PHASE 3: LATE ORGAN PHASE OR CONVALESCENCE PHASE

This phase lasts from thirteen to 20+ days. This phase has two outcomes; either the infection is fatal, or patients enter the convalescence phase. The late organ phase is characterized by shock, convulsions, agitation, obtundation, dementia, coma, severe metabolic issues, marked dehydration, diffuse coagulopathy, and multi-organ failure. In some reports, orchitis and abortion have also been observed (Borchert et al. 2002, Bausch et al. 2006; Mehedi et al. 2011). Generally, the primary death drivers are multi-organ failure and shock (Abir et al. 2022). Mortality mainly occurs between eight and sixteen days following the onset of signs and symptoms (Kassa 2019).

The convalescent phase is characterized by arthralgia, hepatitis, asthenia, ophthalmic disorders, and psychosis (Hartman et al. 2010). The recovered patients are the carriers of MARV. Sources of this virus in carrier individuals are eyes, testicles, amniotic fluids, placenta, fetus, and breast milk (Mohapatra et al. 2022).

8. PATHOPHYSIOLOGY OF MARBURG VIRUS

A virus typically enters the body through damaged skin or syringe needles and damages many types of cells and organs, leading to MHF (Abir et al. 2022). The binding and entrance of MARV have been linked with numerous attachment factors, such as a GP (glycoprotein) on the surface of the virus. The GP1 (GP surface unit) attaches to cellular receptors and inserts GP2 (an internal fusion loop) into the cell membrane of host cells (Hoffmann et al. 2017). MARV enters the blood or lymph and target the cells of the mononuclear phagocytic system, such as, dendritic cells, kupffer cells, macrophages, and monocytes (Rougeron et al. 2015; Asad et al. 2020). The virus replicates in these cells and disseminates systemically

into other body cells like fibroblasts, hepatocytes, epithelial cells, and endothelial cells (Rougeron et al. 2015). Liver, lymphoid tissues and adrenal glands are the primary targets for MARV at the organ level (Mohamadzadeh et al. 2007). The significant replication of the virus takes place in target organs, including the liver, spleen and secondary lymphoid organs (Geisbert and Jaax 1998).

MARV suppresses innate response and dysregulates lymphocyte costimulation (Messaoudi et al. 2015). The infected macrophages trigger the production of cytokines and chemokines such as tumour necrotic factor alpha (TNF-α), monocyte chemo-attractant protein 1 (MCP-1), macrophage inflammatory protein 1 (MIP-1), monocyte chemotactic protein-1, interleukin (IL)-1β, IL-1 receptor antagonist, IL-6, IL-8, IL-10, IL-15, IL-16, growth regulated oncogene-α, NO, Chemokine ligand 3 (CCL3), Chemokine ligand 4 (CCL4), C-X-C motif chemokine ligand 10 (CXCL10), and eotaxin (Rougeron et al. 2015). TNF-α causes apoptosis of T lymphocytes and natural killer cells as well as extensive lymphoid depletion in the thymus, lymph nodes and spleen, leading to lymphopenia. This immunosuppression helps MARV to disseminate systemically (Basler and Amarasinghe 2009; Rougeron et al. 2015).

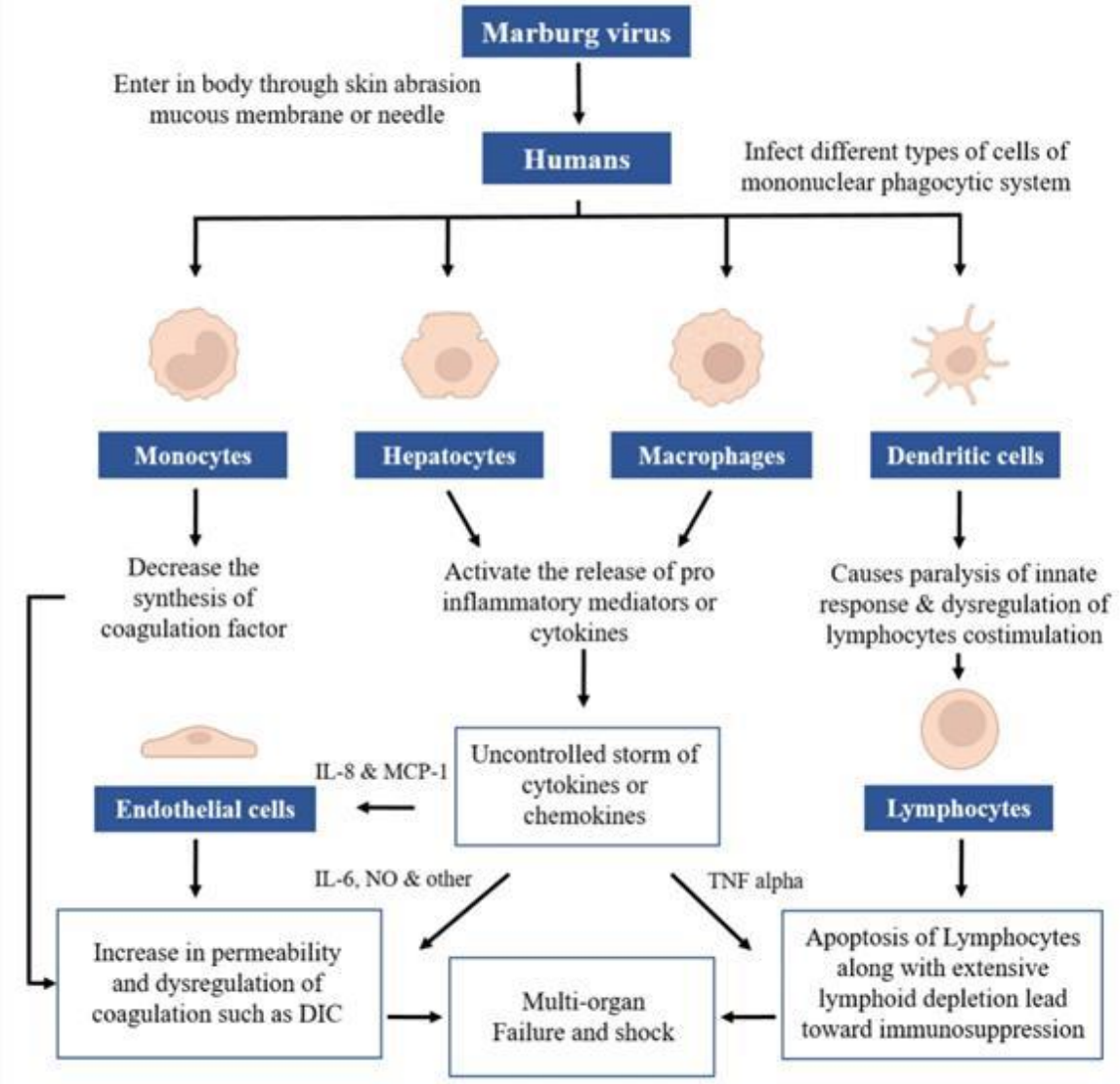

Fig. 6*:* Pathophysiology of MARV infection at cellular level in humans.

MCP-1 and IL-8 cause tissue damage that leads to the expression of adhesion molecules on endothelial cells. This expression of adhesion molecules allows the neutrophils and monocytes to damage sites (Gerszten et al. 1999). TNF-α, together with IL-6, NO, and other vasoactive substances, increases the permeability of the endothelial blood vessels lining. These vasoactive substances also cause coagulopathies, such as disseminated intravascular coagulation (DIC) and reduce the synthesis of clotting factors due to impaired hepatocytes (Adegboro and Adeola 2011; Rougeron et al. 2015). Dissemination of MARV in the adrenal cortical cells causes hypotension and metabolic disturbances. These hemodynamic disturbances, immunosuppression, and coagulopathy lead to shock and multi-organ failure (Kassa 2019). Fig. 6 indicates the pathophysiology of MARV at a cellular level in humans.

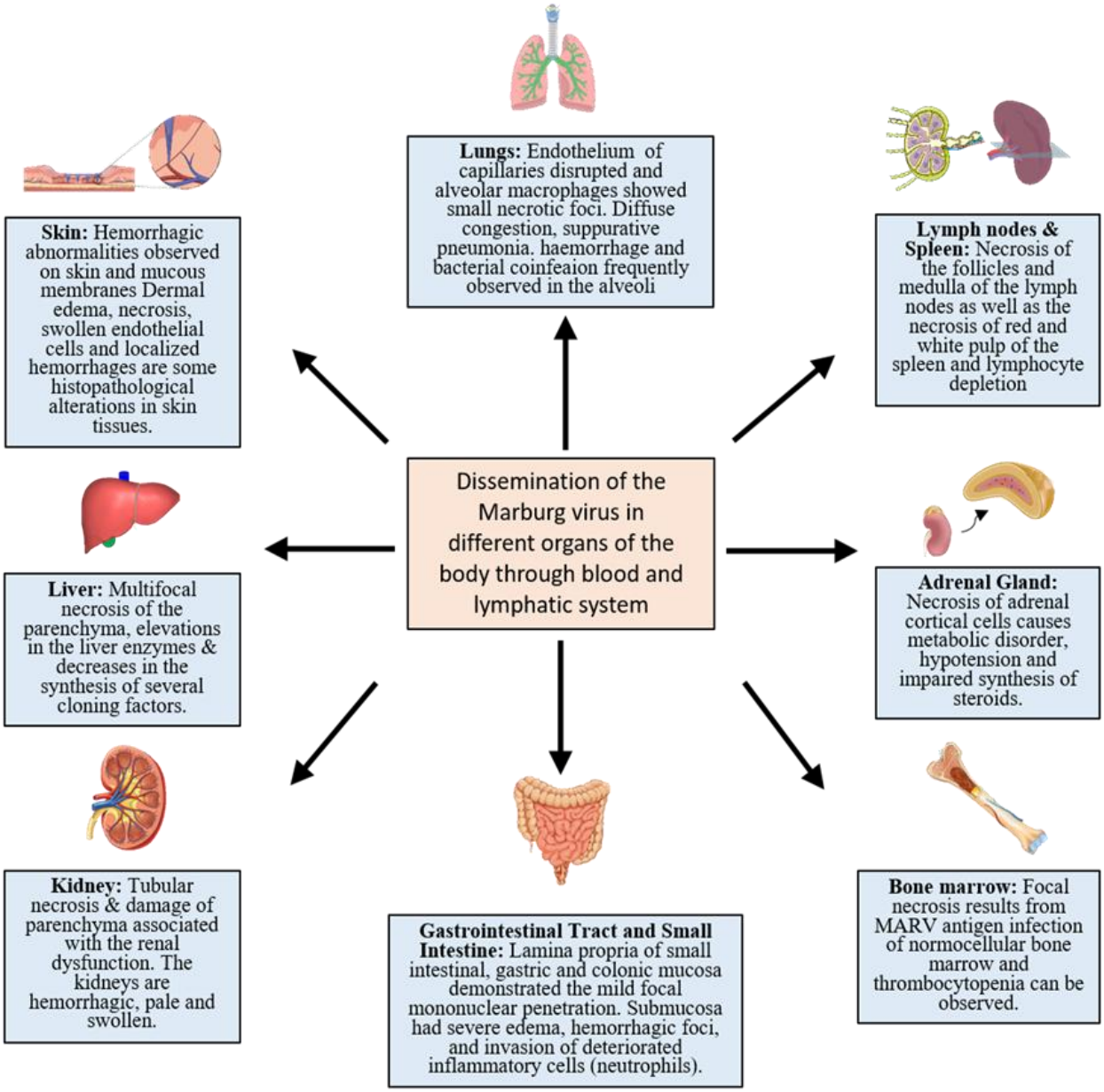

Fig. 7*:* Pathological changes caused by MARV in humans.

9. PATHOLOGICAL CHANGES IN MARV INFECTION

In hepatocytes, necrosis of the parenchyma of the liver causes significant damage to the reticuloendothelial system and coagulation abnormalities. Proteinuria is frequently seen in MHF patients who show renal dysfunction caused by tubular necrosis and damage to parenchyma (Asad et al. 2020). Microscopically, the affected kidneys are hemorrhagic, pale, and swollen, indicating grave damage to the parenchyma (Shifflett and Marzi 2019). The adverse changes occur in the lymphoid tissues, such as necrosis of the medulla and follicles of the lymph nodes, along with necrosis of the red and white pulp of the spleen (Mariappan et al. 2021). Fig. 7 below shows pathological changes caused by MARV in humans. The endothelium of capillaries of alveoli was frequently disrupted, and alveolar macrophages showed small necrotic foci or micro-necrosis and fibrin (Geisbert and Jaax 1998). Diffuse congestion, suppurative pneumonia, hemorrhages, and bacterial coinfection were frequently observed in the lung alveoli (Abir et al. 2022). It is still unclear exactly how MHF causes morphological alteration of the bone marrow. Focal necrosis results from MARV antigen infection of normocellular bone marrow (Zapata et al. 2014). Dermal oedema, necrosis, swollen endothelial cells, and localized haemorrhages are limited histopathological alterations in skin tissues. The cutaneous effects develop during recovery and appear between the second and seventh day following the onset of symptoms (Nkoghe et al. 2012). In the GIT, lamina propria of small intestinal, colonic, and gastric mucosa demonstrated mild focal mononuclear penetration. The submucosa has severe oedema, many haemorrhage foci, and an invasion of deteriorated inflammatory cells (Abir et al. 2022).

10. DIAGNOSIS OF MARV

As MVD has low prevalence, few conditions make a person suspected of MHF. The person must have contacted the bodily fluids of the African natives or recently visited people or animals. Mostly the transmission of virus occurs when the person is a health worker that contacts infected patients or visits outbreak areas. Typhoid fever, rickettsial infections, and malaria have semiological similarities to MHF, so clinical identification is challenging in the early stages of an outbreak (Grolla et al. 2005). Diagnosis of MHF includes molecular, serological, and virological techniques. Blood and serum are the best and most reliable specimens for diagnostic purposes, other specimens, like breast milk, saliva, and urine (uncertain), can be used (Kassa 2019). Blood tests help to rule out the differential of MHF.

Confirmatory diagnostic tests for MARV include a Reverse transcriptase polymerase chain reaction assay (RT-PCR), serum neutralization test, Electron microscopy, Enzyme-linked immunosorbent assay (ELISA) and virus isolation by cell culture (Chakraborty et al. 2022). Contact tracing and case identification are the only approaches to control the disease outbreak, as all above mentioned diagnostic facilities are not available worldwide. IgG ELISAs are mainly used to identify people who recovered from MHF as IgG lasts for several years, whereas IgM-capture ELISA is more typically employed for the diagnosis of acute sickness as IgM are MARV-specific antibodies and emerge two days post-infection (Kassa 2019). Antibody ELISA is used to detect the host immune response. Virus isolation and electron microscopy are limited to specific specialized locations with the required facilities. Conventional RT-PCR, quantitative real-time RT-PCR, and Reverse transcription loop-mediated isothermal amplification have been developed to detect MARV RNA in clinical specimens (Towner et al. 2006).

11. MANAGEMENTAL APPROACHES FOR MARV

A common treatment strategy is using remedies for pain management because of the absence of documented treatment. Supportive treatment often includes; maintenance of blood volume and

electrolytes (Jeffs 2006). Treatments or vaccines with clinical validation to prevent or treat MVD are currently absent, though some reliable techniques can be adopted to control outbreaks and cases (Islam et al. 2023). The supportive therapy used in the past is enlisted in Table 3.

Table 3: Supportive therapy used in the past

Year	Area	Supportive treatment	Reference
1967	-	Cardiac glycosides, Serum, Fluid infusion, Antipyretics, Steroids and Electrolytes.	(Todorovitch et al. 1971)
1980	Kenya	Antimalarial drugs.	(Smith et al. 1982)
1990	Russia	Extracorporeal hemosorbents.	(Nikiforov et al. 1994)
2004-2005	Angolan	Antimalarial drugs, Heparin, Antibiotics, Analgesics, Antiemetics, sedatives, Cimetidine, Oral rehydration and IV fluids.	(Ndayimirije and Kindhauser 2005; Jeffs 2006; Roddy et al. 2007)
2008	Uganda	Blood transfusion, Malaria prophylaxis, Antiemetics and Antibiotics.	(Leggiadro 2010)
2008	Netherland	Hemofiltration, Plasma, IV fluids, Hypertonic saline.	(Clark et al. 2012)

12. CURRENT SUPPORTIVE THERAPY

Remdesivir exhibited clinical effectiveness when administered once daily for 12 days at a dose rate of 5 mg/kg or as a 10 mg/kg initial dose followed by a 5 mg/kg after four days of inoculation (Porter et al. 2020). Phosphorodiamidate positive-charged morpholino oligomers (PMOs), Small virus-like proteins and interfering RNAs are under study as a treatment for advanced diseases since they have been shown to prolong disease survival in animal models (Lawrence et al. 2022).

Cholesterol-conjugated fusion inhibitors have activity against MARV (Pessi et al. 2019). 4-(aminomethyl) benzamide is an effective entrance inhibitor of MARV infection (Gaisina et al. 2020). Galidesivir, favipiravir and aloperine have shown efficacy against MARV infection, and more recently, an inhibitor chemical called FC-10696 has been found to prevent MARV from egressing (Abir et al. 2022). *Nigella Sativa* (Black seeds) is a supportive therapy with antiviral, anti-inflammatory, and antioxidant properties.

Black seed's antiviral activities lower the viral burden of the MARV-infected patient (Maideen 2023). Monoclonal antibody (MR186-YTE) alone can provide 100% protection, and when combined with Remdesivir five days after infection, can provide 80% protection in NHP (Cross et al. 2021). Thus, additional research regarding combination therapy or monoclonal antibodies and their application in humans could be another potential aspect of managing MVD. Table 4 shows complete supportive treatment and vaccination.

13. VACCINATION STRATEGIES

Rodent and NHPs models were used in different research to investigate the effectiveness of MARV vaccines. Some vaccinations have so far undergone human usage trials (Dulin et al. 2021). The Chimpanzee adenovirus serotype three vector vaccine, encoded with glycoprotein from MARV, is in phase 1 of the clinical study (Trovato et al. 2020). BN-Filo vaccine, encoded by the glycoprotein from MARV, Ebola and Sudan, is in phase 2/3 trials after completing the phase 1 trial (Roozendaal et al. 2020).

DNA plasmid vaccine includes GP from MARV Angola, and MARV Sudan completed phase 1 clinical trial (Abir et al. 2022). Trivalent vaccines in a single vial have recently been developed, and tests on mice and NHPs models revealed strong antibody levels. This vaccine may simplify administering and distributing immunizations in remote and underdeveloped locations (Preston et al. 2021). A recombinant vesicular stomatitis virus-based vaccine that indicates glycoproteins of MARV has demonstrated encouraging outcomes if administered 48 hours after exposure (Asad et al. 2020). VSV-based vector and Recombinant

AD5 (showing Musoke glycoproteins) usage is currently the best approach toward MARV (Mehedi et al. 2011). Experimental methods are still used on both human and animal models to check the effectiveness of treatment and vaccines (Table 4).

Table 4: Evaluation of MARV treatment and vaccination in the NHP model (Abir et al. 2022)

Sr. No	Animal model	MARV strain	Compound used	Dose	1st dose after infection	Dose number	Rate of survival
			Antibody treatment				
01	Rhesus macaque	Angola	MR191-N	50mg/kg	4th &	2	100%
					5th day	2	80%
02	Rhesus macaque	Ci67	Purified immunoglobin- E	100mg/kg	15-30 minutes	3	100%
			Antiviral drugs treatment				
01	Cynomolgus macaque	Musoke	BCX4430 (Galidesivir)	15mg/kg	1st & 2nd day	28	100%
						26	100%
02	Cynomolgus macaque	Angola	GS-5734 (Remdesivir)	10mg/kg loading dose then 5mg/kg	5th day (5mg/kg)	12	83%
						12	50%
03	Rhesus macaque	Ravn	siRNA NP	0.5mg/kg	3rd &	7	100%
					6th day	7	100%
			Pre-exposure vaccine				
01	Cynomolgus macaque	Musoke, Angola, Ravn	rVSV-MARV	2x10^7 PFU	-	1	100%
02	Cynomolgus macaque	Angola	DNA MARV GP	4mg	-	4	100%
03	Cynomolgus macaque	Musoke, Ci67, Ravn	VLPs+QS-21 adjuvant	1mg VLps +0.1ml QS-21	-	3	100%
04	Rhesus macaque	Popp	Inactivated MARV	7µg	-	2	50%
			Post-exposure vaccine				
01	Rhesus macaque	Musoke	rVSV-MARV	10^7 PFU	20-30 minutes	1	100%
02	Rhesus macaque	Musoke	rVSV-MARV	2x10^7 PFU	1st &	1	83%
					2nd day	1	33%

14. PREVENTION AND CONTROL OF MARV

Effective controlling of MARV is difficult because no proper treatment and vaccine (licensed) is available. So the control of MARV is done by breaking its secondary transmission cycle. Persons who have contacted the index case should check their temperature twice daily for three weeks since contact and report it to the public health officer, and if fever develops should be quarantined (Timen et al. 2009). Due to the danger of sexual transmission, WHO advises safe sex for male survivors of MHF for 12 months after the development of symptoms until their semen results negative for MVD twice (Mohapatra et al. 2022).

The first approach is to reduce the likelihood of bat-to-human transfer brought on by extended exposure to mines or caves where fruit bat colonies are found, and people should wear gloves and other suitable protective clothes when working, conducting research, or visiting mines or caves. The second approach is to limit the possibility of transmission from one human to another, occurring due to direct contact or contact with fluids of the body of infected patients (Kassa 2019).

To investigate MARV infection, samples from humans and animals should be manipulated by qualified experts and managed in biosafety level 4 laboratories, which are fully furnished with maximum

containment facilities (Sah et al. 2022). All animal products, like raw and undercooked meat, must be thoroughly cooked before being consumed by humans (Dhama et al. 2022).

Proper burial of the deceased, identifying the infected persons, and isolating infected persons from healthy ones help control and prevent the disease. Using proper personal protective equipment like gloves, masks and washing your hands after taking care of sick patients help control and prevent the disease. WHO suggests that when in close contact (1-meter distance), the caretaker of the patient should use a mask, long-sleeved gown, and gloves ("Marburg Virus Disease." *World Health Organization*, 7 Aug. 2021, www.who.int/news-room/fact-sheets/detail/marburg-virus-disease. Accessed 05 July 2023). The staff should have a separate room to change clothes, and a separate container should be used to collect and burn all patient waste (Bauer et al. 2019). The corpse of a patient should be covered in a coffin that has been bleach-sprayed before being buried (Bauer et al. 2019).

15. FUTURE PERSPECTIVE

Although MARV originates in Africa, its outbreaks with high CFR and complex transmission cycles indicate that it can affect the whole continent. More studies focused on MARV are still essential to deliver clear direction for managing patients and the progress of vaccine development. To design a proper management course, it is crucial to conduct more trials on NHP models to understand the complex pathogenesis and the effect of different drugs. A proper surveillance system approach should be adopted for outbreak prevention and management. The ecology of MARV and the transmission cycle should be properly studied to control disease outbreaks. Taking measures like Seroepidemiological surveys of the MARV endemic locations and international travellers is beneficial. It will assist in developing a region-specific plan to halt the spread of the MARV disease in future. Proactive planning, collaborative activities involving public health experts, scientists, biologists, legislators and awareness campaigns can create effective measures to combat MVD. The public health sector should educate the community for future epidemic preparation.

16. CONCLUSION

In conclusion, the main focus is on the future perspectives after exploring various managemental approaches to find a research gap so that a proper study should be conducted to limit the chances of MVD from becoming an epidemic. Many past and recent studies regarding this virus are summarized its complex pathogenesis and comprehensive transmission cycle to devise a plan and strategies for control and prevention. Mapping systems and data regarding endemic areas and outbreaks also help to plan a strategy for international travel and bans.

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Marburg Virus: A Potential Zoonotic Pathogen

24

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ABSTRACT

Marburg virus disease (MVD), a zoonotic illness transmitted chiefly through contact with the Egyptian fruit bat, has been a concern since 1967, notably with outbreaks in 1998 and 2004. Exposure to fruit bats in caves, alongside person-to-person transmission, fueled these outbreaks. MVD unfolds in three phases, marked by fever, muscle pain, aggression, and loss of appetite. MARV infection causes severe hemorrhagic fever, often leading to organ failure and a fatality rate of up to 90%. Due to rare outbreaks, comprehensive research for effective treatments is challenging. Significant outbreaks hit Marburg, Frankfurt, and Belgrade in 1967, with subsequent cases in Angola, DRC, Kenya, South Africa, Uganda, Guinea, Tanzania, and recently Ghana. WHO advocates bat avoidance, hygiene, PPE use, safe handling, screening, and awareness as preventive measures. Global collaboration among diverse experts is pivotal to prepare against MVD and mitigate potential global health threats.

Key words: Marburg virus, Egyptian fruit bat, zoonotic disease, transmission dynamics, global health initiatives, human primates.

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1. INTRODUCTION

Marburg virus (MARV) belongs to genus *Marburgvirus* under *Filoviridae* family and has potential to cause severe and deadly Marburg disease (MARD) (Bukreyev et al. 2014). MARV has been categorized as pathogen of category A by Centers for Disease Control and Prevention (CDC) and assigned as a Risk Group 4 Pathogen classification via World Health Organization (WHO) (Zhao et al. 2022). MARV is categorized as a zoonotic virus, indicating its ability to be transmitted from animals to humans. Reservoir host for MARV is Egyptian fruit bat (*Rousettus aegyptiacus*), which means that this particular bat species harbors virus without experiencing significant illness (Towner et al. 2009). Following initial zoonotic transmission from an infected animal to a human, subsequent transmission of virus is amplified through close human-to-human interaction. This transmission can take place through direct contact with bodily fluids or through contact with contaminated fomites, which refer to objects or materials that are likely to harbor infection (Dhama et al. 2022). Illness gives rise to hemorrhagic fever and disruptions in organ functionality, namely hepatic failure, brain infection, involvement of spleen, and issues affecting renal system. Additionally, complications related to coagulation are observed (Mehedi et al. 2011). Up until March 2018, a total of thirteen outbreaks of MARV disease had been documented, with the majority being taking place in sub-Saharan Africa. Among these outbreaks, the most substantial one occurred in Angola between 2004 and 2005, boasting a case-fatality rate of 90% (Amman et al. 2017). Given potential and significant threat MARV poses to public health and safety, it is crucial to implement systematic surveillance measures to effectively address its reoccurrence and increasing mortality rates associated with disease (Towner et al. 2006).

2. VIRAL GENOME AND STRUCTURE

The genome of MARV is approximately 19,000 nucleotides in length and undergoes transcription to produce eight significant sub-genomic messenger RNAs (mRNAs). These mRNAs are responsible for encoding seven structural proteins (Rougeron et al. 2015). Genomes of MARV consist of non-segmented negative-sense (NNS) RNA and exhibit a size range of 19,111 to 19,114 nucleotides (nts). These genomes are comprised of seven monocistronic genes arranged linearly. Each gene contains a highly conserved transcription start and stop signal, an unusually long 3' and 5' untranslated region, and an open reading frame (ORF). Genes are separated by short intergenic regions, which can vary in length from 4 to 97 nts. Core of Marburg virus particles is ribonucleoprotein complex (known as nucleocapsid) and consists of RNA genome, which is tightly associated with nucleocapsid protein sand tubular structures formed by this nucleocapsid within virus. Outer diameter of these structures is 45-50 nm, with an electron-dense central axis measuring 19-25 nm (Fig. 1) (Tiwari et al. 2018).

This genomic organization is a characteristic feature of MARV and is important for expression of individual viral genes. The 3' and 5' ends of viral genome contain extracistronic regulatory regions that play crucial roles in transcription and replication. These regions contain cis-acting signals, including transcription and replication promoters, which are essential for viral gene expression and genome replication. Non-segmented negative strand (NNS) RNA viruses generally have two types of genomic replication promoters including a bipartite promoter found in paramyxoviruses of *Paramyxovirinae* subfamily, and a more compact and continuous replication promoter observed in rhabdo- and pseudo viruses (Morrison et al. 2003; Easton et al. 2004).The bipartite promoter configuration found in *Paramyxovirinae* subfamily is connected to the "rule of six," i.e., the entire genome length must be a multiple of six. The identification of a bipartite structure in the mapping of the MARV genomic replication promoter was unexpected, considering the non-compliance of filoviruses with the rule of six. Genomic replication promoter of MARV consists of two elements. First element is located at the 3' end of the genome, known as leader, and contains initial promoter region. MARV's glycoprotein, GP,

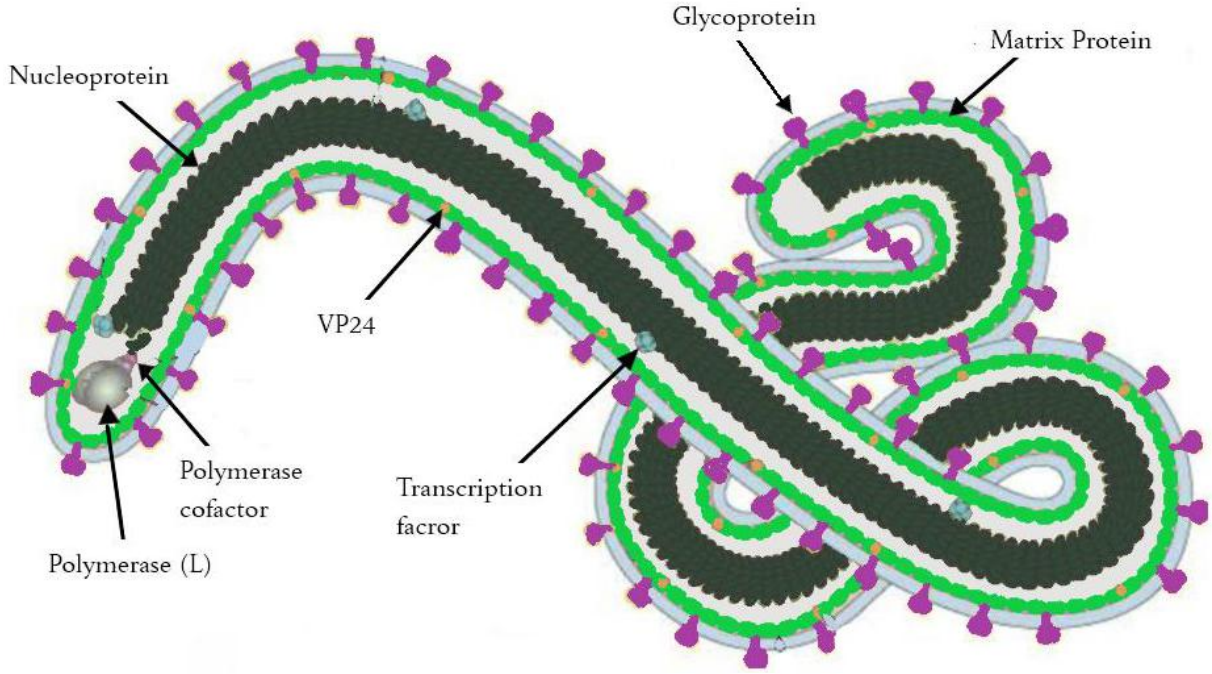

Fig. 1: Structure of Viral genome: The nucleoprotein enwraps genomic and antigenomic RNAs. VP24 is commonly referred as second, minor matrix protein. In event of an infection, VP24 plays a significant role in release of viral particles. It is encoded by fourth gene, glycoprotein is a single surface protein that facilitates attachment to target cells and aids in virus entry in form of homotrimeric spikes. Encoded by third MARV gene, matrix protein serves as counterpart of M proteins found in other NNS RNA viruses. Transcription factor proteins form a tight association within nucleocapsid by binding to NP. Polymerase cofactor protein functions as polymerase cofactor and is vital for both transcription and replication processes. Primary constituent of MARV polymerase complex L is estimated to have a molecular weight of 267 kD.

is encoded by fourth gene and plays a crucial role in attaching to target cells and facilitating virus entry. GP is a type I transmembrane protein that is incorporated into viral envelope as trimeric spikes (Raoul et al. 2019).

Precursor GP of MARV divides into two disulfide-linked subunits: GP1 (160 kD) and GP2 (38 kD). GP1, which forms ectodomain, is responsible for binding to entry factors and receptors, while GP2, which contains fusion peptide, mediates fusion of the viral and cellular membranes (Pigott et al. 2015). Domain of GP2 contains 30 amino acids, which are necessary for incorporation of GP. Cytoplasmic tail of GP2 enhances viral entry efficiency by maintaining structure of the ectodomain. The region responsible for receptor binding in MARV GP was identified within the amino-terminal portion of GP1, covering amino acids 38 to 188 residues (Kudo et al. 2020). On other side, highly glycosylated mucin-like domain is not essential for virus entry.A significant stage in the entry process of MARV involves the proteolytic activation of GP1 through endosomal proteases. This activation, in turn, enables the binding of the receptor binding region to the endosomal entry factor known as the Niemann-Pick C1 protein (Brauburger et al. 2012).

3. HISTORY AND GEOGRAPHICAL DISTRIBUTION

MARV has fatality rate of 24 to 88 % (Abir et al. 2022). During initial outbreak of Marburg hemorrhagic fever (MHF) in 1976, the first six patients were found to have been working in a plant that was believed

to be infested by insectivorous bats. This provided evidence that bats could be a source of human infection in MHF outbreaks (Languon and Quaye2019). In Durba outbreak, it was further confirmed that bats served as a source of human infection. During previous outbreak, at least nine different genetic variations of MARV were identified among affected individuals, indicating genetic diversity within virus population (Swanepoel et al.2007).Recently, evidence has emerged of six additional mutations in bats, providing support for theory that there may be additional variants of virus that have gone unreported. This is likely due to limitations of laboratory testing, which has typically focused on a small number of individuals. To sustain multiple genetic virus variants, there needs to be a substantial host population with ongoing accomplishment by migration or reproduction of sensitive individuals (Amman et al. 2020).
After initial identification in 1967, there was an eight-year period in which MARV remained dormant. However, in 1975, an Australian teenager who had moved to Zimbabwe was divulged to a sanatorium in South Africa, exhibiting indications evocative of those examined in 1967 epidemic in Europe. This case brought attention back to MARV (Slenczka and Klenk2007). From 1975 to 1985, there were sporadic outbreaks of the MARV on African continent, affecting only a small number of individuals. Mortality rates associated with MARV disease were low. Consequently, MARV was initially considered to be less threatening. However, in 1987, an outbreak occurred in Nairobi, Kenya, with the mode of origin traced back to Mount Elgon National Park (Petersonet al. 2006). In 1988 and 1990, there were outbreaks of MARV in Koltsovo, Soviet Union (now Russia), with suspected origin being laboratory infections resulting from unspecified breaches in safety requirements (Roffeyet al. 2002).
MARV re-emerged in two significant waves: from 1998 to 2000 in Democratic Republic of the Congo (DRC) (Bausch et al. 2006), and then again from 2004 to 2005 in Angola, Western Africa (Towner et al. 2006). These outbreaks highlighted the MARV as a significant threat to public health (Feldmann 2006). During MARV outbreaks from 1998 to 2000 in the DRC, it was discovered that 9 distinct virus modifications were moving among affected sufferers, indicating multiple independent introductions from the natural reservoir into human population (Languon and Quaye 2021). Table 1 highlighted the various outbreaks of Marburg virus from 1967-2023 in different regions of the world.

4. TRANSMISSION ROUTES

Previous investigations have highlighted several pathways for bat-to-bat transmission. Notably, excretion of MARV through urological, anal, and spit samples by infected bats represents a significant route of transmission (Abir et al. 2022). Additionally, there have been reports of MARV detection in blood samples from bats that had close contact with infected individuals. Collectively, these findings suggest a form of "horizontal transmission", where MARV is transmitted from bats carrying the pathogen to other bats nearby (Schuh et al. 2017). A distinct investigation has revealed that in addition to horizontal transmission, MARV can also be passed "maternally," as evidenced by inclusion of the virion in multiple tissues such as parotid glands, thoracic organs, bowels, nephritic organs, and female reproductive tract of bats that were deliberately inoculated with MARV (Pawęska et al. 2012). A few other theoretical pathways have been proposed, including biting, sexual contact, and transmission through hematophagous arthropods (Dhama et al. 2022).
Transmission of MARV from reservoir to host entails utilization of "intermediate hosts," which primarily consist of non-human primates and animals hunted for exotic meat. These intermediate hosts play a pivotal role as primary "vectors", facilitating transmission of MARV (Chakraborty et al. 2022). Nevertheless, the precise mechanism of transmission from reservoir to human hosts in the case of this virus remains to be fully understood. Potential pathways of transmission from reservoirs to both humans and non-human primates, as indicated by diverse studies, encompass contact with bat saliva, urine, fecal droppings, and consumption of fruits contaminated with MARV (Fichet-Calvet et al. 2014).

Table 1: Outbreaks of Marburg virus from 1967-2023 in different countries

Country	Number of cases	Year(s)	Reference
Germany	30	1967	Martini et al. 1971
Yugoslavia (now Serbia)	2	1967	Martini et al. 1971
South Africa	3	1975	Conrad et al. 1978
Kenya	2	1980	Smith et al. 1982
Kenya	1	1987	Johnson et al. 1996
Soviet Union (now Russia)	1	1988	Kuhn 2008
Soviet Union (now Russia)	1	1990	Nikiforov et al. 1994
Democratic Republic of the Congo	154	1998-2000	Bausch et al. 2006
Angola	252	2004-2005	Ligon 2005
Uganda	4	2007	Adjemian et al. 2011
USA	1	2008	Sah et al. 2022
Netherlands	1	2008	Timen et al. 2009
Uganda	1	2014	Luke et al. 2014
Zimbabwe	3	1975	Paassen et al. 2012
Uganda	1	2008	Stroher et al. 2001
Colorado	1	2008	Fujita et al. 2008
Ghana	2	2022	Jack et al. 2022
Russia	1	1991	Kimman et al. 2008
Russia	1	1995	Ignatye et al. 1996
Uganda	15	2012	Gear et al. 1975
Uganda	4	2017	Nyakarahuka et al. 2019
Guinea	1	2021	Aborode et al. 2021
Tanzania	8	2023	Larik et al. 2023
Equatorial Guinea	9	2023	Sohan et al. 2022
USSR	1	1990	Nikiforov et al. 1994
USSR	1	1988	Deb et al. 2023

Within human hosts, MARV can be transmitted through sexual intercourse, as evidenced by identification of viral antigens in the ejaculate of ailing males (Coffin et al. 2018). Additionally, direct contact with body fluids such as teardrops, mucus, and breast milk of infected individuals is also considered asa significant route of transmission (Shifflett and Marzi 2019). Case studies have also indicated the possibility of transmission to the fetus through placenta (Bebell and Riley 2015; Schwartz et al. 2019; Coler et al. 2022). Improper handling of MARV-infected corpses poses a significant risk as it may result in irresponsible transmission of virus. Furthermore, certain studies have suggested the potential for fomites or aerosol-borne transmission of virus (Leffel and Reed 2004; Dobler et al. 2012; Al-Moraissi et al. 2022).

5. SUSCEPTIBLE TARGET HOSTS

MARV has been found to have bats as central reservoirs and natural hosts. Specifically, Egyptian fruit bat (*Rousettus aegyptiacus*), belonging to *Pteropodidae* family of fruit bats, is considered as a primary reservoir for the MARV. Bats can carry the virus without showing symptoms of illness and may transmit it to other species, including humans. Close association between bats and MARV highlights importance of understanding the role of these natural hosts in transmission and spread of virus (Towner et al. 2009; Sah et al. 2022). Correct MARV varies in type and is inaccessible to various bat species in different African countries. In Kenya, Sierra Leone, Zambia, Uganda, Gabon, South Africa, and Leone, RNA of MARV is distinguished within bats (Pawęska et al. 2020). In 1999 in DRC, 12 MARV strains were obtained

from bats belonging to Chiroptera order, although specific species were unidentified. In 2007 in Uganda, one strain was acquired from *Hipposidero scaffer*, a bat species. These findings highlight the role of bats as reservoirs for MARV (Guito et al. 2021) and geographic diversity of virus strains circulating among bat populations. Indeed, MARV has been detected in blood and oral samples of bats that have come into contact with infected MARV positive bats. Virus has been found in various tissues of infected *Egyptian Rousettus* bats, including the rectum, salivary glands, urine, intestines, lungs, bladder, kidneys, and female reproductive tract (Schuh et al. 2017).

Consumption of bush meat from infected animals and handling of contaminated fruits that carry MARV are considered primary sources of transmission to non-human primates and humans, who are accidental hosts of virus (Amman et al. 2015). In the northeastern region of DRC, investigations have been conducted to identify reservoir hosts for MARV, focusing on local wildlife, including bats. From 1998 to 2000, there were outbreaks of Marburg hemorrhagic fever (MHF), and during this time, investigations were undertaken to study the presence of MARV in bats. Antibodies towards disease were noticed in serum in 20.5 %of fruit bat species and 9.7 %of one insectivorous species (Abir et al. 2022). Additionally, nucleic acid of MARV originated in twelve bats; encompassing 3.0 to 3.6 %of two insectivorous bat species and one species of fruit bat. However, efforts to segregate virus from these bats were not productive (Swanepoelet al. 2007). These findings suggest potential involvement of bats as reservoir hosts for the MARV, although supplementary learning is required to comprehend exact responsibility, they play in transmission dynamics of virus.

6. CLINICAL SIGNS AND SYMPTOMS

MVD symptoms have been mainly documented in three major reported outbreaks (Slenczkaand Klenk 2007). Incubation period for MVD, based on most reported cases of exposure and disease, ranges from 3 to 21 days. However, actual duration of incubation period can be modified by route of infection. MVD follows a three-phase progression. First phase is known as Phase of Generalization (Days 1-4), and symptoms include high fever (39-40°C), chills, muscle pain, and extreme fatigue. Gastrointestinal symptoms such as anorexia, abdominal discomfort, nausea, vomiting, and watery diarrhea may also occur during this phase (Asad et al. 2020). These gastrointestinal symptoms can be managed with various treatment options to provide relief to patients. Within first 4-5 days after surgery, patient developed symptoms of enanthem (a rash inside the mouth), dysphasia (difficulty swallowing), and pharyngitis (a sore throat) (Elsheikh et al. 2023).

Second phase is known as early organ phase (Day 5-13), during which patients may experience a range of symptoms. These include high fever, aggression, delirium, confusion, and irritability, which are neurological symptoms commonly observed during this phase. In addition, abnormal vascular permeability can occur, leading to symptoms such as conjunctival injection (redness of the eyes) and edema (swelling). Patients may also present with bleeding manifestations as ecchymoses (bruises), hematomas (collections of blood), bloody diarrhea, melena (black, tarry stools), and mucosal bleeding (Paassen et al. 2012).These symptoms are indicative of severe systemic effects of disease, including vascular dysfunction and coagulation abnormalities. Prompt medical attention and supportive care are crucial to manage these complications and improve patient outcomes. Third and last phase known as Late Organ or Convalescence Phase (Day 13+), in which organs such as liver, pancreas, and kidneys can be significantly impacted. Virus can cause damage to these organs, resulting in their dysfunction and contributing to overall severity of condition (Bente et al. 2009).

MARV predominantly induces a highly severe form of hemorrhagic fever, characterized by exceptionally high case fatality rates that often surpass 80 % (Hensley et al. 2005). In 1987, an investigation conducted in Kenya employed immunohistochemical and electron microscopy techniques to identify viral antigens

and virions in both circulating and tissue-associated macrophages. Furthermore, flow cytometric analyses revealed presence of MARV infection in macrophages within population of peripheral blood mononuclear cells in infected macaques (Mehedi et al. 2011). Besides this, lymph nodes, liver, and spleen exhibited most severe necrotic lesions. These organs, recognized for their profusion of reticuloendothelial cells, facilitate translocation of infected cells, resulting in spread of virus to numerous organs and establishment of a systemic infection. Other cell types susceptible to infection include hepatocytes, cells in adrenal cortex and medulla, and fibroblasts. Endothelial cells, on other hand, are targeted later in course of MARV infection in various tissues (Bente et al. 2009).

In terms of organ specificity, MARV predominantly targets liver and lymphoid tissues. Liver, in particular, serves as crucial site for MARV replication, emphasizing its significance in lifecycle of virus (Messaoudi et al. 2015). Lymphoid tissue undergoes a transformation characterized by presence of plasma cells and monocytoid cells. In vicinity of necrotic regions, basophilic bodies can be observed, either within necrotic cells or as inclusion bodies within parenchymal cells. Nonetheless, no organs remain unaffected through infection, exhibiting pathological changes characterized via focal or disseminated necrosis. Interestingly, these alterations occur in absence of significant inflammatory responses. In MVD patients, renal dysfunction commonly manifests as proteinuria (Ristanović et al. 2020). Grossly, affected kidneys display a pale, swollen appearance, indicating severe parenchymal damage accompanied by signs of tubular insufficiency (Koch et al. 2018). Microscopically, human samples reveal notable necrosis in follicles and medulla of lymph nodes, as well as in red pulp of the spleen (Geisbert et al. 2000). Additionally, there is a notable depletion of lymphocytes. In skin tissue, histopathological changes primarily involve varying degrees of dermal edema and focal hemorrhage, plus swelling and necrosis of endothelial cells (Qiu et al. 2014).

7. PATHOGENESIS

MARV infection typically occurs through unswerving touch by contaminated fluids of the body or through straight touch among unhygienic fauna or creatures. Small membrane abrasions and mucosal surfaces serve as entry points for the virus in a deceased body. Dendritic cells, monocytes, and macrophages, which are part of mononuclear phagocyte system, are untimely main cells of the MARV, as observed in various mammalian species (Alves et al. 2010). A virus has been observed in contaminated guinea pigs to replicate into macrophages prematurely twenty-four hours after infection (Ryabchikova and Price 2004). In cynomolgus macaques, infected monocytes have been detected as early as two days after exposure (Fritz et al. 2008). Macrophages and monocytes have also been acknowledged as untimely intention cells within creature models of MARV infection (Cooper et al. 2018). Cell culture studies have confirmed that individual macrophages and monocytes are extremely vulnerable to MVD because they create catching particles. Additionally, primary human endothelial cells and monocyte-derived dendritic cells (mDCs) have been shown to support MARV replication (Bosio et al. 2003). Spleen, liver, and lymph nodes are early sites of virus replication where extensive necrotic lesions are observed (Daddario-DiCaprio et al. 2006).

These appendages hold an elevated number of macrophages and monocytes (Stroher et al. 2001). It is suggested that the relocation of contaminated macrophages with monocytes keen on nearby tissues or dissemination of disease without any charge through bloodstream or lymph nodes contributes to spread of infection towards several appendages, resulting in general contagion (Schnitzler and Feldmann 2003). Extensive scrutiny has been directed towards examining free-cell viruses within tissues. Moreover, appendages of infected animals have exhibited notable signs of illness, including a significant presence within the bloodstream (Geisbert et al. 2010). In addition to dendritic cells, macrophages, and

monocytes, a wide range of cell types, including medullary cells, hepatocytes, fibroblasts, and adrenal cortical cells, are susceptible to Marburg virus infection (Yen and Basler 2016). Endothelial cells in various tissues are also targeted by a virus during MARV infection, although they are infected later in the course of disease. Involvement of endothelial cells in MARV infection and occurrence of vascular damage is still a matter of debate. Limited evidence of contaminated endothelial cells has been seen in non-human primate infections. Revolutions during the endothelium are believed to be caused by paracrine possessions of cytokines. At the delayed point of Marburg virus infectivity, viral components are inaccessible to almost all organs (Hensley et al. 2011).

Despite the presence of necrotic lesions and lofty viral consignment, minimal tenderness is monitored in affected organs and tissues, demonstrating a dysregulated resistant reaction. Significant liver pathology, characterized by elevated serum levels of liver enzymes, is commonly observed in MVD. This can lead to disruption of clotting factors and development of coagulation abnormalities (Warfield et al. 2009). A combination of these factors, along with overall disease progression and associated pathology, likely contributes to multi-organ dysfunction seen in severe cases. It is worth noting that lymphocytes are not highly susceptible to MARV infection. A hallmark of MVD is significant observation of lymphocyte apoptosis, characterized by programmed cell death of lymphocytes. However, precise molecular mechanisms underlying lymphocyte exhaustion and its role in pathogenesis of MVD are still not fully understood. Further research is needed to elucidate specific molecular pathways involved and their contribution to disease. Cytokine secretion, particularly the release of TNF-α, might cooperate with inducing apoptosis of lymphocytes in MARV infection. Infected cells are known to secrete cytokines including TNF-α which can trigger programmed cell death (Stroher et al. 2001).

8. IMMUNE RESPONSE

Indeed, understanding of innate and acquired immune responses in MARV infections is still limited. However, it has been described that MARV infection can lead to an inflammatory response characterized by uncontrolled release of chemokines and uneducable anti-inflammatory cytokines, including IL-1, 6, 8, 10, MIP-1a, and TNF-α. This excessive immune response often referred as cytokine storm that can contribute to pathogenesis of disease. Further research is needed to gain a comprehensive understanding of host immune reactions in MARV infections and their impact on disease outcomes. Expression of TNF-α and IL-6 in MARV-infected mice has been observed in a limited number of studies, and further research is needed to fully understand the immune response in animal models and its relevance to human infection (Ignatyev et al. 2000; Terajima et al. 2007; Nakayama and Saijo 2013). In vitro investigations have shown that MARV infection can induce the production of IL-6, IL-8, and TNF-α in monocytes/macrophages, indicating their involvement in activation of these immune cells (Fernando et al. 2015). Additionally, studies using tissue culture systems have demonstrated that TNF-α can increase endothelial cell permeability, suggesting its role in mediating vascular dysfunction during MARV infection (Albariño et al. 2013; Alfson et al. 2018).

During early phase of MARV infection, hematological changes such as leukopenia (reduced white blood cell count) and severe leukocytosis (increased white blood cell count) are usually observed. This can lead to significant eosinophilia (increased eosinophils), monocytosis (increased monocytes), and neutrophilia (increased neutrophils). These hematological abnormalities may contribute to immunosuppression in patients with MHF (Miraglia et al. 2019). Immunosuppression, resulting from hematological changes, can weaken the immune response and make MHF patients more susceptible to additional bacterial infections over extended sickness and healing period (Oda et al. 2016).

The specific mechanisms underlying these hematological changes in MHF patients, which contribute to immune suppression and subsequent infections, are currently being investigated. Further research is necessary to fully understand interaction between the virus, immune system, and hematological abnormalities during MARV infection. Contact between T lymphocytes and monocytes or macrophages (infected or activated) in viral infection activates Fas death receptor (Fas (CD95/APO-1) is a key member of the tumor necrosis factor receptor super family, activating apoptosis and crucially regulating the immune system) signaling pathways (Geisbert et al. 2020). Proinflammatory cytokines and nitric oxide levels increasing in blood can potentially trigger severe sepsis and apoptosis within veins. Contribution of MARV glycoprotein to lymphocyte dysfunction has not been well understood (Gross et al. 2020). Convalescent serum from patients was used to directly detect MARV antigens through immune-fluorescent-based assays during 1967 outbreaks, confirming the production of MARV-specific antibodies (Emperador et al. 2019).

9. DIAGNOSIS

Control of MVD outbreaks relies on key measures including isolation, identification, and contact tracing of infected individuals, plus laboratory diagnostics. However, clinical diagnosis of MVD in early stages of an exposure can be challenging due to presence of similar clinical symptoms to other tropical infectious diseases like malaria, rickettsia infection, and typhoid fever. This similarity in symptoms can result in significant delays in implementing appropriate infection control measures and initiating proper disease management for affected patients (Kassa 2019). It emphasizes importance of accurate and timely diagnostic techniques to distinguish MVD from other similar diseases, enabling prompt intervention and effective outbreak management. In areas experiencing an epidemic, special attention is required for diagnosis of MVD, and it is essential to consider travel history of individuals (Grolla et al. 2011). Diagnostic methods in laboratories typically include molecular, serological (serum), and virological techniques. Most appropriate method is to test blood (or serum), although fluids such as saliva (oral swab) or urine can also be used (Hartman et al. 2010).

Tissue samples obtained from autopsies can also be utilized for diagnostic purposes. In cases where blood sample is not available, breast milk can be used as an alternative specimen source (Reynolds and Marzi 2017). When dealing with suspected cases of MARV, it is advised to first contact state health department to obtain necessary permissions and guidelines for managing patients under investigation. Following guidance of state health department, specimens should be transferred directly to CDC and take preventive measures during testing. It is advised to perform these tests in the BSL-4 lab, which ensures highest level of containment and safety precautions (Racsa et al. 2013). Primary diagnostic techniques used for identification of viral genome in MVD may include reverse transcription PCR (RT-PCR) or Enzyme-linked immune-sorbent assay (ELISA) for antigen detection (Park et al. 2016). Additional methods include serum neutralization tests, electronic microscopy, and immune-histochemistry. Electron microscopy and virus isolation are also used for confirmation of virus (Brauburger et al. 2012).

ELISA serves as an alternative and confirmatory test for diagnosing MHF by detecting the antigens. This assay utilizes serum or viral protein-specific antibodies to bind to antigens (Towner et al. 2009). The IgM ELISA is mainly used to identify viral antibodies during early days of symptom onset, disappearing after infection occurs within 31 to 169 days. In contrast, IgG antibodies have been present in blood for many years (Keshwara et al. 2019). Therefore, IgM ELISA is primarily utilized for diagnosis of acute infection, but IgG ELISA is used to determine whether an individual has recovered from MHF infections or not (Sannathimmappa et al. 2021).

10. TREATMENT AND VACCINATION

Currently, no specific treatments are available for MVD. Supportive care, including fluids and symptom management, is primary approach. Experimental treatments, such as transfer of antibodies, interferon treatment, and cytokine inhibition, have shown promising results in animal models but require further research (Bausch et al. 2003). Use of recombinant nematode coagulant protein 2 (rNAPc2) in NHP models as treatment for MARV infection has not been successful. Even when administered within 30 to 60 minutes after MARV infection treatment did not provide adequate protection (Geisbert et al. 2013). Alternative treatment approaches are being explored, but there is currently no effective treatment specifically for MVD. To block the viral protein expression, some treatments are used in MRV-infected animals, specifically phosphorodiamidate morpholino-oligomers (PMO). However, the efficacy of this approach in NHP models is yet to be determined and it is important to note that these therapies are used in controlled laboratory settings, and their effectiveness may vary in real-world scenarios (Nozakiand Abou-Fayssal 2010).

To prevent MARV outbreaks resulting from laboratory accidents, strict safety measures and protocols are implemented to minimize the risk of exposure and ensure safe handling of virus. A vaccine or treatment for MVD has not yet approved, however, certain preventive measures have been implemented. These measures primarily focus on maintaining electrolyte and fluid balance, regulating blood pressure and oxygen levels, and providing blood and clotting factor replacements, which are often disrupted by infection. In cases where the disease moved forward to a modern design or combination of therapies, this was emphasized as an effective approach (Ye et al. 2023). For example, a combination of two drugs, antiviral medications and a candidate MARV-specific monoclonal antibody (mAB) has shown increased effectiveness (Hickman et al. 2022). However, further advancements are needed to improve the efficiency of herbal remedies, metabolites related to plants having immune-elevating properties, nutrition-rich foods, phytochemicals, and nutraceuticals. These include development of new chemical ligands, antiviral drugs, and broad counterpoise antibodies that can effectively treat MVD (Zhang et al. 2018).

11. DISEASE PREVENTION AND CONTROL

In absence of a licensed vaccine or widely available therapy for MVD, efforts to control infection have been challenging. In non-epidemic countries, isolated cases of MVD have been reported due to factors like infected animals or tourists spreading filovirus (Nyakarahuka et al. 2017). It is crucial to avoid spread of these viruses, and controlling outbreaks has become increasingly difficult in affected regions (Green 2012). In the past, control of MVD infection involved the collaborative efforts of various medical departments and organizations, including WHO and the CDC (Pittalis et al. 2009). Primary and secondary modes of transmission of MVD are crucial factors to address when controlling outbreaks. By focusing on interrupting transmission chain, as through isolation of infected individuals and providing proper care, it is possible to control spread of disease. Effective infection control measures and prompt response can contribute to managing and containing MVD outbreaks (Harris 2023).

Nosocomial infections, which occur within healthcare settings, have been a significant concern in spread of MVD. However, advancements in preventive medicine and increased education of healthcare workers have helped limited transmission of disease in recent epidemics. Epidemiological surveillance helps to understand outbreak's magnitude and identify transmission patterns. In disaster areas, secondary infections often arise when caring for sick or coming into close contact with the deceased during funeral rites. It is essential to implement appropriate burial and disinfection methods as well as develop plans to

prevent the spread of disease within affected region. Educating local communities about preventive measures and safe practices is important for controlling transmission of MVD. By promoting awareness and providing guidance, risk of further spread can be mitigated. Bio-security and epidemiological efforts are not enough to control outbreaks, highlighting the need for additional psychological support in affected communities (Roddy et al. 2007).

12. CONCLUSION

Since the initial case in 1967 involving contact with wildlife, there have been multiple outbreaks of MARV. Despite numerous attempts at treatment, achieving success has remained elusive. An enhanced comprehension of the clinical trajectory and pathology of MVD could yield improvements in patient care and lead to a reduction in mortality rates. The evolution of disease diagnosis has resulted in more refined test accuracies. Ongoing research efforts into diverse treatment modalities and vaccines are aimed at effectively addressing the challenges posed by this formidable virus. While certain compounds and vaccines offer partial mitigation for MVD, a comprehensive understanding of the precise pathogenesis of MARV infection following contact with reservoir animals is essential. Equally vital is unraveling the mechanisms underlying the development of asymptomatic infections. An augmented number of clinical trials are imperative for securing Food and Drug Administration (FDA) approval for treatments and vaccinations. Globally collaborative efforts involving experts from various disciplines are paramount in bolstering preparedness for MVD and in mitigating potential global health threats.

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Current Status and Future Prospective of Vancomycin-Resistant Staphylococcus Aureus (VRSA)

25

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ABSTRACT

S. aureus is a highly virulent gram-positive bacterium that belongs to the Micrococcaceae family. It possesses a cell wall composed of peptidoglycan, which consists of NAM (N-acetylmuramic) and NAG (N-acetylglucosamine) acid subunits. This bacterium also harbors surface proteins that have virulence factors. S. aureus produces toxins that cause endocarditis, pneumonia, osteomyelitis and bacteremia. The significant mortality and morbidity associated with these diseases make S. aureus a major public health concern. Antibiotic-resistant strains pose a significant challenge for physicians in effectively treating staphylococcal infections. According to available statistics, vancomycin-resistant S. aureus (VRSA) has been reported in Asia, America, and Africa, while no reports have been documented in Oceania. The prevalence rates of VRSA were found to be 1.2% among 5043 isolates in Asia, 3.6% among 140 isolates in America, and 2.5% among 493 isolates in Africa. In Europe, the prevalence rate of VRSA was lower at 1.1% among 179 isolates. Healthcare providers must identify the specific strain of bacteria causing the infection to determine the appropriate treatment regimen. Several alternate approaches to antibiotics against multi-drug resistant S. aureus that have been investigated are i.e., nanoparticles, bacteriophages, bacteriocins, ionized water etc. Clinical trials should be conducted to evaluate efficacy and safety margin of these alternate approaches.

Keywords: Vancomycin-resistant S. aureus, Prevalence, Alternate approaches.

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1. INTRODUCTION

Staphylococcus aureus is a highly virulent gram-positive bacterium that belongs to the Micrococcaceae family. It possesses a cell wall composed of peptidoglycan, which consists of NAM (N-acetylmuramic) and NAG (N-acetylglucosamine) acid subunits (Leonard et al. 2008; Sutton et al. 2021). This bacterium also harbors surface proteins that have virulence factors. S. aureus produces toxins that cause endocarditis, pneumonia, osteomyelitis and bacteremia (Mitchell et al. 2005; Murray 2005; Roberts et al. 2005). The significant mortality and morbidity associated with these diseases make S. aureus a major public health concern. One of the challenges in treating S. aureus infections is the bacterium's ability to develop resistance against multiple antibiotics (Ortega et al. 2010). The development of resistance in S. aureus against antibiotics has been observed since 1942 and continues till today. The first methicillin-resistant strain isolates were identified in 1942, and penicillin-resistant strains in 1961 (McKee et al. 1943; Jevons 1961). Antibiotic-resistant strains pose a significant challenge for physicians in effectively treating staphylococcal infections. Healthcare providers must identify the specific strain of bacteria causing the infection to determine the appropriate treatment regimen (Oli et al. 2017). In this chapter, the general characteristics, pathogenicity, mechanism, and current status of resistance in S. aureus are discussed. Alternative therapeutic approaches to combat vancomycin-resistant Staphylococcus infections have also been explored, considering the limited effectiveness of traditional antibiotics against these strains.

2. STRUCTURE OF STAPHYLOCOCCUS AUREUS

2.1. CELL WALL

The cell wall of S. aureus is composed of approximately 50% peptidoglycan, a structural component of the bacterial cell wall. Peptidoglycan consists of polysaccharide subunits i.e., N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM). These subunits are connected by 1,4-β linkages, forming the backbone of peptidoglycan chains (Kim et al. 2015). Within the peptidoglycan structure, tetrapeptide bonds and a bridge of pentaglycin connected to NAM form cross-linkages. In addition to peptidoglycan, ribitol teichoic acids are significant components of the S. aureus cell wall. These teichoic acids are linked to peptidoglycan, providing additional structural stability. Lipoteichoic acid, another type of teichoic acid, is found in the cytoplasmic membrane of S. aureus. It is attached to the glycolipid terminus end, contributing to the overall architecture of the cell wall (Mistretta et al. 2019). Peptidoglycan in S. aureus also exhibits endotoxin-like activity that can trigger immune responses in the host organism. Upon recognition by the immune system, peptidoglycan can induce the release of cytokines, leading to the activation of macrophages and complement system with platelet aggregation (Kumar et al. 2020).

3. ENZYMES

Staphylococcus species, including S. aureus, produce several enzymes contributing to their pathogenicity. These enzymes, such as hyaluronidase, lipase, esterase, staphylokinase, deoxyribonuclease, phospholipase, and protease, can break down host tissue and facilitate the spread of bacterium to nearby tissues. Furthermore, enzymes are involved in antibiotic resistance employed by these bacteria. For instance, β-lactamase is an enzyme that can deactivate penicillin, rendering it ineffective. One notable enzyme produced by staphylococci is coagulase. Coagulase can convert fibrinogen, a soluble protein, into fibrin, the main component of blood clots. This enzymatic activity allows staphylococci to form protective barriers, shielding them from the host immune response and promoting bacterial survival. Additionally, coagulase acts as a prothrombin activator, initiating the blood clotting cascade (Quinn et al. 2011; Kobayashi et al. 2015).

4. CAPSULE

Microcapsules are produced by many species of staphylococci. Currently, 11 distinct types of microcapsular serotypes have been identified, which are based on polysaccharides. Among these serotypes, types 5 and 8 are particularly associated with human infections. Type 5 microcapsules are commonly isolated from methicillin-resistant S. aureus (MRSA) strains, indicating their prevalence in these antibiotic-resistant bacteria. Microcapsules are protective layers composed of polysaccharides that surround the bacterial cells. They serve as a defense mechanism against the host immune system, shielding the bacteria from phagocytosis and other immune responses. The presence of microcapsules contributes to the virulence of staphylococci by enhancing their ability to establish and persist in host tissues (O'Riordan et al. 2004).

5. TOXINS

Staphylococcus species are known to produce various toxins that can be categorized based on their mechanisms of action. One category is cytotoxins, specifically a 33-kilo Dalton protein called alpha-toxin. These cytotoxins create pores in mammalian cells and induce proinflammatory changes, leading to cell damage (Otto 2014). Another class of toxins produced by Staphylococcus is pyrogenic toxin super-antigens. These toxins bind to class II proteins of the major histocompatibility complex (MHC) and trigger the release of cytokines, resulting in extensive T-cell proliferation. This immune response can cause harmful effects on the body. Enterotoxins are another group of toxins produced by Staphylococcus. They are responsible for food poisoning. The ingestion of contaminated food or exposure to these toxins can lead to symptoms such as vomiting, diarrhoea, and abdominal pain. Another category of toxins is toxic shock syndrome toxins (TSST). They are responsible for excessive lymphokine production leading to tissue damage. Exfoliative toxins can cause skin erythema (redness) and separation. Examples of exfoliative toxins produced by Staphylococcus include epidermolytic toxins A and B, which affect the skin integrity and can result in the detachment of the upper layers of the skin (Ortega et al. 2010; Pinchuk et al. 2010).

6. SURFACE PROTEINS

Surface proteins, also known as cell wall-anchored (CWA) proteins, play a crucial role in the virulence of S. aureus. Among various staphylococcal spp., S. aureus is known to express 24 different CWA proteins. These proteins are located on the bacterial surface and are covalently bonded to the peptidoglycan layer of the cell wall. The presence of these proteins contributes to both the pathogenic and commensal nature of S. aureus (Lacey et al. 2016). The bacterial growth conditions influence the expression of cell wall-anchored proteins. For instance, most of these proteins are expressed when the bacterium is grown under iron-deficient conditions, although some may also be expressed during the exponential or stationary growth phases. CWA proteins can be classified into four groups based on their structural and functional characteristics. The MSCRAMM (microbial surface component recognizing adhesive matrix molecule) is the most significant group. MSCRAMM proteins play a key role in mediating bacterial adhesion to host tissues. 90% of S. aureus contains protein A (42KD) in their cell wall. Protein A binds with the "Fc and Fab" regions of IgG and B-lymphocytes and inhibits direct phagocytosis and opsonization, respectively (Foster et al. 2014; Speziale et al. 2014; Arora et al. 2016; Hinton-Sheley and Phoebe 2019).

7. GENOME

Staphylococcus bacteria have a circular chromosome in their genome, consisting of approximately 2800 base pairs (bp). In addition to the chromosome, they can also possess plasmids, transposons, and

prophages. These genetic elements are involved in the transfer of many genes, including those responsible for antibiotic resistance. The genes associated with antibiotic resistance can be located on the extrachromosomal elements and the chromosomes. The inherent genetic material of bacteria can carry resistance genes and acquire additional genetic elements via horizontal gene transfer. The extrachromosomal elements, such as plasmids, transposons, and prophages, act as vehicles to transfer genes between various species of Gram-positive bacteria and staphylococcal bacteria. This horizontal gene transfer allows for the spread of genetic traits, including antibiotic resistance, among bacterial populations (Kumar et al. 2020).

8. VANCOMYCIN: BACKGROUND AND IMPORTANCE IN ANTIBACTERIAL TREATMENT

In 1957 E.C Kornfield isolated Vancomycin, a tricyclic glycopeptide antibiotic, from a fungus, Streptomyces orientalis, found in the forests of Borneo. Initially known as "compound 05865" vancomycin exhibited activity against anaerobic and gram-positive bacteria. It is a bactericidal agent and inhibits peptidoglycan's polymerization in the cell wall of the bacterium. This mechanism makes vancomycin effective against many pathogens. It is also effective in combating secondary infections after surgery. FDA has approved Vancomycin against many bacteria, including Pseudomembranous colitis Clostridium difficile, Enterococcal, Staphylococcus enterocolitis, Streptococcal, and Staphylococcal spp. (Aqib et al. 2022).

9. VANCOMYCIN MODE OF ACTION

Vancomycin is primarily effective against Gram-positive bacteria, including Clostridia, Corynebacterium, Staphylococci, Pneumococci, Enterococci, Streptococci, and Listeria. It is commonly employed in treating infections caused by methicillin-resistant S. aureus (MRSA) and in patients allergic to semisynthetic penicillin or cephalosporins (Rubinstein et al. 2014). The mechanism of action of vancomycin involves inhibiting the proper synthesis of the cell wall. There is a structure in bacterial cell wall structure that shields them from being swollen and bursting due to the high osmolarity inside the cell. The cell wall, particularly the peptidoglycan component, undergoes expansion during bacterial growth. This expansion relies on incorporating a lipid II precursor molecule into the developing peptidoglycan chain. Enzymes called penicillin-binding proteins (PBPs) facilitate this process. Vancomycin interacts with D-Ala–D-Ala moieties via hydrogen bonds. When vancomycin binds to the lipid II molecule, it induces a change that hinders the formation of the peptidoglycan chain. This inhibition prevents the subsequent transpeptidation process, which is vital for properly constructing the bacterial cell wall (Hu et al. 2016). By disrupting cell wall synthesis, vancomycin effectively inhibits bacterial growth and division, leading to the death or suppression of susceptible bacteria. As a result, the bacterial cell wall cannot be properly constructed, leading to the decomposition of the cell wall and, ultimately, bacterial lysis, as shown in Fig. 1. Vancomycin's complex structure restricts its ability to penetrate the membrane of the Gram-negative bacteria. Consequently, its bactericidal effect against Gram-negative bacteria is limited (Acharya et al. 2022).

10. DEVELOPMENT OF VANCOMYCIN RESISTANCE IN S. AUREUS

Vancomycin became an important therapeutic option for treating serious infections caused by methicillin-resistant S. aureus (MRSA) in the late 1980s. However, around the same time, a new problem emerged in Europe with the identification of VRE (vancomycin-resistant enterococci). In VRE, vancomycin resistance was primarily intervened by transposons, often present on plasmids that

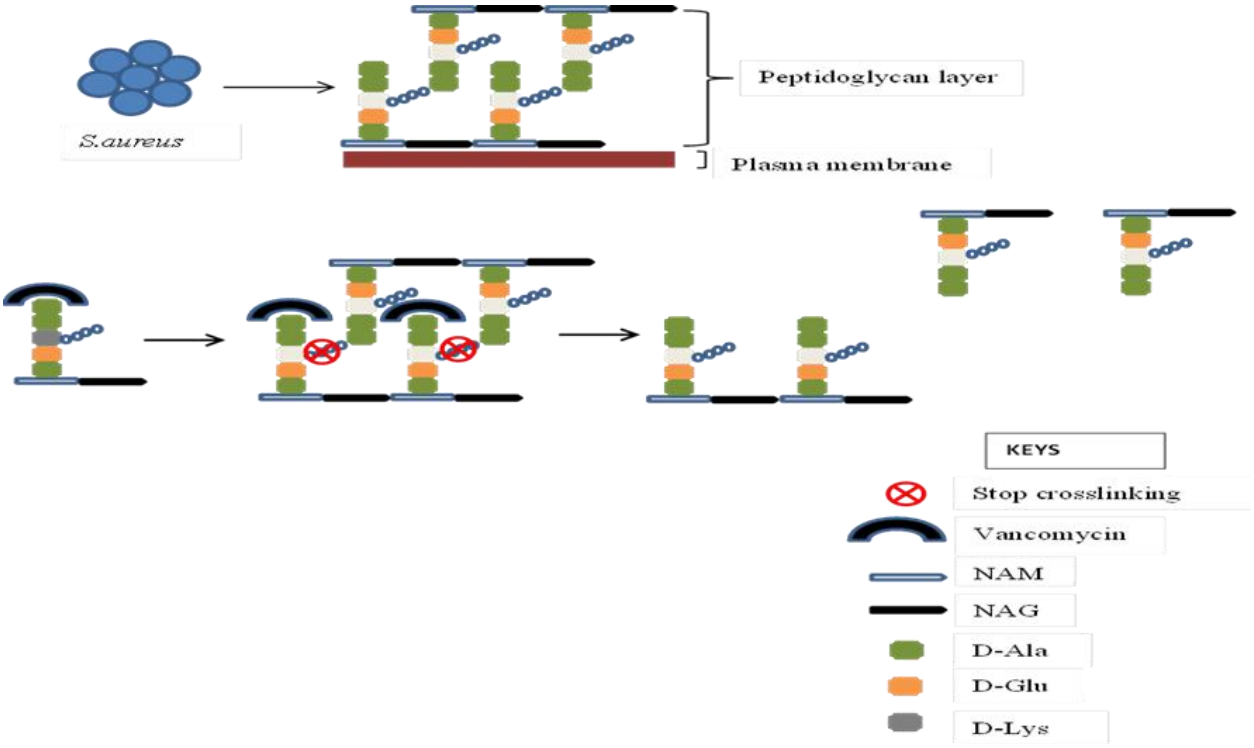

Fig. 1: Mode of action of Vancomycin

enhanced concerns about the potential dissemination of vancomycin resistance to other medically significant microorganisms, particularly S. aureus, which is a major cause of infections. These concerns were validated when the vancomycin resistance determinant was successfully transferred from Enterococcus faecalis to S.aureus in mice co-infected with both bacteria, which confirmed the risk of spreading vancomycin resistance to previously susceptible microorganisms. The first documented case of VRSA occurred in Michigan, USA, in 2002. Subsequently, another VRSA strain was isolated in Pennsylvania, USA, in the same year. Until now, 52 VRSA strains with vancomycin resistance genes have been reported, with 14 in the USA, 11 in Iran, 16 in India, 1 in Brazil, 9 in Pakistan and 1 in Portugal. The emergence of VRSA strains further underscored the urgent need for effective strategies to combat the development of vancomycin resistance and prevent its dissemination (Cong et al. 2020).

11. THE MECHANISM OF VANCOMYCIN RESISTANCE

Bacterial resistance to vancomycin primarily involves van gene clusters, categorized into different types based on DNA sequences. These clusters encode ligase van gene homologs that produce enzymes forming d-alanyl-d-lactate (d-Ala-d-Lac). At least 11 known van gene clusters: VanA, VanB, VanD, VanF, VanI, VanM, VanC, VanE, VanG, VanL, and VanN, play a critical role in vancomycin resistance. Genes like vanA, vanB, vanD, vanF, vanI, and vanM, encoding d-Ala:d-Lac ligases, lead to high-level resistance with MICs exceeding 256 mg/ml. Conversely, genes encoding d-Ala:d-Ser ligases (vanC, vanE, vanG, vanL, and vanN) cause low-level resistance, with MICs ranging from 8 to 16 mg/ml. Enterococcus species are the most common carriers of acquired vancomycin resistance, with the vanA gene cluster specifically linked to vancomycin-resistant S. aureus (VRSA) strains. This cluster contains five crucial proteins i.e., VanS, VanR, VanH, VanA, and VanX, all contributing to vancomycin resistance. The vanA

gene cluster resides within a transposon called Tn1546. VanS and VanR form a two-component system regulating the cluster genes in the presence of vancomycin. VanH, VanA, and VanX modify precursor molecules from D-Ala-D-Ala to the resistant form, D-Ala-D-Lac. Vancomycin's target is the terminal d-Ala-D-Ala moieties of lipid II precursor. However, modification to d-Ala-D-Lac greatly reduces vancomycin's affinity, leading to a nearly 1000-fold decrease in binding affinity and loss of bactericidal effect on strains with modified peptidoglycan precursors (Cong et al. 2020). The brief mechanism of vancomycin resistance is shown in Fig. 2.

12. ZOONOSIS AND HUMANOSIS

The prevalence of MRSA has expanded beyond healthcare settings and is now a concern in the community, particularly in the United States. Community-associated MRSA (CA-MRSA) strains are increasingly replacing the older HA-MRSA (hospital-associated MRSA) strains. MRSA strains in companion animals differ greatly from those in livestock and animals raised for meat production. This distinction is likely because companion animals primarily acquire MRSA from their human owners. In traditional animal husbandry practices, there was less close contact between animals, whereas modern intensive farming methods increase the chances of transmission of MRSA to animals. The emergence of new strains of MRSA, like ST398 in pigs, poses a remarkable zoonotic risk as farm workers may become infected with the new strains. MRSA infections have been reported in various species, including dogs, cats, sheep, chickens, horses, rabbits, seals, and even in one turtle, bat, guinea pig, and chinchilla. Historically, MRSA infections in companion animals were caused by similar strains as in human healthcare settings. When HA-MRSA strains were identified in dogs, it was assumed that transmission had occurred from humans to animals, referred to as "humanosis." (Morgan 2008). Another study reported that VRSA strains isolated from the meat of camel and workers were homologous to each other (Al-Amery et al. 2019).

13. CURRENT STATUS

13.1. VANCOMYCIN RESISTANCE IN S. AUREUS: A SOUTH ASIAN PERSPECTIVE

Following the primary cases of vancomycin-resistant S. aureus (VRSA) in the United States, several other countries have also stated the emergence of vancomycin resistance in clinical isolates of methicillin-resistant S. aureus (MRSA). A graphical picture of the prevalence of VRSA in Pakistan is shown in Fig. 3 (Ghias et al. 2016; Azhar et al. 2017; Hanif et al. 2019; Riaz et al. 2021; Anwaar et al. 2023).
ANSORP (Asian Network for Surveillance of Resistant Pathogens) conducted a study in 2004-2006 and reported that S.aureus with a nosocomial origin is 86.5% prevalent in Sri Lanka (Song et al. 2011). Banerjee et al. (2012) first reported the isolation of the vanA gene in the VISA strain in India. This study enhanced the concerns about the spread of this strain in the hospital staff as patients with VISA strains were asymptomatic. Moses et al. (2020) reported the 6.08% and 46.08% prevalence of VRSA and VISA, respectively, in clinical isolates. Mohanty et al. (2019) conducted a study in Eastern India, isolating 13 hVISA and 18 VISA strains. These remarkable findings show the presence of VISA and VRSA in India and emphasize the urgent control measures to prevent their spread. Chaudhary et al. (2010) conducted a cross-sectional study focusing on dacryocystitis in Nepal and reported an 81.48% prevalence of VRSA strains. Another study was conducted at Allied Sciences and Annapurna Neurological Institute in Nepal and reported the prevalence of VRSA to be 11.11% (Maharjan et al. 2021). However, there is a scarcity of the data regarding research focusing the VISA and VRSA in Nepal. A study conducted in Bangladesh revealed the prevalence of VRSA to be 13.3% in samples of wounds collected from patients in a hospital. They identified the presence of the vanB gene in isolates (Islam et al. 2015).

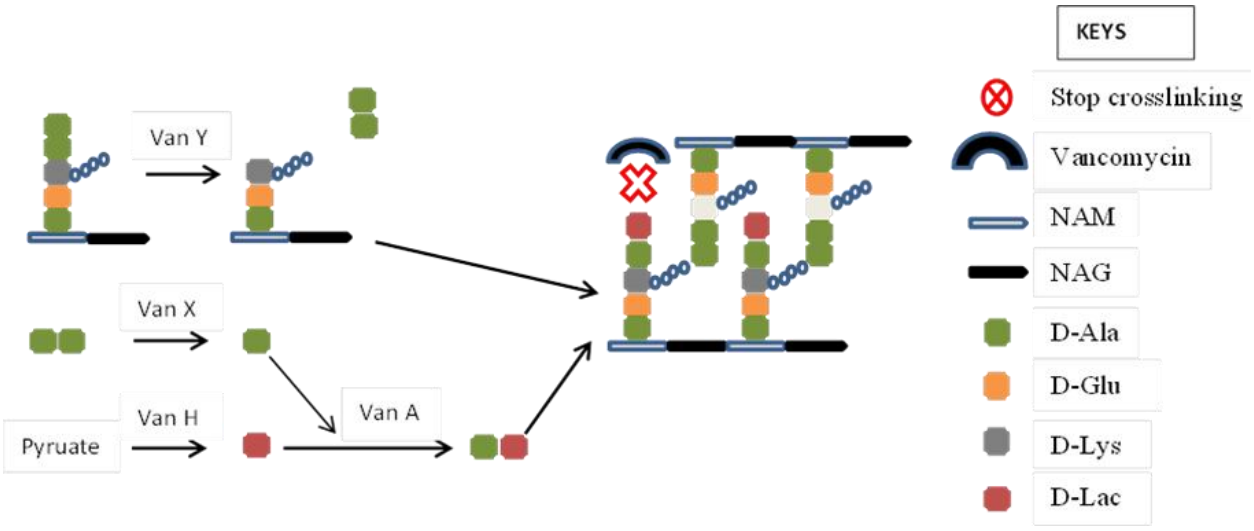

Fig. 2: Mechanism of resistance

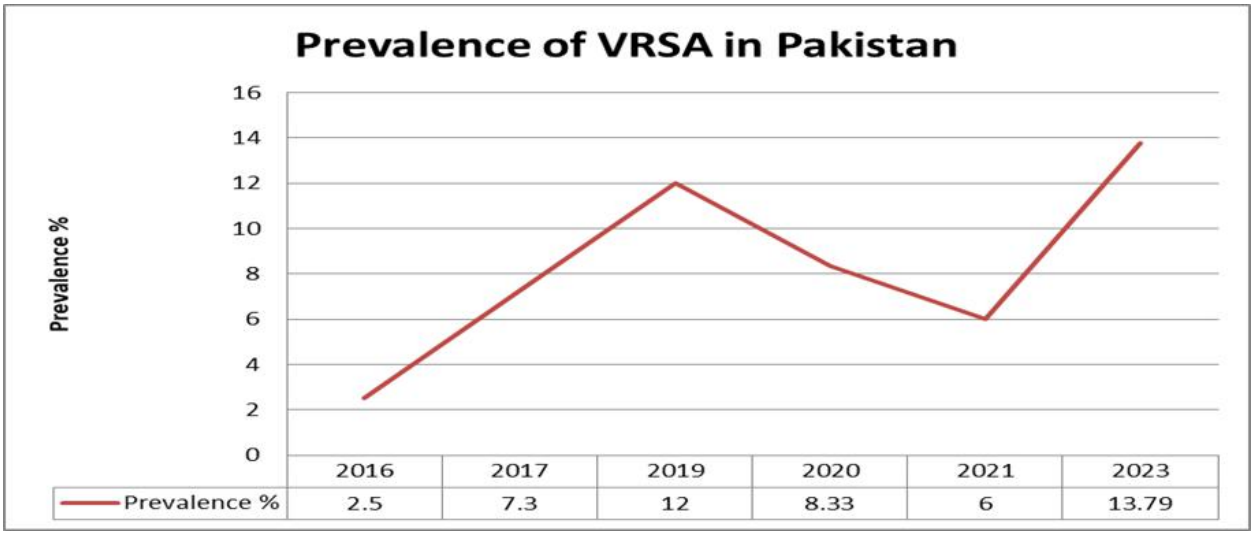

Fig. 3: Prevalence of VRSA in Pakistan

14. GLOBAL PREVALENCE

The prevalence rates of antibiotic-resistant strains of S. aureus vary across different regions. According to available statistics, vancomycin-resistant S. aureus (VRSA) has been reported in Asia, America, and Africa, while no reports have been documented in Oceania. The prevalence rates of VRSA were found to be 1.2% (95% CI 0.7–1.8) among 5043 isolates in Asia, 3.6% (95% CI 0.5–6.6) among 140 isolates in America, and 2.5% (95% CI 0.1–4.8) among 493 isolates in Africa. In Europe, the prevalence rate of VRSA was lower at 1.1% (95% CI 0.0–2.7) among 179 isolates. Regarding vancomycin-intermediate S. aureus (VISA), the prevalence rates were observed to be 2.1% (95% CI 1.6–2.6) among 13,449 isolates in Asia, 1.8% (95% CI 0.8–2.8) among 2198 isolates in Europe, 1.0% (95% CI 0.5–1.4) among 5040 isolates in America, 1.8% (95% CI 0.1–3.4) among 1072 isolates in Africa, and 0.6% (95% CI 0.0–1.3) among 518 isolates in Oceania as shown in Table 1. (Shariati et al. 2020).

Table 1: Continental Prevalence (%) of VRSA and VISA

Continent	Total Isolates	Resistant strains	Country	Prevalence of isolate (%)
			Jordan	4.0
			Bangladesh	4.5
	5043	VRSA	Pakistan	3.3
			Iran	1.3
			India	1.6
			Korea	0.7
			India	4.6
Asia			China	0.5
			Pakistan	5.6
			Iran	3.6
	13,449	VISA	Japan	0.6
			Taiwan	1.9
			Singapore	12.5
			Saudi Arabia	18.0
			Thailand	9.7
	140	VRSA	Brazil	3.6
America	5040	VISA	Brazil	4.1
			USA	0.9
			Nigeria	1.4
	493	VRSA	Algeria	1.4
Africa			Egypt	5.5
			Kenya	4.2
	1072	VISA	Nigeria	15.1
			Algeria	0.6
	179	VRSA	Italy	1.1
			Italy	1.4
Europe			Turkey	2.7
	2198	VISA	Germany	0.7
			France	2.2
			Belgium	2.5
Oceania	518	VISA	Australia	0.7

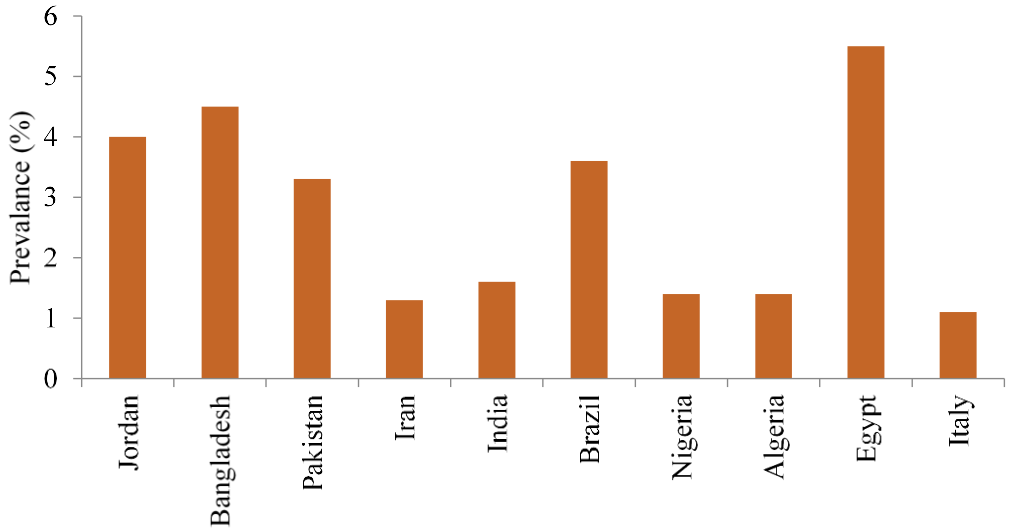

Fig. 4: Prevalence of VRSA in different countries

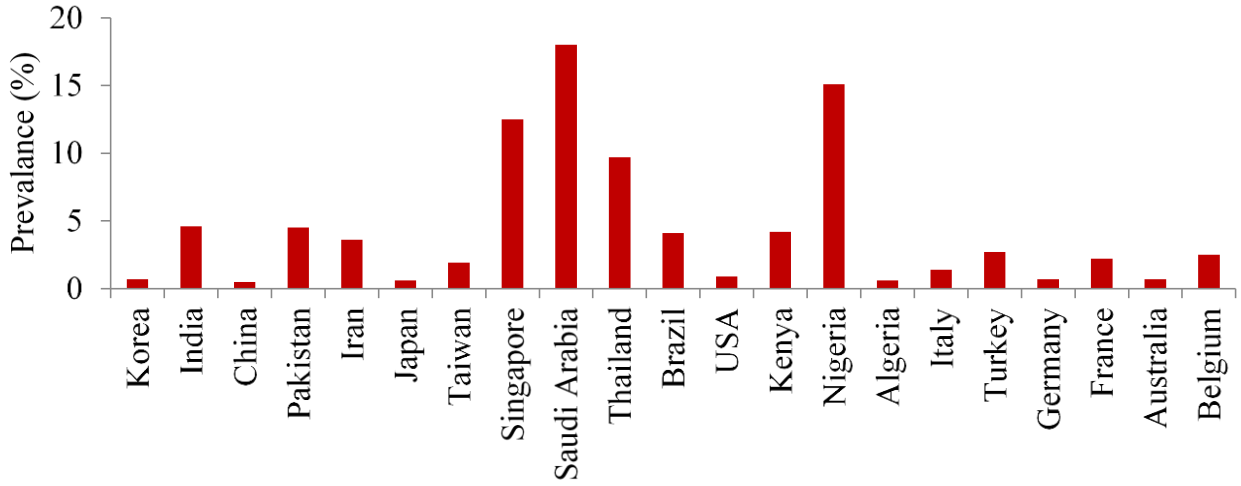

Fig. 5: Prevalence of VISA in different countries

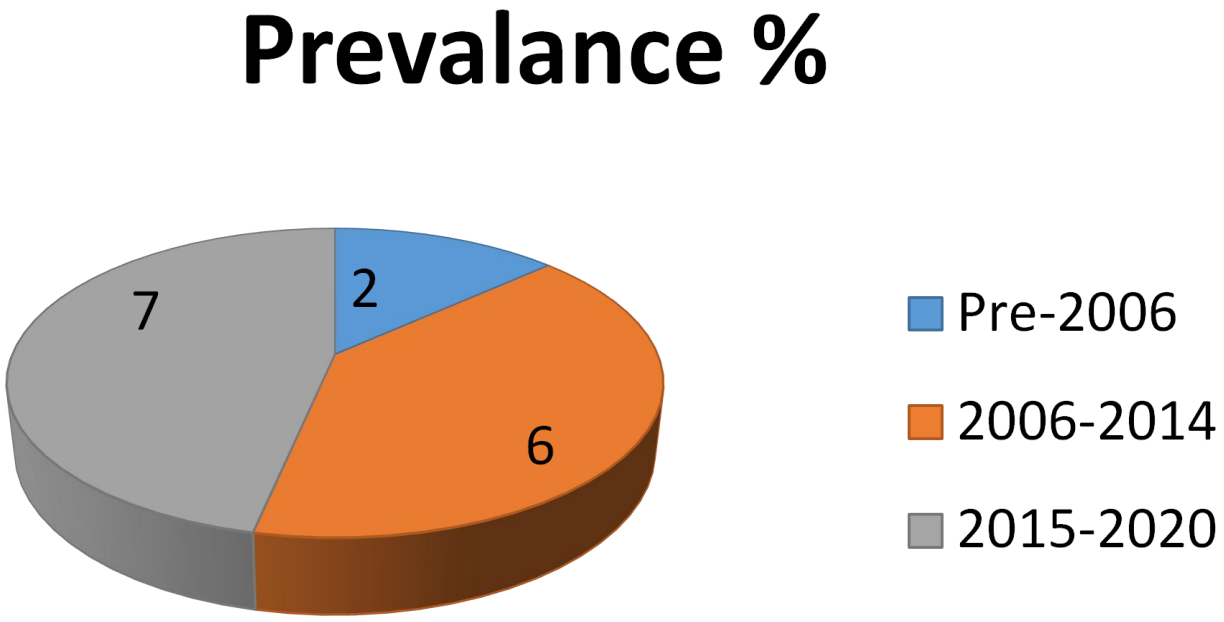

Fig. 6: Prevalence analysis of VRSA in various time periods.

These findings highlight the regional variations in the prevalence rates of VRSA and VISA strains, emphasizing the importance of ongoing surveillance and monitoring of antibiotic-resistant S. aureus strains to inform appropriate prevention and treatment strategies. Fig. 4 and 5 highlights the occurrence of VRSA and VISA across different regions of globe.

15. PREVALENCE ANALYSIS OVER A PERIOD OF TIME

A subgroup analysis was conducted for three periods: pre-2006, 2006-2014 and 2015-2020. The prevalence of VRSA was assessed by examining 11,956 strains of S. aureus.

15.1. PRE-2006 PERIOD

Prior to 2006, the prevalence of VRSA was observed to be 2% (95% CI 0-4) among 466 strains analyzed (Fig. 6). This finding suggests a relatively low occurrence of VRSA during this period.

15.2. 2006-2014 PERIOD

Between 2006 and 2014, the prevalence of VRSA showed a notable increase. Among 6,692 strains examined, VRSA has detected in 6% (95% CI 3-9) cases representing a threefold rise compared to the pre-2006 period, indicating a concerning upward trend (Fig. 6).

15.3. 2015-2020 PERIOD

The most recent period, spanning from 2015 to 2020, has exhibited a further increase in the prevalence of VRSA. Among 5,798 strains analyzed, VRSA was found in 7% (95% CI 4-11) of cases (Fig. 6). Although the rise in prevalence was smaller compared to the previous period, it still signifies a significant progression (Wu et al. 2021).

16. FUTURE PROSPECTIVE

The emergence of antibiotic-resistant S. aureus bacteria, including methicillin-resistant S. aureus (MRSA), has led to exploring alternative strategies to combat these infections. Several approaches that have been investigated are;

Nanoparticles have garnered attention due to their unique physicochemical properties that allow them to inhibit bacterial growth and disrupt biofilm formation. These tiny particles can deliver antimicrobial agents directly to the bacterial cells, making them an attractive option for combating drug-resistant bacteria like S. aureus (Mahal et al. 2023). Bacteriophages, viruses that specifically target bacteria, have shown promise in selectively killing S. aureus strains. Bacteriophage therapy involves using these viruses to infect and destroy bacterial cells, offering a potential alternative to traditional antibiotics (Mohammadian et al. 2022). Bacteriocins, antimicrobial peptides produced by certain bacteria, have exhibited activity against S. aureus. These natural compounds can specifically target and kill the bacteria, making them a potential alternative or adjunct to antibiotics (Xiang et al. 2022). Quorum quenching is a strategy that disrupts bacterial communication systems, which regulate the expression of virulence factors in S. aureus. By interfering with this communication, quorum quenching can impede the ability of the bacteria to cause infections and become resistant (Kaur et al. 2021). Nano needles are microscopic structures that can physically disrupt bacterial membranes, leading to cell death. These tiny needles can deliver antimicrobial agents or physically puncture the bacterial cells, potentially combating antibiotic-resistant S. aureus (Ray et al. 2020). Passive immunization using IgY antibodies or hyperimmune sera has been explored as a potential therapy against S. aureus infections. These antibodies are derived from eggs or animals immunized with S. aureus antigens and can temporarily protect against the bacteria (Tobias et al. 2012). The development of vaccines against S. aureus aims to stimulate an active immune response, providing long-term protection against infection. Various vaccine candidates, including those targeting specific antigens or using novel approaches, are being investigated to prevent S. aureus infections and combat antibiotic resistance (Chand et al. 2023). Certain herbs and natural compounds have demonstrated antimicrobial activity against S. aureus. These natural products, such as essential oils or plant extracts, contain bioactive compounds that can inhibit the growth of drug-

resistant bacteria (Gufe et al. 2023). Phototherapy involves using specific wavelengths of light to kill bacteria. Certain wavelengths, such as blue or ultraviolet light, can have antimicrobial effects and have been investigated as a potential treatment option against S. aureus infections (Woźniak et al. 2022).
Ionized water, produced by ionizing regular tap water, has been explored for its potential antimicrobial properties. Studies have shown that ionized water can exhibit bactericidal effects against S. aureus and may have potential applications in disinfection and wound care (Rahman et al. 2021). The discovery and development of novel antibiotics with activity against VRSA are ongoing. Researchers are exploring alternative treatment options to overcome VRSA resistance mechanisms. Investigating the effectiveness of combination therapy, where multiple antibiotics are used in combination, may help overcome VRSA resistance and improve treatment outcomes (Worthington et al. 2013).
It is important to note that while these alternative approaches hold promise, further research and clinical trials are necessary to fully evaluate their effectiveness, safety, and potential integration into clinical practice. Additionally, a comprehensive approach involving a combination of strategies may be needed to combat antibiotic-resistant S. aureus infections effectively.

17. CONCLUSION

Antibiotic-resistant strains pose a significant challenge for physicians in effectively treating staphylococcal infections. According to available statistics, vancomycin-resistant S. aureus (VRSA) has been reported in Asia, America, and Africa, while no reports have been documented in Oceania. The prevalence rates of VRSA were found to be 1.2% among 5043 isolates in Asia, 3.6% among 140 isolates in America, and 2.5% among 493 isolates in Africa. In Europe, the prevalence rate of VRSA was lower at 1.1% among 179 isolates. Healthcare providers must identify the specific strain of bacteria causing the infection to determine the appropriate treatment regimen. Several alternate approaches to antibiotics against multi-drug resistant S.aureus that have been investigated are i.e., nanoparticles, bacteriophages, bacteriocins, ionized water etc. Clinical trials should be conducted to evaluate efficacy and safety margin of these alternate approaches.

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Peeping into the Post Pandemic (COVID-19) Era: Changes and Modifications

26

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ABSTRACT

The COVID-19 pandemic has brought about significant changes in many areas of society, leading to a resilient, adaptable, and innovative new landscape. A noticeable change is the adjustment of how work is done, with remote and hybrid models becoming lasting norms in the workforce. Due to the pandemic, businesses hastened their digital transformation, incorporating technology as a fundamental element for communication, teamwork, and operational efficiency. Due to ongoing health and safety concerns, there is a heightened focus on implementing protective measures in both public and work environments, which reflects a long-term societal shift. As a result of the pandemic, there has been a significant increase in online commerce, leading traditional businesses to adapt and move towards digital platforms. The way people travel is changing, with more emphasis on traveling within their own country and region, and a continued preference for contactless services. The field of education is experiencing a significant shift, utilizing online and blended learning approaches in conjunction with cutting-edge educational technologies. Global supply chains are undergoing a significant change in focus, prioritizing resilience and diversification to address vulnerabilities that were highlighted during the pandemic. Healthcare systems are constantly being improved, highlighting the importance of being ready for future health emergencies. The current cultural mentality after the pandemic is fostering a greater awareness of environmental issues, causing sustainable practices to become a top priority. At the same time, there is a growing recognition of the importance of mental health, leading to a societal dedication to overall well-being. The period following the pandemic is seen as a time for significant change and societal development, where flexible strategies and creative ideas will mold a stronger and more resilient future.

Keyword: Resilience; Digital Transformation; E-commerce; Health and Safety; Sustainability; Mental Health

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1. INTRODUCTION

The COVID-19 pandemic has been a defining moment in our modern history, affecting virtually every aspect of life as we know it. The pandemic has led to unprecedented changes in how we work, socialize, and interact with each other and has highlighted the vulnerabilities and inequalities in our societies. As we emerge from the pandemic, we must look ahead to the era after COVID-19 and explore the potential long-term impacts on our economies, organizations and political structures (Harris and Jones 2020).

1.1. COVID-19 PANDEMIC AND ITS IMPACT ON THE WORLD

The COVID-19 pandemic is a global health crisis caused by the SARS-CoV-2 virus that emerged in Wuhan, China in December 2019. The virus quickly spread to other countries and was declared a pandemic by the World Health Organization (WHO) in March 2020 (El Zowalaty and Jarhult 2020). The pandemic has profoundly impacted the world, with over 400 million confirmed cases and over 6 million deaths as of March 2023. It has overwhelmed healthcare systems, disrupted economies, and forced countries to implement unprecedented measures such as lockdowns, travel restrictions, and social distancing guidelines (Panneer et al. 2022).

As the world grapples with the COVID-19 pandemic, it is important to look ahead to the era after the pandemic. While the pandemic has profoundly impacted different sectors of society, it has also presented opportunities for positive change and transformation (Leach et al. 2021). The pandemic has highlighted the importance of resilience and preparedness in global health crises. This means investing in healthcare systems, strengthening supply chains, and developing early warning systems to detect and respond to future pandemics. We can learn from the pandemic's lessons by looking ahead and developing strategies to better prepare for future crises (Megahed and Ghoneim 2021).

2. ECONOMIC CHANGES

The COVID-19 pandemic has had a significant economic impact on various sectors, with some being hit harder than others (Ceylan et al. 2020).

2.1. TOURISM AND HOSPITALITY INDUSTRY

The pandemic has caused a significant decline in travel and tourism, leading to the closure of hotels, restaurants, and other tourism-related businesses. This has resulted in widespread job losses and economic hardship, especially in countries that rely heavily on tourism (Skare et al. 2021).

2.2. SMALL BUSINESSES

The pandemic has hit small businesses particularly hard, with many struggling to stay afloat due to reduced demand and supply chain disruptions. Many have had to shut down permanently, resulting in significant job losses and economic disruption (Engidaw 2022).

2.3. HEALTHCARE INDUSTRY

The pandemic has put immense pressure on healthcare systems, with hospitals and clinics overwhelmed by COVID-19 patients. This has significantly increased healthcare spending and priorities shifting toward pandemic response (Farsalinos et al. 2021).

2.4. TECHNOLOGY AND E-COMMERCE

The pandemic has accelerated the shift towards online shopping and remote work, leading to a surge in demand for technology and e-commerce services. Companies like Amazon, Microsoft, and Zoom have seen significant growth in revenue and profits (Amankwah et al. 2021).

2.5. MANUFACTURING AND SUPPLY CHAIN

The pandemic has exposed vulnerabilities in global supply chains, with disruptions in transportation and logistics causing delays and shortages of essential goods. This has increased demand for local manufacturing and supply chain resilience (Sudan and Taggar 2021).

2.6. CHANGES IN WORK CULTURE AND THE RISE OF REMOTE WORK

The COVID-19 pandemic has caused significant changes in work culture, with remote work becoming more widespread. As lockdowns and social distancing measures were implemented, many businesses had to adapt quickly to enable employees to work from home (Waizenegger et al. 2020). Despite these challenges, remote work is likely to continue to be a significant part of work culture in the era after the pandemic. Many businesses have seen the benefits of remote work in increased productivity and reduced overhead costs, and employees have become more accustomed to working from home. This shift towards remote work has also opened up new opportunities for businesses, such as access to a broader pool of talent and increased flexibility regarding where and when work is done (Toquero 2020).

2.7. EXAMINATION OF THE LONG-TERM EFFECTS ON INDUSTRIES SUCH AS TRAVEL, HOSPITALITY, AND ENTERTAINMENT

The COVID-19 pandemic has significantly impacted industries such as travel, hospitality, and entertainment, and the effects were likely felt in the long term (Kenny and Dutt 2022).

2.8. TRAVEL INDUSTRY

The travel industry has been severely affected by the pandemic, with international travel restrictions and border closures causing a significant decline in demand. While the industry is likely to recover somewhat once travel restrictions are lifted, there may be lasting effects, such as a shift towards domestic travel and a preference for alternative transportation such as road trips. Additionally, concerns around health and safety may lead to increased demand for travel insurance and other forms of protection (Bulin and Tenie 2020).

2.9. HOSPITALITY INDUSTRY

The pandemic has also hit the hospitality industry hard, with many hotels, restaurants, and other businesses forced to close temporarily or permanently. While some companies may bounce back once restrictions are lifted, others, notably smaller independent companies, may struggle to recover. Additionally, concerns around health and safety may lead to changes in how hospitality businesses operate, such as increased use of contactless technology and other measures to minimize physical contact (Smart et al. 2021).

2.10. ENTERTAINMENT INDUSTRY

The entertainment industry, including movie theaters, concert venues, and sports arenas, has also been affected by the pandemic, with many events and performances canceled or postponed. While the industry is likely to recover somewhat once restrictions are lifted, there may be lasting effects, such as a shift towards virtual events and online streaming. Additionally, concerns around health and safety may lead to changes in how events and performances are organized, such as reduced capacity and increased use of technology to enable social distancing (Nhamo et al. 2020).

2.11. POSSIBLE ECONOMIC RECOVERY STRATEGIES FOR DIFFERENT COUNTRIES

The COVID-19 pandemic has significantly impacted economies worldwide. Many countries are experiencing declines in GDP and rising unemployment rates (Kaye 2021).

2.12. FISCAL STIMULUS

One possible strategy for economic recovery is to implement fiscal stimulus measures such as tax cuts, infrastructure spending, and direct cash transfers to individuals and businesses. This can help to boost demand and encourage investment, leading to economic growth (Loayza and Pennings 2020).

2.13. MONETARY POLICY

Another strategy is implementing monetary policy measures such as interest rate cuts and quantitative easing to stimulate the economy. This can help lower borrowing costs and increase credit availability, encouraging investment and consumption (Casula et al. 2021).

2.14. INVESTMENT IN EDUCATION AND TRAINING

Investing in education and training can help to build a skilled workforce, which can increase productivity and competitiveness in the long term. This can include programs to retrain workers who have lost their jobs due to the pandemic (Casula et al. 2021).

2.15. SUPPORT FOR SMALL BUSINESSES

Small businesses have been particularly hard hit by the pandemic, and providing support such as grants, loans, and tax breaks can help to keep them afloat and stimulate economic growth (Casula et al. 2021).

2.16. GREEN RECOVERY

Many countries are considering a "green recovery" strategy involving investing in renewable energy, energy efficiency, and other environmentally friendly initiatives. This can create jobs and stimulate economic growth while helping report the global climate crisis (Karakosta et al. 2021).

2.17. INTERNATIONAL COOPERATION

Finally, international cooperation can be an effective strategy for economic recovery, particularly in the context of global supply chains and trade. This can involve reducing trade barriers, sharing information and best practices, and collaborating on research and development (Casula et al. 2021).

3. SOCIAL CHANGES

The COVID-19 pandemic has led to significant changes in social norms and behavior, as people worldwide have had to adapt to new ways of living and interacting with each other (Amankwah et al. 2021).

3.1. FACE-MASK

Wearing face masks in public has become a common practice in many parts of the world, as people seek to reduce the spread of the virus. While this may have initially been seen as unusual or uncomfortable, it has become an accepted social norm in many places (Martinelli et al. 2021).

3.2. SOCIAL DISTANCING

Social distancing measures such as avoiding crowds and keeping at least six feet from others have also become part of the new normal. This has led to changes in how people interact, with many social activities moving online or to outdoor spaces (Kamga and Eickemeyer 2021).

3.3. REMOTE WORK

The pandemic has significantly increased remote work, as many employers have shifted to online platforms to keep their businesses running. This has led to changes in work-life balance and has made remote work a more acceptable and widespread practice (Soto-Acosta 2020).

3.4. HEALTH AND HYGIENE

The pandemic has heightened awareness around health and hygiene, with people taking extra precautions such as washing their hands more frequently and avoiding touching their face. This increased focus on health and hygiene will likely persist even after the pandemic (Finger et al. 2021).

3.5. MENTAL HEALTH

The pandemic has also significantly affected mental health, with many people experiencing increased stress, anxiety, and depression. This has led to greater awareness of the importance of mental health and a greater willingness to seek help and support (Roy et al. 2020).

3.6. EXAMINATION OF THE EFFECTS ON MENTAL HEALTH AND WELLBEING

The COVID-19 pandemic has significantly impacted mental health and wellbeing, with people worldwide experiencing increased stress, anxiety, and depression (Varma et al. 2021).

3.7. ISOLATION AND LONELINESS

Social distancing measures and lockdowns have led to increased isolation and loneliness, particularly for vulnerable populations such as the elderly, those living alone, and people with pre-existing mental health conditions. This can lead to feelings of sadness, anxiety, and depression (Kasar and Karaman 2021).

3.8. ECONOMIC STRESS

The pandemic has led to widespread job losses and economic uncertainty, contributing to stress, anxiety, and depression. Financial pressures can also lead to relationship problems and difficulties in meeting basic needs such as housing and food (Friedline et al. 2021).

3.9. FEAR AND UNCERTAINTY

The pandemic has created a sense of fear and uncertainty, with many people worried about their health and the health of their loved ones and the broader social and economic impacts of the pandemic. This can increase stress and anxiety (Simon et al. 2020).

3.10. DISRUPTION TO ROUTINE

The pandemic has disrupted many people's daily routines, leading to feelings of disorientation and loss of control. This can contribute to stress, anxiety, and depression (Lau et al. 2022).

3.11. STIGMA AND DISCRIMINATION

The pandemic has also led to stigmatization and discrimination, particularly towards specific groups such as healthcare workers, people with COVID-19, and people from ethnic or racial backgrounds. This can lead to feelings of shame, fear, and anxiety (Miconi et al. 2021).

3.12. POSSIBLE SOLUTIONS TO ADDRESS MENTAL HEALTH CHALLENGES IN THE POST-PANDEMIC ERA

There are several potential solutions to address the mental health challenges that have arisen during the COVID-19 pandemic and those that are likely to persist in the era after the pandemic (Cowie and Myers 2021).

3.13. INCREASE ACCESS TO MENTAL HEALTH SERVICES

One of the most important solutions is to increase access to mental health services, including counseling, therapy, and medication. This can be done through initiatives such as expanded insurance coverage, telemedicine services, and community-based mental health clinics (Roy et al. 2020).

3.14. PROMOTE SELF-CARE AND RESILIENCE

Promoting self-care and resilience is also essential, helping individuals develop coping strategies to manage stress and anxiety. This can include mindfulness, meditation, exercise, and healthy eating (Hossain and Clatty 2021).

3.15. ADDRESS SOCIAL AND ECONOMIC FACTORS

The pandemic has highlighted the importance of addressing social and economic factors that impact mental health, such as poverty, unemployment, and social isolation. Initiatives such as financial assistance programs, affordable housing, and community outreach programs can help mitigate these factors' negative impacts (Iosue et al. 2020).

3.16. REDUCE STIGMA AND DISCRIMINATION

Addressing stigma and discrimination around mental health is also crucial. This can include initiatives such as public education campaigns, workplace diversity and inclusion programs, and mental health advocacy (Peprah and Gyasi 2021).

3.17. FOSTER SOCIAL CONNECTION AND SUPPORT

Finally, fostering social connection and support is vital to promoting mental health and well-being. This can include initiatives such as community events, peer support programs, and workplace wellness programs (Simms et al. 2023).

3.18. INCREASED CONNECTIVITY

Social media and technology have made connecting with people across distances and time zones easier. This has allowed people to maintain relationships with friends and family members who live far away and build new connections with people worldwide (Heshmat and Neustaedter 2021).

3.19. CHANGES IN COMMUNICATION

Social media and technology have also changed how people communicate, with many relying on text messages, emails, and social media platforms to stay in touch. This can make communication more convenient but can also lead to misinterpretation or misunderstandings (Brindha et al. 2020).

3.20. GREATER EXPOSURE TO DIVERSE PERSPECTIVES

Social media and technology have also increased exposure to diverse perspectives and experiences. This can help people to broaden their horizons and develop greater empathy and understanding (Islam et al. 2020).

3.21. DECREASED FACE-TO-FACE INTERACTION

On the other hand, social media and technology can also lead to decreased face-to-face interaction. This can particularly concern younger generations who may be less comfortable with in-person social interaction (Nguyen et al.2020).

3.22. NEGATIVE IMPACTS ON MENTAL HEALTH

Social media and technology can also negatively impact mental health, mainly when used in excessive or unhealthy ways. This can include addiction, cyberbullying, and increased anxiety or depression (Weinstein 2018).

4. POLITICAL CHANGES

4.1. ANALYSIS OF THE RESPONSE OF DIFFERENT GOVERNMENTS TO THE PANDEMIC

The response of different governments to the COVID-19 pandemic has varied widely.

4.2. TIMING AND SEVERITY OF LOCKDOWN MEASURES

Some governments implemented strict lockdown measures early in the pandemic, while others responded slower. The severity of lockdown measures has also varied widely, with some countries enforcing strict stay-at-home orders and others taking a more relaxed approach (Anttiroiko 2021).

4.3. AVAILABILITY OF TESTING AND CONTACT TRACING

The availability of testing and contact tracing has also varied widely between countries. Some countries have been able to ramp up testing quickly and contact tracing programs, while others have struggled to keep up with demand (Aleta et al. 2020).

4.4. ECONOMIC SUPPORT MEASURES

Governments have also differed in their approaches to providing economic support to individuals and businesses affected by the pandemic. Some countries have implemented generous support programs, while others have been more limited in their support (Dzigbede et al. 2020).

4.5. POLITICAL LEADERSHIP

Political leadership has also been a key factor in government responses to the pandemic. Some leaders have been proactive in their response, communicating clearly with the public and taking decisive action, while others have been criticized for downplaying the severity of the pandemic or responding too slowly (Finset et al. 2020).

4.6. PUBLIC TRUST AND COMPLIANCE

The response of different governments to the COVID-19 pandemic has been highly variable, with some countries taking aggressive action to curb the spread of the virus and others struggling to mount an effective response. As we move into the era after the pandemic, it will be important to reflect on the strengths and weaknesses of different government responses and to learn from the experiences of countries around the worl (Frey et al. 2020).

4.7. INTERNATIONAL ORGANIZATIONS IN MANAGING GLOBAL HEALTH CRISES

The COVID-19 pandemic has highlighted the critical role of international organizations in managing global health crises.

4.8. COORDINATING GLOBAL RESPONSES

Organizations like the World Health Organization (WHO) have been vital in coordinating global responses to the pandemic. They have guided countries on best practices for managing the virus, and have facilitated the sharing of information and resources between countries (Gostin et al. 2020).

4.9. SUPPORTING RESEARCH AND DEVELOPMENT

International organizations have also supported research and development efforts to develop vaccines, treatments, and diagnostics for COVID-19. This includes funding research, coordinating clinical trials, and facilitating the distribution of vaccines and other medical supplies.

4.10. PROVIDING FINANCIAL SUPPORT

Organizations like the International Monetary Fund (IMF) and the World Bank have financially supported countries affected by the pandemic, including loans and debt relief (Van Hecke et al. 2021).

4.11. SUPPORTING VULNERABLE POPULATIONS

International organizations have also supported vulnerable populations affected by the pandemic, including refugees, migrants, and those living in poverty (Daher-Nashif 2022).

4.12. ADVOCATING FOR GLOBAL COOPERATION

The COVID-19 pandemic has highlighted the important role of international organizations in managing global health crises. While there have been some criticisms of the response of certain organizations, such as the WHO, many have played a critical role in coordinating global responses and supporting research, financial, and humanitarian efforts. As we move into the era after the pandemic, it will be important to continue strengthening international organizations' capacity to respond to future global health crises (Ratzan et al. 2020).

4.13. POSSIBLE CHANGES IN POLITICAL AND GOVERNANCE STRUCTURES IN RESPONSE TO THE PANDEMIC

The COVID-19 pandemic has also changed political and governance structures in many countries.

4.14. INCREASED RELIANCE ON TECHNOLOGY

Governments may increasingly rely on technology to manage crises and provide services to citizens. This could include increased use of digital platforms for communication, remote work, and online learning.

4.15. EXPANDED ROLE OF PUBLIC HEALTH AGENCIES

The pandemic has highlighted the importance of public health agencies in managing infectious disease outbreaks. Governments may therefore choose to expand the role and capacity of public health agencies to better prepare for future health crises (Nuzzo et al. 2019).

4.16. GREATER FOCUS ON PUBLIC HEALTH AND SOCIAL SAFETY NET PROGRAMS

The pandemic has also exposed the vulnerabilities of many social safety net programs and healthcare systems. Governments may therefore invest more in public health and social safety net programs to better protect vulnerable populations (Razavi et al. 2020).

4.17. CHANGES IN POLITICAL LEADERSHIP

The pandemic has put political leaders under increased scrutiny, and some have been criticized for their response to the crisis. This may lead to changes in political leadership, as voters seek leaders better equipped to manage health crises and other emergencies (Dodds et al.2020).

4.18. INCREASED PUBLIC PARTICIPATION IN DECISION-MAKING

The COVID-19 pandemic can potentially bring about significant changes in political and governance structures in many countries. While the exact nature of these changes will depend on various factors, such as political culture and institutional capacity, it is clear that the pandemic has highlighted the importance of effective governance and the need for more resilient systems and institutions (Kuhlmann et al. 2021).

5. ENVIRONMENTAL CHANGES

5.1. EXAMINATION OF THE IMPACT OF THE PANDEMIC ON THE ENVIRONMENT

The COVID-19 pandemic has had both positive and negative effects on the environment.

5.2. REDUCTION IN GREENHOUSE GAS EMISSIONS

The pandemic led to a significant reduction in greenhouse gas emissions due to reduced transportation and industrial activity. In some countries, carbon emissions were reduced by as much as 25% (Nguyen et al. 2021).

5.3. INCREASE IN SINGLE-USE PLASTICS

The increased use of personal protective equipment (PPE) and takeout food containers has increased single-use plastics, which negatively impacts the environment (Winton et al. 2022).

5.4. CHANGES IN WASTE MANAGEMENT

The pandemic has also led to changes in waste management practices, with some countries experiencing an increase in medical waste and others experiencing a decrease in household waste (Yousefi et al. 2021).

5.6. CHANGES IN LAND USE

The pandemic has led to changes in land use, with some cities creating more pedestrian and bicycle-friendly infrastructure to encourage active transportation, while others have expanded outdoor dining areas (Young et al. 2020).

5.7. IMPACTS ON WILDLIFE

Some animals have been less disturbed by the pandemic, while others have been more disturbed by human behavior. The pandemic reduced greenhouse gas emissions but increased single-use plastics and waste management. After the pandemic, we must prioritize environmental sustainability and invest in green infrastructure and more sustainable systems and practices to rebuild (Zand and Heir 2021).

5.8. ANALYSIS OF CHANGES IN ENERGY CONSUMPTION AND TRANSPORTATION

The COVID-19 pandemic has brought about significant changes in energy consumption and transportation.

5.9. REDUCTION IN TRANSPORTATION EMISSIONS

As a result of lockdowns and restrictions on movement, transportation emissions have decreased significantly. The use of public transportation, in particular, has declined, while the use of personal vehicles has increased in some areas (Huang et al. 2021).

5.10. CHANGES IN ENERGY DEMAND

The pandemic has also led to changes in energy demand, with some countries experiencing a decrease in order due to reduced industrial activity and others experiencing an increase in demand due to increased residential energy consumption (Kanda and Kivimaa 2020).

5.11. INCREASE IN RENEWABLE ENERGY INSTALLATIONS

Despite the pandemic, there has been an increase in the installation of renewable energy systems in some countries. This may be partly due to government incentives and policies prioritizing renewable energy development (Hoang et al. 2021).

5.12. SHIFT TO REMOTE WORK

The pandemic has led to a significant shift to remote work, with many employees working from home instead of commuting to an office. This has reduced transportation emissions and energy demand associated with office buildings (Tian et al. 2022).

5.13. IMPACTS ON THE AVIATION INDUSTRY

The aviation industry has been one of the hardest hit by the pandemic, with reduced demand for air travel leading to significant financial losses for airlines. This has also reduced aviation-related greenhouse gas emissions (Rababah et al. 2020).

5.14. POSSIBLE LONG-TERM STRATEGIES FOR SUSTAINABLE DEVELOPMENT

Sustainable development is an important goal that can help ensure that future generations have access to the resources and quality of life needed to thrive.

5.15. INVEST IN RENEWABLE ENERGY

Renewable energy sources, such as solar and wind power, can help to reduce greenhouse gas emissions and promote energy independence. Governments and private companies can invest in renewable energy infrastructure and technology to help transition to a more sustainable energy system (Gielen et al. 2019).

5.16. PROMOTE SUSTAINABLE AGRICULTURE

Agriculture is a major source of greenhouse gas emissions and can negatively impact soil health and water quality. Sustainable agriculture practices, such as crop rotation, conservation tillage, and cover crops, can help reduce emissions and promote soil health (Battaglia et al. 2021).

5.17. DEVELOP GREEN INFRASTRUCTURE

Green infrastructure, such as parks and urban forests, can help to reduce air and water pollution, mitigate the urban heat island effect, and provide important habitat for wildlife. Governments can invest in green infrastructure to help promote sustainable development and improve quality of life for citizens (Young et al. 2020).

5.18. SUPPORT SUSTAINABLE TRANSPORTATION

Sustainable transportation options, such as public transit, cycling, and walking, can help to reduce transportation emissions and promote active and healthy lifestyles. Governments can invest in sustainable transportation infrastructure and policies to promote these options (Battaglia et al. 2021).

5.19. REDUCE WASTE

Waste management is an important issue for sustainable development, as landfills and incineration can negatively impact air and water quality. Governments can invest in recycling and composting infrastructure, promote waste reduction and reuse, and implement policies to reduce single-use plastics (Silva et al. 2021).

5.20. PROMOTE SUSTAINABLE CONSUMPTION

Sustainable consumption is an important aspect of sustainable development. Governments can promote sustainable consumption through education campaigns, product labeling, and other policies encouraging responsible consumption choices (Prothero et al. 2011).

6. CONCLUSION

COVID-19 affected the economy, work culture, social norms, mental health, governance, and environment. Conclusions include. Pandemic industries gained. Industry reuse. Telework may reduce office use. Tourism, hospitality, and entertainment need new models. Post-pandemic mental health support is needed. Pandemic governance and global health cooperation arose. The pandemic reduced transportation energy demand and emissions. Sustainable energy, agriculture, green infrastructure, transportation, waste reduction, and consumption require long-term investments. Long-term strategies can address post-pandemic challenges and opportunities. COVID-19 weakened. The pandemic made digital technologies more efficient, convenient, and accessible across all industries. Increase productivity and flexibility. Pandemic spending increased healthcare and prevention. Wellness, prevention, and mental health improve. Pandemic emissions were sustainable. Businesses and governments must promote renewable energy, sustainable agriculture, green infrastructure, and sustainable transport. Pandemic revealed social inequality. Affordable housing, workplace diversity, education, and healthcare help governments and businesses reduce inequality. Epidemics show global cooperation. Collaboration promotes peace, prosperity and teamwork. Pandemic improved.

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Immune Boosters to Combat Zoonotic Viral Diseases

27

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ABSTRACT

Zoonotic viral diseases continue to be a long-standing danger to worldwide health, demanding thorough plans to strengthen the human body's defenses against potential infections. This summary delves into the idea of using immune boosters as a proactive method to fight against zoonotic viruses. The discussion covers a wide range of strategies, including dietary choices, lifestyle changes, and the use of supplements. Eating a diet full of nutrients is essential, with vitamins C and D, as well as zinc, playing crucial roles in supporting the immune system. Probiotics, present in fermented foods, support a strong and healthy gut microbiome, improving overall immune function. Consistent physical activity, quality sleep, and effective stress reduction are all vital elements that work together to build up the body's ability to fight off infections. Staying hydrated and consuming foods rich in antioxidants help to maintain the integrity of our cells, thus supporting our immune system. The potential immune-boosting properties of herbal supplements like echinacea and elderberry are being carefully investigated and considered for incorporation. It is recommended to consult with healthcare professionals because there may be potential interactions or reasons why certain medications should not be taken together. The chapter emphasizes the significance of a comprehensive and tailored strategy for boosting the immune system, recognizing the diversity of individual reactions. It also highlights the crucial role of vaccination in preventing zoonotic diseases and triggering specific immune reactions. While these methods of boosting the immune system can improve overall health, they are not replacements for medical treatments. It is crucial to seek prompt medical help if you suspect you have a zoonotic infection. As the world faces new viral challenges, it is essential for the global community to develop a thorough immune-boosting plan to strengthen public health resilience.

KeywordS: Zoonotic viral diseases; Immune boosters; Infection prevention; Holistic health; Public health resilience

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1. INTRODUCTION

1.1. ZOONOTIC VIRAL DISEASES EXPLANATION

Zoonotic viral diseases are infectious illnesses that arise from the transmission of viral pathogens from animals to human beings. The etiology of these aforementioned ailments is primarily attributable to viral agents that are endemic to animal populations, comprising feral fauna, domesticated stock, and companion animals. In the majority of instances, viruses prove to be innocuous to the animals they infect. However, upon transmission to humans, they have the potential to elicit illness and, in severe cases, fatality (Prince et al. 2022).

Zoonotic viral diseases have emerged as a noteworthy public health issue as they possess the potential to rapidly spread and instigate epidemics and pandemics. Several examples of viral diseases that are transmissible from animals to humans, which are commonly referred to as zoonotic diseases, include Ebola, SARS-CoV-2, also known as the virus responsible for causing the COVID-19 pandemic, as well as influenza, more typically recognized by its popular name, the flu, among numerous others (Contini et al. 2020).

Transmission of zoonotic viruses from animals to humans can take place through diverse pathways, including but not limited to direct contact with infected animals or their bodily fluids, consumption of food or water contaminated with the virus, and the bite of an infected arthropod, such as a mosquito or tick. The incidence of zoonotic viral infections is considerably heightened in regions where individuals coexist in intimate proximity with animals or where there is a substantial incidence of animal trade or consumption (Kruse et al. 2004).

It is of paramount importance to avert the transmission of zoonotic viruses as a means of reducing the likelihood of outbreaks and safeguarding the well-being of the general populace. The realization of aforementioned objectives may be attained via a plethora of strategies, which may encompass the advancement of inoculations, intensified vigilance and tracking of animal communities, and implementation of public health education initiatives aiming at fostering prudent animal product manipulation and consumption practices (Wimalawansa 2020).

1.1. IMMUNE BOOSTERS IN PREVENTING AND TREATING DISEASES IMPORTANCE

Enhancing the immune system through the utilization of immune boosters plays a significant role in averting and managing zoonotic viral diseases due to a host of reasons.

1.2. THE IMMUNE SYSTEM STRENGTHENING

Immune enhancers, whether innate or man-made have the potential to fortify the immune system which is indispensable in combatting viral infections. An effective immune system possesses superior ability in identifying and combating viral pathogens, thereby potentially averting or mitigating the onset and progression of infectious disease (Islam et al. 2022).

1.3. VACCINE EFFICACY ENHANCING

Enhancement of vaccine efficacy is reportedly achievable via immune boosters, which have been identified as one of the most efficacious strategies in the prevention of viral infections. The implementation of immune enhancers, such as adjuvants, has been demonstrated to augment the

immune response elicited by vaccines, culminating in heightened resistance against the viral strain (Slifka and Amanna 2014).

1.4. VIRAL REPLICATION REDUCING

Several immunity-enhancing agents, for instance, antiviral medications, possess the capacity to specifically target the virus and mitigate its capacity to reproduce within the organism. This intervention has the potential to retard the pace of disease advancement, diminish the gravity of symptoms and enhance the probability of recuperation (Dube et al. 2021).

1.5. OVERALL HEALTH SUPPORTING

Adopting a wholesome dietary plan and maintaining a healthy lifestyle can significantly enhance immunological function and mitigate the susceptibility to viral infections.
Immune enhancers possess the capability of significantly impacting the protection and management of zoonotic viral infections, through the fortification of the immune system, amplification of vaccine effectiveness, conduction of viral replication reduction, and assistance in maintaining holistic well-being. By integrating immunomodulators in both prevention and treatment tactics, it is plausible to mitigate the repercussions of zoonotic viral illnesses on human welfare (Arshad et al. 2020).

2. IMMUNE SYSTEM OVERVIEW

2.1. FUNCTIONS OF IMMUNE SYSTEM

The immune system is a complex hierarchical organization comprised of cells, tissues, and organs with concerted function aimed at the preservation of the body by shielding it against a spectrum of pathogens, including viruses, bacteria, fungi, and parasites (Marshall et al. 2018). The immune system's main functions.

2.2. PATHOGENS IDENTIFICATION AND ELIMINATION

The immune system demonstrates the capacity to discern and discriminate between self and non-self-entities, which encompasses the molecular constituents present on the pathogens' surface. Upon identification of a pathogen, the immune system has the ability to initiate a response mechanism to eradicate the pathogen from the host organism (Medzhitov 2007).

2.3. IMMUNE RESPONSE MOUNTING

The immune system mounts a response against pathogens through the generation of specialized cellular components, including white blood cells that are capable of specifically targeting and eradicating the foreign agent. The immune system is capable of generating antibodies, a class of proteins that demonstrate the ability to identify and counteract specific pathogens (Spiering 2015).

2.4. IMMUNOLOGICAL MEMORY GENERATING

Upon encountering a pathogen, the immune system has the capacity to elicit immunological memory, a phenomenon that confers the ability to mount a swifter and more efficient response to subsequent infections caused by the same pathogenic agent (Quast and Tarlinton 2021).

2.5. BODY SYSTEMS COORDINATING

The immune system is responsible for the crucial function of safeguarding the body against pathogens and upholding a state of general wellness. To achieve this, it engages in intricate interactions with other systems of the body, including the nervous and endocrine systems, in order to regulate immune responses. It is crucial to maintain a robust and harmonious immune system to thwart infections and combat illnesses (Ziemssen and Kern 2007).

2.6. THE HEALTHY IMMUNE SYSTEM IMPORTANCE IN COMBATING VIRAL INFECTIONS

The maintenance of a robust immune system is of paramount importance when addressing the challenge of viral infections owing to various compelling factors.

2.7. ELIMINATION OF EFFECTIVE VIRUS

A robust immune system is more proficient in eradicating viruses by generating specialized T and B cells, which possess the capability to specifically target and eliminate infected cells, as well as neutralize the virus (Li et al. 2020).

2.8. MEMORY OF IMMUNOLOGICAL

The phenomenon of immunological memory observed in a healthy immune system following an initial infection confers the ability to mount a rapid and potent response against future infections caused by the same virus (Dan et al. 2021).

2.9. SYMPTOMS OF REDUCED SEVERITY

A robust immune response has the potential to mitigate the gravity of symptoms that are linked with viral infections, including but not limited to fever, fatigue, and myalgia (Woods et al. 2020).

2.10. COMPLICATIONS OF LOWER RISK

A healthy immune system is less predisposed to experience complications that are linked with viral infections, including encephalitis or pneumonia. An optimal immune system is crucial in mounting an effective defense against viral infections. A robust and balanced immunological response can serve to forestall infections, mitigate the severity of clinical manifestations, and decrease the susceptibility to developing complications. The implementation of various strategies aimed at preserving a robust immune system, including the consumption of a nutritionally-balanced diet, adherence to a consistent exercise regimen, and sufficient sleep, are of paramount significance in the prevention and management of viral infections (Khan et al. 2022).

2.11. DIFFERENT COMPONENTS OF THE IMMUNE SYSTEM

2.11.1. IMMUNE SYSTEM DIVIDED INTO TWO COMPONENTS

2.11.1.1. INNATE IMMUNE SYSTEM

The innate immune system represents the initial barrier against pathogens and is constituted by non-specific mechanisms which possess the capability to promptly react towards a vast array of pathogens.

The human immune system comprises both anatomical and physiological barricades, such as the epidermis and mucosal linings, in addition to specialized cellular components such as macrophages, neutrophils, and natural killer (NK) cells. These cells have the ability to identify and purge pathogens using non-specific mechanisms including phagocytosis and the excretion of cytotoxic substances (Cota and Midwinter 2012).

2.12. ADAPTIVE IMMUNE SYSTEM

In contrast, the adaptive immune system is a discerning defensive mechanism that has the capability of selectively recognizing and targeting particular pathogens. The present system encompasses distinct cell types, notably T and B cells, capable of discerning and reacting to particular antigens, specifically proteins that appear on the exterior of infectious agents. The adaptive immune response constitutes a more intricate and protracted process, yet it confers enduring immunity against distinct pathogens. The adaptive immune system possesses the ability to generate immunological memory, thereby facilitating expedited and optimized response to subsequent infections caused by the same pathogen. The conjoined actions of the innate and adaptive immune systems serve as a robust mechanism for effectively shielding against potentially harmful pathogens. The innate immune system offers an expedient, unspecific reaction to a diverse array of pathogens, whereas the adaptive immune system elicits a nuanced, focused response to distinct pathogens. The integral role of both innate and adaptive components of the immune system cannot be understated with regard to upholding holistic well-being and safeguarding the body against potential infectious agents (Marshall et al. 2018).

3. BOOSTERS IMMUNE

3.1. IMMUNE BOOSTERS

Immunomodulatory agents may be administered in various forms, including supplements, vitamins, herbs, natural remedies, as well as lifestyle interventions such as dietary modifications, exercise, and stress management techniques (Noureen et al. 2022).
Although certain immune boosters have been scientifically validated as efficacious, a vast number of them have not received sufficient trials, and therefore, their potency and safety remain uncertain. Consultation with a healthcare provider is crucial prior to the consumption of any immune booster in order to ascertain its safety and suitability with respect to individual requirements (Pudalov et al. 2020).

3.2. IMMUNE BOOSTER'S TYPES

There exists a myriad of immune-enhancing interventions, encompassing both organic and artificial modalities.

3.3. IMMUNE BOOSTERS NATURAL

Immune-enhancing agents of a natural origin are obtained from botanical resources including plants, herbs, and comestibles (Singh et al. 2021).

3.4. EXAMPLES OF NATURAL IMMUNE BOOSTERS

Vitamin C, a robust antioxidant with the potential to enhance immune function and defend against infections, is naturally present in citrus fruits, berries, and leafy greens (Saha et al. 2021). Zinc, an

essential nutrient for immune function, can be sourced from various food items such as oysters, red meat, and poultry. Its role in combating infections is noteworthy (Kanwar and Sharma 2022). Echinacea, a frequently utilized botanical remedy, is purported to bolster the body's immune response while ameliorating the intensity of symptoms associated with cold and influenza viral infections (Namdeo 2021). Probiotics, which are present in fermented foods such as yogurt, kimchi, and sauerkraut, have been shown to enhance intestinal health and fortify immune responses (Şengün and Güney 2021). Synthetic immune boosters refer to artificially produced compounds that have been formulated to augment the functionality of the immune system (Nath et al. 2021).

Immune checkpoint inhibitors are a class of synthetic agents that function by obstructing specific molecules that possess the capacity to restrain the immune system's functioning, thereby enabling it to effectively combat cancer cells (Ge et al. 2018).

3.5. THE IMMUNE BOOSTERS WORK

The mechanism by which immune boosters enhance the body's immune system function may differ depending on the particular immune booster being examined. In a broad sense, immune boosters operate through the amplification of the immune system's functionality, primarily accomplished by the inducement of immune cell production or the activation of pre-existing immune cells (Bartleson et al. 2021).

For instance, certain natural agents that enhance immunity, including vitamin C and zinc, represent indispensable nutrients that play crucial roles in promoting optimal immune system performance. The acquisition of optimal levels of vitamin C is a crucial determinant for the synthesis of white blood cells, whereas zinc plays a pivotal role in the progression and efficacy of immune cells, particularly T and NK cells. The provision of essential nutrients to the body has been shown to significantly enhance immune function, thereby decreasing susceptibility to various infections and diseases (Cámara et al. 2021).

Various natural immune enhancers, such as Echinacea and probiotics, function by directly stimulating the immune system. Echinacea is purported to stimulate the production of leukocytes and other components of the immune system, while probiotics have the ability to foster the proliferation of advantageous microorganisms in the gastrointestinal tract, thereby fortifying immune function (Provenza and Villalba 2010).

4. NATURALLY IMMUNE BOOSTERS

4.1. BOOST IMMUNITY FOODS AND NUTRIENTS

Zinc is a mineral which plays an indispensable role in the growth and operation of the immune system's T cells and NK cells. Excellent dietary sources of zinc consist of mollusks such as oysters, beef, chicken, legumes, nuts, and whole grains (Vishwakarma et al. 2022).

Vitamin D is a crucial nutrient that plays a vital role in enhancing immune function, and scientific evidence suggests that it can effectively safeguard against respiratory infections. Fatty fish like salmon and tuna, fortified milk and cereal, as well as exposure to sunlight, serve as viable sources of vitamin D (Smith et al. 2020).

Probiotics refer to the so-called advantageous microorganisms that inhabit the gastrointestinal tract and assist in bolstering immune functionality. Various food items are considered to be good sources of probiotics, such as yogurt, kefir, kimchi, and sauerkraut (Damián et al. 2022).

The nutritional properties of garlic entail active elements that exhibit antimicrobial and immune-enhancing effects. Evidence supports the efficacy of these compounds in promoting health and well-being. This particular ingredient possesses the potential to enhance both the taste and nutritional value of a diverse range of culinary preparations (Chakraborty and Majumder 2020).

Turmeric, a plant-derived substance, exhibits a bioactive constituent named curcumin which possesses notable anti-inflammatory and immunomodulatory attributes. This ingredient may be incorporated into various types of dishes, such as curries, soups, and smoothies, to enhance the flavor profile and impart notable health advantages (Mrityunjaya et al. 2020)

Green tea is known to possess polyphenols, which have been demonstrated to exhibit immune-stimulatory properties. This drink can be consumed both hot and cold, providing a variety of nutritional benefits (Otto 2022).

4.2. HERBAL SUPPLEMENTS USED IN IMMUNE BOOSTERS

Moreover, apart from dietary intake, a plethora of herbal supplements have been conventionally employed to enhance the immune system.

Echinacea, an herb long revered for its medicinal properties, has been widely utilized throughout history for its ability to enhance immune function and provide relief from various types of infections. The mechanism of action is presumed to involve the activation of the biosynthesis of leukocytes and various immunological cells. Echinacea supplements can be procured in diverse forms such as capsules, tablets, and tinctures (Catanzaro et al. 2018).

The fruit of elderberry has been conventionally employed to remedy colds and flu. The chemical composition of this substance includes flavonoids, which possess antioxidant and anti-inflammatory attributes that could potentially enhance immune function. Elderberry supplements are offered in a range of preparations such as syrups, lozenges, and capsules (Srivastava et al. 2020).

The herb known as Astragalus, with a longstanding history of use in traditional Chinese medicine spanning thousands of years, has attracted significant attention within the academic and medical communities. It is postulated that it exerts a beneficial effect on the immune system through the activation of white blood cells and other related immune cells. A multitude of formats of Astragalus supplements can be readily obtained, encompassing capsules, tablets, and tinctures (Shahrajabian et al. 2019).

Andrographis, an herbal remedy with origins in Ayurveda medicine, has found common use in treating symptoms of cold and influenza. The substance in question comprises compounds that have demonstrated anti-inflammatory and immune-enhancing properties. There exist diverse types of Andrographis supplements which come in different forms, such as capsules and tablets (Gaur et al. 2010).

Ginger, a plant root with a long history of medicinal use, has traditionally been utilized for its therapeutic benefits in the treatment of colds and flu. The composition of the substance comprises elements that possess attributes that are conducive to mitigating the effects of inflammation and fortifying the immune system. Ginger supplements can be obtained in diverse formats, which include capsules, tablets, and teas (Agarwal 2021).

4.3. MODIFICATIONS OF LIFESTYLE

Regular physical activity has been demonstrated to possess immunomodulatory capacities. This intervention exhibits the potential to elevate circulation, enhance lymphatic circulation, and activate the

synthesis of immune cells. The objective is to engage in moderate exercise for a minimum of 30 minutes on a daily basis throughout the majority of the week (Hasan 2022).

Sufficient sleep is paramount to promoting immune system capabilities. Insufficient slumber may lead to impaired immune response and heightened vulnerability to infections. It is recommended that individuals strive to obtain between 7 and 8 hours of sleep per night (Yousfi et al. 2020).

The management of stress is paramount, as its chronic manifestation may serve to compromise the immune system, thereby elevating the vulnerability of infections. The exploration of efficacious stress management techniques, including those incorporating meditation, yoga, or deep breathing exercises, has the potential to bolster immune function (Vagga and Dhok 2020). The implementation of proper hygiene practices has the potential to mitigate the transmission of infectious diseases. Observing proper hygiene practices, such as frequent hand washing, cough and sneeze etiquette, and minimizing contact with ill individuals, are effective ways of preventing the spread of disease (Mieth et al. 2021).

Smoking cessation is of paramount importance since smoking is known to have deleterious effects on immune function and amplifies the likelihood of contracting infectious diseases. The act of ceasing cigarette smoking can yield both immediate and enduring advantages with regard to immune health (Eltorai et al. 2019).

5. SYNTHETIC OF THE IMMUNE BOOSTERS

5.1. IMPORTANCE OF VACCINES AND PREVENTING VIRAL INFECTIONS

The employment of vaccines constitutes a fundamental initiative in countering the dissemination of viral infections. The mode of action of these agents is rooted in fostering immune recognition and response against specific viral pathogens. Vaccines consist of either a weakened or killed version of the virus, or an immunogenic viral constituent, which is capable of stimulating an immune response. Upon receiving a vaccination, the immune system of an individual is intentionally and safely exposed to the virus, thereby facilitating the production of an immunological response to the virus without inducing any manifestations of the disease (Shih et al. 2020).

5.2. VACCINES INHIBITING VIRAL INFECTIONS

The administration of vaccines has been found to offer protection against severe and potentially fatal illnesses, including measles, polio, and influenza (Soriano et al. 2022).

Herd immunity is a phenomenon wherein a sufficient proportion of individuals within a given community have been immunized against a specific virus, leading to a decrease in the likelihood of transmission of the virus. As a result, even individuals who are unable to receive vaccinations, such as infants or those with compromised immune systems, are shielded from the virus as it is less likely to spread (Pollard and Bijker 2021).

The prevention of outbreak and epidemics by means of vaccines is an efficacious strategy that involves mitigating the number of individuals who can contract and propagate viral infections. This approach serves to curtail the morbidity and mortality rates of infectious diseases (Li et al. 2020).

Vaccines present a cost-effective measure in the prevention of infectious diseases. Notably, they offer the potential to substantially ease the financial burden associated with medical care, hospitalization, and diminished productivity resulting from illness. Vaccination represents a significant tool in curtailing viral infections and safeguarding the health of the general population. Adhering to the recommended

vaccine schedules is crucial to guarantee that both individuals and communities are safeguarded against diseases that can be prevented through vaccination (Kohli et al. 2021).

5.3. ROLE OF ANTIVIRAL DRUGS FOR TREATING VIRAL INFECTIONS

Antiviral drugs are a therapeutic class of pharmacological agents developed specifically for the treatment of viral infections. These drugs operate by disrupting viral replication mechanisms or by impeding the viral pathogen's ability to propagate and spread among host cells. Antibiotics, being designed to target bacterial infections, are distinct from antiviral drugs which are specifically tailored to combat viruses and are not effective against other microorganisms (Meganck and Baric 2021).

5.4. USED OF ANTIVIRAL DRUGS TO TREAT VIRAL INFECTION

The management of acute infections entails the administration of antiviral agents, which impede the proliferation of viruses and mitigate the intensity and duration of symptoms. Influenza, herpes, and hepatitis are among the viral infections that can be effectively treated using antiviral drugs (Tompa et al. 2021).

Antiviral drugs have been demonstrated to be efficacious in averting the transmission of specific viral infections, such as human immunodeficiency virus (HIV) and hepatitis B, from maternal to fetal during the duration of gestation or at the time of delivery (Hou et al. 2019).

The management of chronic infections is a paramount concern in the medical field. Certain viral infections, such as human immunodeficiency virus (HIV) and hepatitis B and C, have the propensity to progress into a chronic state, necessitating the utilization of prolonged antiviral drug therapy to both mitigate symptoms and avert complications (Terrault et al. 2018).

Emergency therapy may involve the administration of antiviral agents in situations such as critical viral infections, including the Ebola virus or severe acute respiratory syndrome (SARS), wherein prompt intervention is crucial, and failure to treat expeditiously may result in severe morbidity or mortality (Cao et al. 2020).

It is imperative to acknowledge that antiviral medications are not universally efficacious against all viral infections, as their effectiveness is contingent upon numerous variables such as the specific type of virus and the particular stage of the infection being treated. Furthermore, the utilization of antiviral medications may result in the manifestation of adverse effects and drug interactions; hence, it must be administered solely under the supervision and recommendation of a healthcare professional (Kursat et al. 2020).

5.5. MONOCLONAL ANTIBODIES USE SEVERE VIRAL INFECTION

Monoclonal antibodies, herein referred to as mAbs, represent a category of synthesized proteins with the capability of being manipulated to selectively recognize and bind to distinct proteins located on the outer membranes of viruses. In the field of medicine, immunomodulatory have been implemented as a therapeutic strategy for combating highly consequential viral infections. Their primary purpose is to enhance the immune system's ability to identify and eliminate the infectious virus (Raytthatha et al. 2020).

5.6. MONOCLONAL ANTIBODIES USES

The therapeutic strategy for COVID-19 involves the administration of monoclonal antibodies, which have been granted emergency use authorization. These therapeutic agents function through the mechanism

of attaching to the spike protein located on the exterior of the SARS-CoV-2 virus, thus impeding its ability to invade cells and concurrently lessening the gravity of the disease manifestation in patients who have contracted the infection (Kelley et al. 2022).

The management of Ebola virus infection involves the use of monoclonal antibodies as a therapeutic option, which demonstrate the ability to lower viral load in the bloodstream, resulting in enhanced survival rates (Iversen et al. 2020).

The prevention of viral infections can be achieved through the utilization of monoclonal antibodies, particularly in individuals who have encountered the virus. This approach is particularly applicable to those who are susceptible to experiencing severe disease resulting from influenza or respiratory syncytial virus (RSV) (Behzadi and leyvagrado 2019).

The management of chronic viral infections has garnered considerable attention, with monoclonal antibodies emerging as a possible therapeutic avenue. These antibodies have been extensively researched as a potential treatment option for hepatitis B and HIV, specifically in their ability to aid in immune system stimulation and reduce the viral load in circulation (Iannacone and Guidotti 2022).

The efficacy of monoclonal antibodies as a viable remedy for severe viral infections has exhibited promising outcomes. The efficacy of antiviral therapies may exhibit variability contingent on the virus type and the stage of the pathogenic infection. Additionally, these treatments can potentially elicit undesirable outcomes, including but not limited to allergic and infusion reactions. The appropriate utilization of monoclonal antibodies necessitates the expert guidance of a healthcare practitioner (Chung et al. 2021). Fig. 1 shows the list of zoonotic viral diseases.

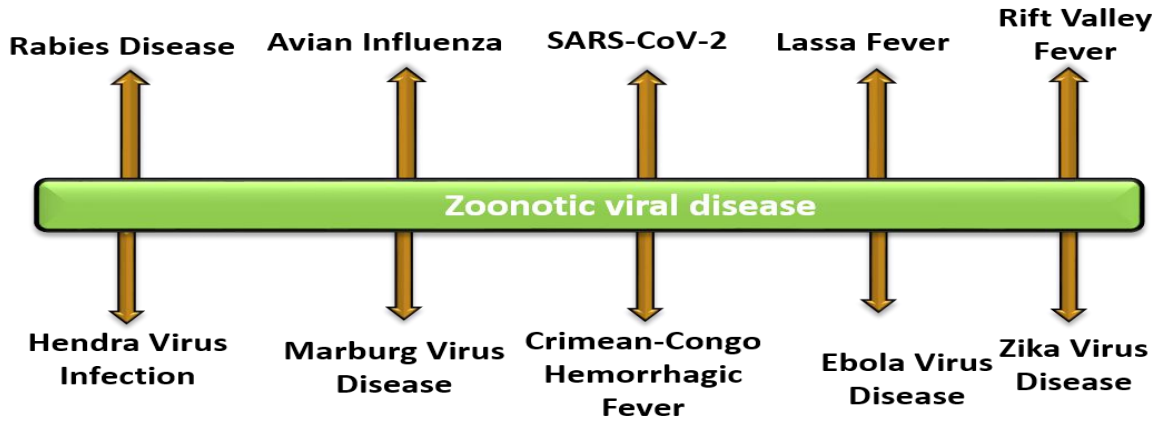

Fig. 1: Zoonotic viral disease

6. PREVENTION AND TREATMENT OF ZOONOTIC VIRAL DISEASES

6.1. ZOONOTIC VIRAL DISEASES EXAMPLES

Ebola virus disease (EVD) is caused by a virulent virus that exhibits high levels of infectivity. Human transmission of the virus primarily occurs via contact with infected animals, most notably fruit bats, monkeys, and chimpanzees. The virus has the potential to precipitate a grave hemorrhagic fever syndrome and engenders a high fatality rate (Caron et al. 2018).

The causative agent of the COVID-19 pandemic is SARS-CoV-2, a viral pathogen that primarily affects respiratory function. The etiology of the virus under consideration is conjectured to have originated in

bats and has been postulated to have been transferred to humans via an animal host which serves as an intermediary vector, potentially a pangolin (Ortiz-Prado et al. 2020).

The H1N1 influenza, commonly known as swine flu, is a strain of influenza virus that is typically prevalent in swine species. The transmission of the virus to humans may occur via direct exposure to infected pigs or through indirect exposure to contaminated surfaces (Jilani et al. 2018).

Rabies is a viral zoonotic disease that can be transmitted to humans via the bite of an infected animal, including but not limited to dogs, cats, and bats. The pathogen targets the nervous system and poses a significant risk of morbidity and mortality if not appropriately managed in a timely manner (Horta et al. 2022).

MERS-CoV, an acronym for Middle East respiratory syndrome coronavirus, is a contagious viral illness that can be contracted by humans through exposure to infected dromedary camels. The virus has the capability to induce serious respiratory illness and exhibits a significant fatality rate (Conzade et al. 2018).

Zika virus disease represents a pathogenic ailment which is contracted by humans upon being bitten by infected Aedes mosquitoes that are known to serve as carriers of this arbovirus infection. The mode of transmission of this viral illness is predominantly orchestrated through mosquito bites, with several other vertical transmission routes having also surfaced in recent times. The virus has been observed to engender minor ailments in the majority of individuals, whereas its impact on pregnant women could lead to grave complications, including congenital malformations in neonates (Veeresha et al. 2022).

There is a plethora of viral diseases that are zoonotic in nature. The implementation of preventive measures is crucial in inhibiting the proliferation of said diseases. This may entail refraining from any form of interaction with afflicted animals, observing proper sanitary practices, and acquiring vaccination, if available (Khan et al. 2021).

6.2. STRATEGIES OF PREVENTION

Vaccination is considered to be one of the most efficacious means for treating the Contagious effects of viral disease. Vaccinations operate through the stimulation of the immune system to produce specialized proteins known as antibodies, which possess the capability to neutralize the virus if an individual is exposed to it subsequent to vaccination. Several viral diseases, such as influenza, measles, and hepatitis B, can be treated with vaccines (Zhang et al. 2020).

The utilization of Personal Protective Equipment for instance, masks, gloves, and gowns, plays a vital role in reducing the risk of exposure to infectious materials. The implementation of PPE is beneficial in preventing the transmission of viral diseases amongst individuals. Personal Protective Equipment holds particular significance for healthcare professionals who are at risk of exposure to infected patients (Hirschmann et al. 2020).

Effective hand hygiene practices, such as washing one's hands with soap and water or utilizing alcohol-based hand sanitizers, have been shown to inhibit the transmission of viral diseases by eliminating any viruses that may be present on the hands (Lee et al. 2020).

Social distancing is a set of preventive measures that involves maintaining a minimum distance of six feet from individuals and abstaining from large gatherings as a means of curbing the transmission of viral diseases. The practice succeeds in limiting the possibility of close interaction among individuals, which effectively deters the spread of such diseases (Pandi-Perumal et al. 2021).

Limiting the movement of individuals through travel restrictions is a viable strategy to contain the dissemination of viral diseases. Such measures effectively diminish the number of people traveling to or from regions experiencing elevated levels of infection (Chinazzi et al. 2020).

Controlling the diffusion of zoonotic viral diseases frequently necessitates the implementation of animal control measures to curtail propagation of the disease within animal populations. The prevention of disease dissemination often entails vaccinating animals, imposing quarantine protocols, or engaging in the targeted euthanization of infected livestock (Fritz and Byers 2023).

6.3. TREATMENT OF ZOONOTIC DISEASES

The possible course of action for addressing zoonotic viral diseases exhibits variability contingent upon both the identity of the virus in question and the perceived levels of severity pertaining to the infection. Several conventional treatment options are available.

The provision of supportive care is frequently considered the primary therapeutic modality for addressing zoonotic viral illnesses. Possible academic rewriting: Diverse interventions can be employed to manage the clinical presentation of a patient with a severe respiratory illness. These could encompass interventions aimed at mitigating oxygen deprivation, restoring abnormal fluid and electrolyte balances, and addressing coexisting infectious complications. The specific treatment options may depend on the individual patient's condition and the underlying disease etiology. Providing adequate supportive care is crucial for patients who are afflicted with severe infections and necessitate hospitalization (Baseler et al. 2017).

Convalescent plasma, a blood derivative, is harvested from individuals who have successfully recuperated from a viral illness. The plasma comprises of antibodies that exhibit therapeutic potential in the context of viral infections by serving as an effective tool to combat the virus. Consequently, it can be utilized as an intervention strategy for patients currently affected by the infection. Convalescent plasma has been employed as a therapeutic intervention for a variety of viral ailments, among which SARS-CoV-2 ranks as a prominent example (Ranganathan and Iyer 2020).

Experimental therapeutics may be employed in certain instances for the management of zoonotic viral illnesses. Novel antiviral drugs, gene therapies, and immunomodulatory agents may be employed as potential therapeutic interventions. Notwithstanding, these interventions are commonly employed solely in clinical examinations and are not extensively accessible (Xu et al. 2020).

7. CONCLUSION

This chapter emphasizes the importance of immune boosters in preventing zoonotic viral diseases that transfer from animals to humans, causing severe health complications and deaths. This chapter covered the immune system's functions, including innate and adaptive responses, and discussed different immune-boosting agents. The text discussed nourishments, supplements, lifestyle adjustments, and preventive measures such as vaccinations and medications for zoonotic viral afflictions. The chapter emphasizes the need for innovative research to find effective treatments for illnesses. Improving the immune system can be done through natural supplements, herbal remedies, and lifestyle changes such as exercise and rest. Immune boosters can increase immune cell quantity and efficacy, antibody synthesis and overall immune system performance. They can help reduce the intensity and duration of viral infections. They can mitigate infections, especially zoonotic diseases. Immune boosters can help combat these diseases. Augmenting agents boost immunity, preventing viral infections, reducing complications, and promoting overall health.

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Outbreak of the Ebola Virus

28

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ABSTRACT

The emergence of the Ebola virus presents a major public health concern due to its ability to spread quickly and its high fatality rates. Ebola virus disease (EVD) is caused by the Ebola virus, which is transmitted to humans through contact with infected animals and then spreads through direct human-to-human contact. The virus causes a serious and potentially deadly disease with symptoms including fever, weakness, muscle pain, and in certain instances, bleeding both internally and externally. In the past, outbreaks have happened in countries in Central and West Africa, with the Democratic Republic of Congo often being a particularly affected area. The characteristics of each outbreak differ and are shaped by factors such as the quality of local healthcare services, public knowledge, and the timeliness of global intervention. Control measures usually include isolating individuals who are infected, following strict hygiene practices, using protective gear, and conducting safe burial processes. Public health initiatives are essential in teaching communities about how to prevent and detect illnesses at an early stage. Recent progress in the creation of vaccines has presented a valuable asset in the battle against Ebola. Vaccination initiatives, in conjunction with global cooperation and backing from entities such as the World Health Organization, aid in controlling and handling outbreaks. Efficient and synchronized action are still crucial in reducing the effects of the Ebola virus, emphasizing the continued dedication of the worldwide community to tackling new contagious diseases and protecting public health. It is crucial to closely watch and tackle the underlying reasons for these outbreaks in order to prevent them from happening again and to improve global readiness.

Keywords: Ebola virus outbreak; Ebola virus disease (EVD); Public health; Epidemic control; Vaccination efforts

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1. INTRODUCTION

1.1. EBOLA VIRUS

The Ebola virus is a highly infectious and pathogenic virus belonging to the Filoviridae family. The nomenclature of the initial incidence of Ebola virus is attributed to its occurrence within the vicinities of the eponymous river situated in the Democratic Republic of Congo (Tseng and Chan 2015).

The Ebola virus is contracted by humans through the exchange of biologicalfluids with infected animals, including but not limited to fruit bats, monkeys, and gorillas. Subsequently, the virus spreads from person to person via direct contact with biological fluids, including blood, saliva, urine of those individuals who have been infected. Through the occurrence of indirect contact with contaminated surfaces, such as clothing and bedding, the viral agent may propagate (Rewar and Mirdha 2014).

The manifestation of symptoms related to Ebola virus infection can occur within a period of 2-21 days following contact, and typically involve fever, fatigue, myalgia, cephalalgia, pharyngitis, emesis, diarrhea and skin rash. As the condition advances, it can result in hemorrhages within the body and dysfunction of biological organs, ultimately culminating in mortality in as many as 90% of instances (Beeching et al. 2014).

Ebola virus infection lacks a definitive remedy or pharmacotherapy, and the optimal strategy for controllingits dissemination is predicated on early identification, quarantine of afflicted persons, and the appropriate implementation of infectious disease control measures. In recent times, considerable strides have been made in the development of vaccines that exhibit favorable outcomes in clinical trials. Furthermore, persistent efforts are being made to create novel therapies and preventive measures to counteract the effects of this lethal virus (Dhama et al. 2018).

1.2. OVERVIEW OF THE EBOLA VIRUS OUTBREAK 2014-2016

The Ebola virus eruption that occurred between 2014 and 2016 can be considered as the most significant and intricate outbreak of the illness since its inception in the year 1976. The incidence of the outbreak initially surfaced in Guinea in December 2013 and expeditiously disseminated to nearby countries, namely Sierra Leone and Liberia. The Ebola virus outbreak was propagated through global travel, resulting in its dissemination to diverse countries such as Nigeria, Senegal, Mali, and the United States (Barry et al. 2018).

The eruption was deemed to have exhibited extensive transmission, as evidenced by the verification of over 28,000 cases that were either confirmed, deemed credible, or considered to be supposed, in addition to a mortality rate exceeding 11,000 individuals. The high population density in urban areas is correlated with an increased number of deaths and cases of disease. This is attributable to the slow initial response and challenges faced in curtailing the propagation of the disease (Dénes and Gumel 2019).

The epidemic's deleterious effects encompassed significant societal and monetary repercussions, manifesting as disruptions to healthcare infrastructure and the economy, in addition to the stigmatization of afflicted communities. The global reaction was exceptional, as evidenced by the coordination of more than 28,000 personnel from various nations who were dispatched to the affected countries to deliver medical aid and logistical assistance (Nuriddin et al. 2018).

The cessation of the outbreak was officially announced in 2016, notwithstanding, its enduring repercussions on impacted communities, healthcare frameworks, and worldwide health security persist. The concomitant emergence of the Ebola virus outbreak prompted a rise in research and development endeavours pertaining to treatments and vaccines targeting the aforementioned pathogen (Global and Security 2023).

2. EBOLA VIRUS HISTORY OF OUTBREAKS

2.1. GEOGRAPHIC HISTORY OF EBOLA VIRUS OUTBREAKS

The Ebola virus has been the subject of limited outbreaks since its initial identification in 1976. A concise chronicle of notable epidemic instances and their corresponding geographical factors.

2.1.1. 1976 OUTBREAK

The initial emergence of the Ebola virus was characterized by two simultaneous outbreaks in geographical regions of Sudan and the Democratic Republic of Congo (DRC, formerly Zaire).

2.1.2. 1995 OUTBREAK

A sudden episode of infectious disease outbreak was documented in the Kiewit region of the Democratic Republic of Congo, wherein 315 individuals were formally diagnosed with the ailment, leading to 254 cases of fatalities (Sivanandy et al. 2022).

2.1.3. 2000 OUTBREAK

An outbreak in Uganda resulted in 425 confirmed cases and 224 fatalities (Rai et al. 2022).

2.1.4. 2007 OUTBREAK

The Democratic Republic of Congo experienced two distinct episodes of outbreak, whereby the cumulative number of cases and fatalities reached 264 and 187 respectively (Lamunu et al. 2004).

2.1.5. 2014-2016 OUTBREAK

The most extensive epidemic on record transpired in West Africa, whereby Guinea, Liberia, and Sierra Leone encountered the highest extent of impact. The total number of confirmed, probable, and suspected cases exceeded 28,000, with a corresponding number of fatalities exceeding 11,000 (Den Boon et al. 2019).

2.1.6. 2018-2020 OUTBREAK

The Democratic Republic of Congo encountered an epidemic, resulting in a cumulative count of 3,481 cases and 2,299 fatalities (Goldstein et al. 2020).

2.1.7. 2021 OUTBREAK

In Guinea, there was a recent incidence of outbreak onsets commencing in January and ceasing in June, which rendered 16 confirmed cases and ultimately resulted in 12 fatalities (Sanyaolu et al. 2021).

2.2. OUTBREAKS CONTRIBUTING FACTORS

The emergence of Ebola virus outbreaks may be attributed to various factors, including.

2.2.1. ANIMAL-TO-HUMAN TRANSMISSION

The fruit bat, being the primary reservoir host, is accountable for the dissemination of the Ebola virus. The contraction of the virus occurs among humans upon their exposure to infected animals, including but not limited to fruit bats, primates, and forest antelopes (Irving et al. 2021).

2.2.2. HUMAN-TO-HUMAN TRANSMISSION

The Ebola virus has the potential to transmit among individuals through direct exposure to contaminated biological fluids, such as blood, saliva, sweat, and vomitus of an infected person (Sanyaolu et al. 2021).

2.2.3. POOR HEALTHCARE INFRASTRUCTURE

Numerous countries where Ebola outbreaks occur exhibit deficient healthcare infrastructures characterized by a dearth of qualified healthcare personnel, substandard medical facilities, and incomplete resources to contain the dissemination of the virus (Kamorudeen et al. 2020).

2.2.4. CULTURAL PRACTICES

Several educational practices, namely interment ceremonies that involve direct contact with the deceased, have the potential to heighten the risk of viral transmission (Organization 2018).

2.2.5. POPULATION DISPLACEMENT

The pivotal demographic changes, resulting from armed conflict, political instability, or environmental disasters, have the potential to foster circumstances that augment the dissemination of communicable diseases (Caminade et al. 2019).

2.2.6. INTERNATIONAL TRAVEL

The global mobility of people and goods may contribute to the dissemination of infectious diseases across international boundaries, particularly when infected individuals relocate to foreign nations (Baker et al. 2022).

3. THE 2014-2016 OUTBREAK OF EBOLA VIRUS

3.1. THE OUTBREAK TIMELINE

The chronology of the Ebola virus outbreak, occurring between 2014 and 2016, necessitates scholarly discourse. (Kamorudeen et al. 2020).

3.1.1. DECEMBER 2013

The initial incidence of the Ebola virus in Guinea was notified (Ohimain and Silas-Olu 2021).

3.1.2. MARCH 2014

The World Health Organization (WHO) has officially verified the nature of the pathogen to be Ebola.

3.1.3. MAY 2014

The transmittable pathogen disseminates across the regions of Sierra Leone and Liberia (Brandt et al. 2021).

3.1.4. JUNE 2014

The World Health Organization (WHO) has officially declared the outbreak as a Public Health Emergency of International Concern (Kenyi 2019).

3.1.5. JULY 2014

The virus spreads to Nigeria (Kenyi 2019).

3.1.6. AUGUST 2014

According to the World Health Organization (WHO), the current outbreak can be categorized as a "public health emergency of international concern (Kenyi 2019).

3.1.7. SEPTEMBER 2014

According to the Centers for Disease Control and Prevention of the United States, by January 2015, it is anticipated that there may be as many as 1.4 million occurrences (Kelley 2020).

3.1.8. OCTOBER 2014

The United States experiences a diagnosis of the initial occurrence of Ebola, which subsequently gives rise to significant apprehension among the population (Earnshaw et al. 2019).

3.1.9. NOVEMBER 2014

According to the World Health Organization, there has been a concerning surge in the incidence of cases (Lewnard et al. 2014).

3.1.10. JANUARY 2015

According to the World Health Organization (WHO), the epidemic has reached its highest point in Liberia, but persists in its rapid expansion in the countries of Sierra Leone and Guinea (Bullard and Bullard 2018).

3.1.11. MARCH 2015

The incidence of cases is observed to exhibit a decrease, however, it is important to note that the World Health Organization cautions against interpreting this as indicative of the termination of the outbreak (Ngo et al. 2021).

3.1.12. MAY 2015

Liberia is declared Ebola-free (Organization 2015).

3.1.13. NOVEMBER 2015

Sierra Leone is declared Ebola virus free (Kamara et al. 2017).

3.1.14. JANUARY 2016

Guinea is declared Ebola virus free (Anis 2019).

3.2. COMMUNITIES AND AFFECTED COUNTRIES

The principal focus of this study is on three West African nations, namely Guinea, Liberia, and Sierra Leone. Individuals have been impacted by the Ebola virus pandemic that occurred between 2014 and 2016. Moreover, a limited number of cases were reported in Nigeria, Mali, Senegal, Spain, the United Kingdom, and the United States. The outbreak had a disproportionate impact on specific societies situated within these nations. One illustration of this phenomenon is the heightened susceptibility of healthcare providers to contracting the virus due to their close proximity to infected patients. The conventional interment procedures that necessitate intimate physical proximity with the deceased individual, have also played a role in the propagation of the virus (Wendelboe et al. 2018).

Furthermore, the virus exerts a significant influence on pre-existing vulnerable demographic groups, such as impoverished individuals, females and minors, and those facing restricted healthcare accessibility. The COVID-19 pandemic has resulted in a disruption of healthcare facilities, which has inadvertently affected individuals suffering from other illnesses, including malaria and tuberculosis (Sivanandy et al. 2022).

The epidemic resulted in significant societal and economic repercussions within the impacted nations, encompassing loss of life, diminished healthcare accessibility, fluctuating economic stability, and marginalization of combatants (Anis 2019).

3.3. THE PERSONNEL IMPACT ON HEALTHCARE SYSTEMS

The Ebola virus outbreak that occurred between 2014 and 2016 had a remarkable effect on healthcare systems and medical personnel in the countries that were severely affected (Kamorudeen et al. 2020).

3.3.1. OVERWHELMING OF HEALTHCARE SYSTEMS

The sudden and widespread occurrence of the outbreak imposed considerable strain on healthcare facilities that were already suffering from inadequate capacities. This resulted in a dearth of essential amenities such as hospital beds, medical apparatus, and qualified healthcare personnel (Otu et al. 2018).

3.3.2. INFECTION OF HEALTHCARE WORKERS

Healthcare workers are significantly more susceptible to contracting the virus owing to their proximity to infected patients. During the Ebola virus epidemic, a significant number of healthcare professionals suffered from infection and ultimately succumbed to the disease (Aruna et al. 2019).

3.3.3. DISRUPTION OF ROUTINE HEALTHCARE SERVICES

The diversion of resources towards the management of the Ebola outbreak caused disruption to typical healthcare services, resulting in a decrease in the provision of immunization services, maternal and child health services, as well as treatments for other conditions including malaria and tuberculosis (Shet et al. 2022).

3.3.4. FEAR AND STIGMATIZATION OF HEALTHCARE WORKERS

As a result of the elevated likelihood of contracting the Ebola virus, healthcare personnel were stigmatized and subjected to unfavorable treatment by their respective communities (James et al. 2019).

3.3.5. MENTAL HEALTH IMPACT ON HEALTHCARE WORKERS

During the outbreak, healthcare professionals incurred significant levels of tension, nervousness and exhaustion resulting in enduring implications for their psychological well-being (Chigwedere et al. 2021).

3.3.6. STRENGTHENING OF HEALTHCARE SYSTEMS

Despite the existing obstacles, the current outbreak affords an opportunity to nations with lofty aspirations to reinforce their healthcare infrastructure and elevate their readiness for prospective epidemics (Buseh et al. 2015).

3.4. AID EFFORTS AND INTERNATIONAL RESPONSE

The Ebola virus outbreak that occurred within the West African region between 2014 and 2016 prompted a globally-coordinated response involving a multitude of governmental bodies, non-governmental organizations and other pertinent stakeholders. The response endeavor involved a multifaceted approach that integrated the provision of fiscal assistance, deployment of healthcare personnel, the delivery of medical provisions and gear, as well as the delivery of research backing (Yerger et al. 2020).

3.5. THE IMPORTANCE OF INTERNATIONAL RESPONSES AND AID DETERMINATIONS

3.5.1. HEALTHCARE WORKERS

Numerous international organizations such as the World Health Organization and Médecins Sans Frontières dispatched medical personnel to the affected regions for the purpose of assisting in the Ebola containment efforts. The United States government dispatched military personnel to provide support for the response operations (Ahmed et al. 2022).

3.5.2. MEDICAL SUPPLIES AND EQUIPMENT

International entities and donor nations furnished medical provisions and equipment, comprising of personal protective gear, medical enclosures and laboratory supplies (Huber et al. 2018).

3.5.3. RESEARCH SUPPORT

International organizations and contributing countries have endeavored to advance research efforts pertaining to the development of vaccines and treatments for the Ebola virus (Graham 2019).

4. EBOLA VIRUS TRANSMISSION AND SYMPTOMS

4.1. TRANSMITTED EBOLA VIRUS

The transmission of the Ebola virus primarily occurs via direct contact with the biological fluids released by an individual or animal who has been infected. The viral has been detected within various biological fluids, including blood, saliva, vomit, feces, urine, sweat, semen, and breast milk, among individuals affected by the illness. The virus possesses the capacity to endure on various surfaces and materials that have come into contact with the biological secretions of an individual infected with the pathogen (de La Vega et al. 2018).

4.2. THE TRANSMISSION OF THE VIRUS CAN OCCUR THROUGH THE FOLLOWING MODALITIES

4.2.1. DIRECT CONTACT

Exposure to the various biological fluids of an individual experiencing an illness, facilitated by compromised integumentary barriers or epithelial linings, such as those found in the ocular, nasal, or oral cavities (Mehtar and Bearman 2018).

4.2.2. CONTACT WITH CONTAMINATED OBJECTS

The transmissible nature of the Ebola virus arises from its capacity to disseminate via direct contact with surfaces or substances that have been contaminated with biological fluids of an infected individual. Such substances encompass various implements, not exclusively limited to needles, syringes, and medical equipment (Hasan et al. 2019).

4.2.3. CONTACT WITH INFECTED ANIMALS

Smartly paraphrased: The Ebola virus is transmitted to humans through contact with infected animals such as fruit bats, monkeys, and apes. This event can happen when infected animals are hunted or handled with the intention of being consumed (Caron et al. 2018).

4.2.4. PERSON-TO-PERSON TRANSMISSION

The virus can be passed from one person to another through close contact, such as taking care of or living with an infected individual (Jacob et al. 2020).
It is crucial to emphasize that the Ebola virus is not transmitted through the air, consumption of contaminated food or water, and is less easily spread compared to certain other contagious diseases (Rewar and Mirdha 2014).
Preventing the spread of Ebola virus requires following the right infection control practices, such as using protective gear, sanitizing surfaces and equipment and maintaining strict hand hygiene protocols (Brown 2019).

4.3. PREVENTION AND CONTROL METHOD OF EBOLA VIRUS

The strategy for controlling and reducing the spread of Ebola involves a comprehensive approach that includes various measures and actions at both the individual and public health level (Jacob et al. 2020).

4.3.1. EDUCATION AND AWARENESS

Education campaigns present a promising opportunity to educate the general public about the transmission patterns and symptoms of Ebola virus disease (EVD), as well as emphasizing preventive measures to stop the contagion from spreading (Ajilore 2017).

4.3.2. PERSONAL PROTECTIVE EQUIPMENT

People in charge of taking care of or being in contact with infected individuals, along with healthcare staff, are strongly recommended to use personal protective gear like gloves, gowns, masks, and goggles (Phan et al. 2019).

4.3.3. INFECTION CONTROL MEASURES

By implementing rigorous hand hygiene practices and comprehensive disinfection procedures for surfaces and equipment, effective infection control measures can successfully prevent the spread of viral pathogens (Mankadi et al. 2020).

4.3.4. CONTACT TRACING

Effectively identifying and monitoring individuals who have come into contact with infected individuals can play a vital role in reducing the spread of the contagion (Sareen et al. 2018).

4.3.5. QUARANTINE AND ISOLATION

People who have acquired an infection should be isolated and given medical attention in healthcare facilities. Moreover, people who have not been protected against the mentioned infection should be separated for a specific time period in order to observe any signs of symptoms (Meyer et al. 2018).

4.3.6. SAFE BURIAL PRACTICES

Adhering to proper burial practices, such as using gloves and disinfectants when handling the bodies of infected individuals, can effectively reduce the spread of the pathogen (Boulter and Vasa 2018).

4.3.7. VACCINATION

The field of vaccination and its advancements have resulted in the creation of successful preventative strategies against Ebola virus infection that have undergone rigorous testing and confirmation. In outbreak situations, these vaccines have proven to be highly effective and have been successfully used (Venkatraman et al. 2018).

5. ECONOMIC IMPACTS OF THE EBOLA VIRUS OUTBREAK

5.1. EFFECTS ON AFFECTED COMMUNITIES

Outbreaks of Ebola can have a significant effect on the welfare of individuals affected by the disease. The stigmatization and discrimination of people who are infected or vulnerable to COVID-19 arise as a consequence of the ongoing pandemic. Social exclusion can arise from contagious illnesses, leading the afflicted individuals and their loved ones to experience discrimination and alienation. Ostracism has the potential to induce social isolation, resulting in reduced availability of resources for recuperation (Cénat et al. 2021).

5.1.1. ECONOMIC IMPACTS

People who are infected might have reduced efficiency in their work, which can cause financial issues and lower profits. Organizations might face obstacles in their activities due to concerns about the spread of disease, limited movement, and disrupted supply chains (Brooks et al. 2020).

5.1.2. MENTAL HEALTH IMPACTS

Experiencing the Ebola virus disease or living in an area affected by an epidemic can lead to feelings of fear, emotional strain, and post-traumatic stress disorder (Bah et al. 2020).

5.1.3. DISRUPTION OF HEALTH SERVICES

The spread of the disease might lead to an excessive burden on healthcare workers and facilities, leading to disturbances in regular healthcare services and causing delays in treating other health conditions (Madhav et al. 2018).

In order to accurately record the effects of the Ebola Virus Disease (EVD), it is essential to actively include the affected communities in response endeavors and promote their active participation and backing in these endeavors. Community involvement and assistance greatly contribute to reducing the adverse impacts of EVD outbreaks. The efficient management of the situation relies on key factors such as offering precise and prompt information about the outbreak, involving public figures and medical experts in the response efforts, and recognizing the economic and social consequences of the outbreak (Organization 2018).

It is essential to combat stigmatization and discrimination by accurately representing Ebola Virus Disease (EVD) in a positive and inclusive way, dispelling misconceptions and myths, and treating those affected and their families with dignity and compassion. Efforts like these play a vital role in establishing an atmosphere that promotes comprehension and facilitates successful public health interventions (James et al. 2019).

5.2. ECONOMIC IMPACT ON COUNTRIES

EVD outbreaks can have significant economic impacts on affected nations. The phenomenon can have both immediate and long-lasting effects, potentially impacting several sectors of the economy including healthcare, agriculture, transportation, and commerce (Gatiso et al. 2018).

5.2.1. HEALTHCARE COSTS

The financial ramifications connected to addressing an outbreak of Ebola Virus Disease (EVD) can have a significant impact. These expenses may include costs associated with patient healthcare, the

establishment of isolation and treatment facilities, and the preparation and mobilization of medical personnel (Huber et al. 2018).

5.2.2. DISRUPTIONS IN ECONOMIC ACTIVITY

The apprehension pertaining to the propagation of a contagious ailment can potentially result in a decrease in economic operations, such as a reduction in travel, employment hurdles, and compromised productivity owing to illness or the apprehension of infection (Dramé et al. 2021).

5.2.3. ECONOMIC LOSSES IN THE AGRICULTURAL SECTOR

The depletion of human capital as a result of illness or demise may exert a significant influence on the agricultural sector, resulting in probable food insecurity and subsequent financial repercussions (Huber et al. 2018).

5.2.4. NEGATIVE IMPACT ON SMALL AND MEDIUM-SIZED ENTERPRISES

Small and medium-sized enterprises (SMEs), which serve as the backbone of numerous economies, are susceptible to significant adverse effects resulting from an outbreak of the Ebola virus disease (EVD). These effects may manifest in the form of diminished demand for their commodities or services, disruptions in their supply chains, and constrained access to credit (Leone 2019).

5.2.5. INCREASED PUBLIC DEBT

Governments may necessitate financial borrowing to finance the response to an Ebola Virus Disease (EVD) outbreak, potentially leading to amplified public accountability (Ali et al. 2022).
It is imperative that governments and international organizations extend their support to nations affected by an EVD outbreak in order to mitigate the consequential economic burdens. The provision of assistance to persons and enterprises impacted by recent occurrences in the form of monetary aid, specialized assistance for healthcare infrastructure, and contributions towards entities and subdivisions within the economic sector may be encompassed within the scope of actions undertaken (Shin et al. 2018).

5.3. IMPACT ON GLOBAL HEALTH

The emergence of outbreaks of Ebola virus disease (EVD) has profound implications for global health security, emphasizing the need for meticulous preparation and intervention strategies (Keita et al. 2023).

5.3.1. HIGHLIGHTING THE IMPORTANCE OF PREPAREDNESS

The occurrence of Ebola virus disease (EVD) outbreaks has underscored the significance of ensuring well-preparedness measures for infectious disease outbreaks, not only in the countries affected but also on a global scale. The necessity for robust healthcare systems, proficient inquiry, and prompt reaction capabilities has been accentuated by them (Kodish et al. 2019).

5.3.2. TESTING GLOBAL HEALTH FRAMEWORKS

The Ebola Virus Disease epidemics have validated the operationalization of international health frameworks, including the International Health Regulations and the Global Health Security Agenda. The

authors have noted gaps in preparedness and response, along with the imperative for enhanced coordination and cooperation among national governments and international organizations (Sell 2020).

5.3.3. MOBILIZING INTERNATIONAL RESOURCES

The occurrences of Ebola Virus Disease (EVD) outbreaks have engendered consequential financial and logistical backing from international entities to countries afflicted by this affliction. These advancements have also resulted in amplified cost savings in the domain of research and development pertinent to identifying, formulating and treating EVD and various other communicable ailments (Ali et al. 2022).

5.3.4. ADDRESSING GLOBAL HEALTH INEQUITIES

The emergence of Ebola Virus Disease outbreaks has brought to light the prevalent disparities in global health care, underscoring the necessity for increased commitment towards healthcare systems and infrastructure in low- and middle-income countries. Additionally, there is a pressing need to address the underlying social determinants of health (Rugarabamu et al. 2020).

5.3.5. RAISING AWARENESS ABOUT EMERGING INFECTIOUS DISEASES

The occurrence of Ebola Virus Disease outbreaks has augmented the awareness of the general public regarding the emergence of infectious diseases and their potential consequences on the safety of global health. This has subsequently resulted in a surge of encouragement and resources for global health initiatives (Kraemer et al. 2019).
Outbreaks of Ebola Virus Disease have exerted noteworthy effects on the security and readiness of global health, thereby emphasizing the necessity for sustained investments in health systems and infrastructure, as well as enhanced collaboration and coordination among nations and international organizations (Alonge et al. 2019).

6. CONCLUSION

Ebola outbreaks need robust healthcare systems and swift action to protection global health. The International Health Regulations and GHSA frameworks are under test. This analysis focuses on epidemic readiness and cooperation. This helps nations with money and teaching. It boosts funding for EVD and other contagious diseases research. Ebola outbreaks reveal healthcare inequality in poor nations. Awareness boosts global healthcare endeavors. Ebola outbreaks focus on global health, reducing inequalities, and fostering collaboration. Prepare for future diseases. Efficient resource distribution and capacity planning are crucial in disease outbreak prevention. Improve healthcare systems, workforce, medication access, technology, and disease prevention response capabilities. Disease management relies on politics, finance, and tech. Global collaboration is crucial for preventing outbreaks. Sharing info, expertise, resources, and healthcare aid is vital to prevent disease outbreaks. This includes diagnosis, vaccines, treatment, and social health. Global health security requires collaboration and expertise utilization. Public support and political assurance are vital for promoting enlightenment.

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Vaccine Strategies to Combat COVID-19 Variants

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ABSTRACT

The appearance of SARS-CoV-2 mutations has presented obstacles to the efficacy of current COVID-19 vaccines. This summary investigates various vaccine approaches developed to tackle these mutations and improve overall management of the pandemic. Additional doses of existing vaccines have been administered to strengthen diminishing immunity and prolong protection. Tailored vaccines that target specific viral strains provide a customized solution to ever-changing dangers. Multi-antigen vaccines are designed to enhance immunity against a range of variants by including multiple antigens. The flexibility of mRNA technology enables quick adjustments to address new variants, as demonstrated by Pfizer-BioNTech and Moderna vaccines. Continuous monitoring and international cooperation are crucial in keeping track of the changes in variants and speeding up the development of vaccines. The focus is on investigating T-cell reactions and developing universal vaccines that offer wider immunity against various coronaviruses. It is essential to distribute vaccines fairly around the world in order to stop the spread of variants and prevent the emergence of new strains. It is essential to continue implementing vaccination alongside current public health practices such as wearing masks and practicing social distancing in order to reduce the spread of the virus, particularly in the presence of more contagious variants. This summary highlights the importance of flexibility, cooperation, and continuous changes in vaccine approaches to effectively fight against the changing nature of COVID-19 variants.

Keyword: COVID-19 Variants; Vaccine Strategies; Booster Shots; mRNA Technology; Global Collaboration

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1. INTRODUCTION

The SARS-CoV-2 virus-induced COVID-19 pandemic has significantly influenced public health on a global scale, impacting economies and social systems. Since the onset of the global pandemic, the COVID-19 virus has undergone various genetic alterations, leading to the emergence of novel strains. A subset of these mutations has been linked to augmented transmission rates, heightened virulence, and decreased effectiveness of prophylactic vaccines (Woods et al. 2020).

The appearance of novel variants has prompted apprehension regarding the potency of current vaccines against these variants in contemporary discourse. Consequently, it behooves us to advance proficient immunizations capable of confronting these mutated strains and furnishing extended safeguarding against the pathogen (Kumar et al. 2021).

At present, a number of COVID-19 vaccines have been granted authorization for emergency usage, comprising preparations formulated by Pfizer-BioNTech, Moderna, Johnson & Johnson, and AstraZeneca. The vaccines under consideration have demonstrated considerable efficacy in mitigating the onset of COVID-19 infection, as well as significantly reducing the incidence of severe disease caused by the primary form of the virus. The emergence of novel strains, including the Delta and Omicron variants, has raised apprehensions regarding the effectiveness of existing vaccines in providing sufficient immunity against these variants (Fortner and Schumacher 2021).

1.1. THE EMERGENCE OF NEW VARIANTS DURING THE COVID-19 PANDEMIC

The global outbreak of COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in December 2019 in Wuhan, China, and has subsequently disseminated widely, leading to widespread infections and fatalities across various regions around the world. The mode of transmission of the virus primarily involves respiratory droplets and proximity to individuals who are infected (Lai et al 2020).

The RNA virus known as SARS-CoV-2 undergoes frequent mutations, leading to the emergence of newly evolved variants. The Alpha variant, denoted as the primary major divergence, was initially detected in the United Kingdom in December 2020 and was found to be linked with a heightened propensity for transmission. Subsequent to this development, the Beta and Gamma variants emerged, initially discovered in South Africa and Brazil, respectively. These variants displayed a correlation with heightened transmissibility and diminished effectiveness of vaccines (Rahimi and Abadi, 2022).

1.2. EFFECTIVE VACCINES TO COMBAT VARIANTS

The emergence of novel strains of SARS-CoV-2, the causative agent of COVID-19, has underscored the significance of formulating efficacious vaccines to counter these variants and ameliorate the repercussions of the pandemic (Al Saba et al. 2021).

The utilization of vaccines plays a crucial role in the prevention of the dissemination of contagious illnesses, and their effectiveness in combating COVID-19 has been attested in various clinical studies. The appearance of novel variants possessing distinct genetic mutations, especially in the spike protein of the viral strain, has instigated anxieties regarding the efficacy of extant vaccines (Wang et al. 2023).

This method helps reduce any possible differences in how well the vaccine works and ensures that protection lasts for a long time. Scientists are currently researching vaccines that can target multiple variants or strains at the same time. These vaccines can protect against a wider variety of the virus, making it less likely for the virus to escape the vaccine. Some vaccines, like the Johnson and Johnson vaccine, have shown to protect against different versions of a virus. It is very important to keep

watching and studying the virus and its different types. This helps us quickly find new changes and act fast to make and spread vaccines. It is very important to make sure that vaccines are given out fairly and equally all around the world. The certain mutations, namely the Beta and Delta variants, exhibit diminished receptivity to the neutralizing impact exerted by antibodies produced through existing vaccines, which consequently precipitates a decline in vaccine potency. The aforementioned highlights the criticality of persistent exploration and progression of vaccines that possess the capability to provide extensive safeguarding against various strains (Chen and Lu 2021).

2. CURRENT SITUATION

As of March 2023, several countries worldwide have authorized the usage of several COVID-19 vaccines either for emergency utilization or have granted full approval. Through analysis of clinical trials, evidence confirms the safety and efficacy of said vaccines, and furthermore, they have played an indispensable role in mitigating the transmission of COVID-19. The number of people getting vaccines around the world is very important in preventing new versions of diseases from spreading. Scientists are currently doing research to develop vaccines that specifically target certain worrying variants of the virus. These vaccines can protect us from specific strains of diseases that cause problems. To effectively fight against the different types of COVID-19, we need a well-rounded plan. It is very important to regularly update vaccines, have booster campaigns, and do research for new vaccines. However, it is important to make sure that vaccines are distributed fairly around the world and to remain watchful with surveillance as important strategies to lessen the impact created by these new variations. By using these strategies in a clever way, we can improve safety measures for the public's health and make progress in getting rid of the COVID-19 outbreak (De Francia et al. 2023). The vaccines that are currently available are enlisted in Table 1.

Table 1: Currently available COVID-19 vaccines

Sr. No	Vaccine	References
1	Johnson & Johnson COVID-19 Vaccine	(Livingston et al. 2021)
2	Moderna COVID-19 Vaccine	(Meo et al. 2021)
3	Sinovac COVID-19 Vaccine	(Chuaychoosakoon et al. 2021)
4	AstraZeneca COVID-19 Vaccine	(Knoll and Wonodi 2021)
5	Sinopharm COVID-19 Vaccine	(Saeed et al. 2021)
6	Pfizer-Bio N Tech COVID-19 Vaccine	(King et al. 2022)

The vaccines mentioned employ various mechanisms to provoke an immune response against the SARS-CoV-2 virus responsible for COVID-19. Numerous vaccine formulations incorporate diverse technological modes of action, with specific examples being Pfizer-BioNTech and Moderna's utilization of messenger RNA (mRNA) technology, and Johnson & Johnson and AstraZeneca's incorporation of viral vectors (Azkur et al. 2020).
Despite the high efficacy rates demonstrated in clinical trials, the efficacy of currently available vaccines has been called into question due to the emergence of novel variants of the SARS-CoV-2 virus. Concurrently, current research endeavors are examining the potential influence of variants on the effectiveness of vaccines. As a result, ongoing attempts are being made to formulate novel vaccines that can confer enhanced safeguarding against newly emerging strains (Hodgson et al. 2021).

2.1. DIFFERENT TYPES OF COVID-19 VACCINES

There exist numerous categories of COVID-19 vaccinations at present, each employing a unique approach to evoke an immunogenic response against the pathogenic SARS-CoV-2 virus. An overview of the various categories of vaccines (Han et al. 2021).

2.2. mRNA VACCINES of COVID-19

The vaccines, namely Pfizer-BioNTech and Moderna vaccines, employ messenger RNA (mRNA) as a medium to transmit directives to the cells present in the body to generate a fragment of the spike protein that is present on the exterior of the SARS-CoV-2 virus. This elicits an immunological reaction that confers protection against the virus (Noor 2021).

2.3. VIRAL VECTOR VACCINES OF COVID-19

The vaccines, namely the Johnson & Johnson and AstraZeneca vaccines, utilize a non-pathogenic virus (such as adenovirus) as a vector for the introduction of SARS-CoV-2 genetic material into host cells. Furthermore, this event elicits an immunological response that aids in shielding against viral infection (Negahdaripour et al. 2021).

2.4. PROTEIN SUBUNIT VACCINES OF COVID-19

The aforementioned vaccines utilize a fragment of the SARS-CoV-2 virus, specifically the spike protein, to trigger an immunological reaction. Novavax has successfully developed a vaccine comprising protein subunits, which has been granted authorization for emergency utilization in a number of countries (García-Arriaza et al. 2021).

2.5. INACTIVATED VIRUS VACCINES OF COVID-19

Several vaccines, namely the Sinovac and Sinopharm vaccines, utilize a weakened or inactivated iteration of the SARS-CoV-2 virus to elicit a response from the immune system. This process facilitates the entrenchment of the immune system to the virus without inducing pathogenic effects (Ndwandwe and Wiysonge 2021).

2.6. DNA VACCINES OF COVID-19

The vaccines under consideration utilize DNA as the mode of conveyance of genetic instructions to host cells, stimulating them to synthesize a segment of the spike protein that is present on the exterior of the SARS-CoV-2 pathogen. The aforementioned phenomenon elicits an immune response that confers protection against the viral agent. The INOVIO COVID-19 vaccine, a DNA vaccine, is presently undergoing clinical trials (Silveira et al. 2021).

2.7. LIMITATIONS AND CHALLENGES OF CURRENT VACCINE'S NEW VARIANTS

Notwithstanding the elevated efficacy rates of the presently authorized COVID-19 vaccines, the appearance of novel variants of the virus brings forth a number of challenges and constraints (Schlagenhauf et al. 2021).

2.8. EFFICACY CHALLENGES AGAINST CERTAIN VARIANTS

Certain variants, including the B.1.351 variant which was initially detected in South Africa, harbor mutations in the spike protein that could potentially impede the effectiveness of existing vaccines. Empirical analyses conducted on clinical trials have demonstrated that the Pfizer-BioNTech and Moderna

vaccines exhibit a decreased effectiveness in combating the B.1.351 variant, whereas the Johnson & Johnson vaccine manifests a diminished efficacy against both the B.1.351 and P.1 variants (Bian et al. 2021).

2.9. BOOSTER SHOTS FOR NEED

The diminished effectiveness of extant vaccines against certain variants has spurred debates on the necessity for supplementary doses or revised vaccines to confer immunity against emergent strains (Burki 2021).

2.10. VACCINE HESITANCY OF COVID-19

Despite the established safety and proven efficacy of currently authorized vaccinations, the phenomenon of vaccine hesitancy continues to present a substantial obstacle in the pursuit of herd immunity and effective management of a viral transmission. This phenomenon could potentially be exacerbated due to apprehensions pertaining to the effectiveness of vaccines against evolving variants (Kates et al. 2021).

2.11. LIMITED ACCESS OF GLOBAL VACCINES

The global disparity in the distribution of vaccines has raised apprehensions regarding the emergence of novel variants in regions experiencing restricted accessibility to vaccines. The advent of novel genomic variants in regions with elevated rates of transmission is likely to elevate the probability of additional variations that could exhibit greater resistance to current immunization regimens (Sparke and Levy 2022).

3. DEVELOPING STRATEGIES FOR COVID-19 VARIANT VACCINES

3.1. CLINICAL TRIALS FOR VARIANT VACCINES

There are multiple clinical trials in progress to examine both the safety and effectiveness of variant vaccines in preventing COVID-19. In February 2021, Pfizer-BioNTech commenced clinical trials aimed at evaluating the effectiveness of its mRNA vaccine against the B.1.351 variant, initially detected in South Africa. The investigation is currently being undertaken in South Africa, a region where the variant in question has a high prevalence. New information about mRNA vaccines shows that they can change and work against new virus types, like the Pfizer and Moderna vaccines have shown. These vaccines can quickly change to match the genetic makeup of new variants. This method allows us to quickly make and distribute improved vaccines to keep us safe. Many countries are starting campaigns to give people additional shots to boost their immunity. Getting booster shots of the current vaccines helps give extra protection and a longer-lasting immune response, especially against new variants (Deplanque and Launay, 2021).

3.2. MODERNA VACCINE OF COVID-19

In March of 2021, an announcement was made by Moderna regarding the commencement of clinical trials aimed at evaluating the effectiveness of its mRNA vaccine against the B.1.351 variant. The company is currently conducting trials for both a supplementary dosage of its primary vaccine and a vaccine specific to a variant (Meo et al. 2021).

3.3. JOHNSON AND JOHNSON VACCINE FOR COVID-19

In the month of April in the year 2021, Johnson & Johnson disclosed their commencement of clinical trials for the purpose of assessing the effectiveness of their viral vector vaccine against the B.1.351 variant. The investigation is being undertaken in the nation of South Africa (Livingston et al. 2021).

3.4. NOVAVAX VACCINE OF COVID-19

In January 2021, Novavax unveiled its intention to develop a COVID-19 vaccine customized to combat the B.1.351 variant. It is anticipated by the company that the commencement of clinical trials will take place in the second quarter of the year 2021 (Mahase 2021).

3.5. VALNEVA VACCINE OF COVID-19

Valneva declared in the month of February in the year 2021 that it had commenced clinical trials with the aim to assess the effectiveness of its inactivated virus vaccine against the B.1.351 variant (Mahase 2022).

3.6. BHARAT BIOTECH VACCINE FOR COVID-19

In April of 2021, Bharat Biotech declared the commencement of clinical trials designed to evaluate the efficacy of its inactivated virus vaccine against the B.1.617 variant, which was initially detected in India (Kumar et al. 2021).

4. EFFICACY OF COVID-19 VACCINES VARIANT

4.1. PRE-CLINICAL AND CLINICAL TRIALS EVIDENCE OF THE EFFICACY OF VARIANT VACCINES AGAINST DIFFERENT STRAINS

As of the point of data limitation cutoff in September 2021, insufficient data were accessible regarding the effectiveness of variant vaccines in combating various strains of SARS-CoV-2, including the Delta and Omicron variants. Subsequently, a multitude of studies have been made public which offer valuable insights pertaining to the effectiveness of diverse vaccine variants against these particular strains (Bhattacharya et al. 2022).

4.2. DELTA VARIANT VACCINE

The September 2021 publication in The New England Journal of Medicine explored and analyzed the efficacy of the Pfizer-BioNTech and AstraZeneca vaccine formulations in combatting the Delta variant. Results of the investigation suggest that after administration of the second dose, the Pfizer-BioNTech vaccine demonstrated an efficacy of 93.7% in preventing symptomatic disease, whereas the AstraZeneca vaccine exhibited an efficacy of 74.5%. A recent research article published in The Lancet in September 2021 detailed the efficacy of the Moderna vaccine in combating the Delta variant. In this study, it was determined that the vaccination exhibited a 76% efficacy in mitigating symptomatic infections, as well as an 86% efficacy in reducing the incidence of hospitalization (Bian et al. 2021).

4.3. OMICRON VARIANT VACCINE

A research article published in the highly esteemed medical journal The Lancet during the month of January in the year 2022 expounded on the efficacy of the Pfizer-BioNTech vaccine in combating the Omicron variant. The research demonstrated that the efficacy of the vaccine was 36% for symptomatic infection, while exhibiting a 75% efficacy rate in curtailing severe disease, hospitalization, and mortality. A recent research article published in The New England Journal of Medicine in January of 2022 investigated the efficacy of the Moderna vaccine against the Omicron variant. According to the study, the efficacy of the vaccine revealed a 39% reduction in symptomatic infection, while demonstrating a 58% decrease in hospitalization rates (Collie et al. 2022).

4.4. COMPARISON OF VARIANT VACCINES WITH THE EFFICACY OF ORIGINAL COVID-19 VACCINE

The existing body of literature is scarce in regard to a comprehensive analysis of the relative effectiveness of variant-specific vaccines as compared to the original vaccines for COVID-19. Numerous investigations have postulated the efficacy of the initial vaccines regarding diverse variants, specifically the Delta and Omicron variants (Lopez Bernal et al. 2021).

4.5. VACCINE STRATEGY OF COVID-19

The emergence of novel strains of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) underscores the imperative for an enduring system of observance, oversight, and appraisal of the potency and efficiency of vaccines. According to the available evidence, the COVID-19 vaccines that are currently authorized have been found to offer differing levels of safeguarding against distinctive variants of the virus. It has been observed that certain vaccines exhibit diminished efficacy against certain variants in comparison to others. The aforementioned statement highlights the significance of producing vaccines tailored to target variant-specific mutations. This would consequently enhance the efficacy of the vaccines in conferring optimal protection against these novel strains (Jeyanathan et al. 2020).

5. COVID-19 VARIANT VACCINES SAFETY

5.1. SAFETY DATA FOR VARIANT VACCINES

Currently, a dearth of safety information exists with regard to variant-specific COVID-19 vaccines. Notwithstanding, the safety characteristics of the original COVID-19 vaccines could be deemed as a reliable indication of the safety standards of variant vaccines, attributable to the comparable nature of the manufacturing process and platform technology (Wu et al. 2021).
Clinical trials investigating variant vaccines have ascertained safety profiles that resemble those of the initial vaccines, with the occurrence of adverse events being mostly mild to moderate in nature and of short duration. In a clinical trial encompassing both phase 2 and phase 3 of development, the mRNA-1273.351 variant vaccine produced by Moderna was evaluated. It was reported that the safety profile of this vaccine was akin to that of the original mRNA-1273 vaccine, with predominantly mild to moderate adverse events being observed. In a Phase 2/3 clinical trial of the Pfizer-BioNTech BNT162b2.351 variant vaccine, it was observed that the safety profile was akin to that of the original BNT162b2 vaccine. The adverse events reported were mostly mild to moderate in nature (Dai et al. 2022).

5.2. POSSIBLE CONTINUING SAFETY CONCERNS

Monitoring the long-term safety of variant vaccines is of utmost importance as potential safety concerns may emerge over an extended period. Presently, no substantial indications exist to suggest the existence of any noteworthy safety uncertainties concerning COVID-19 vaccinations, including those specific to variant strains (Hernández et al. 2021).
The extant safety data gathered from clinical trials and post-authorization surveillance have demonstrated that the vaccines exhibit a generally acceptable safety profile and tolerability. The vast majority of recorded adverse events tend to exhibit mild to moderate characteristics and typically remit within a few days, with the occurrence of severe adverse events being infrequent. The advantages of receiving the COVID-19 vaccine with regards to mitigating severe illness, hospitalization, and mortality substantially surpass the potential hazards associated with adverse impacts (Pilkington et al. 2020).

6. COVID-19 VARIANT VACCINES ARRANGEMENT AND APPLICATION

6.1. CONCERNS FOR VACCINE PRODUCTION

The successful and efficient deployment and implementation of vaccines are paramount in controlling and mitigating the widespread impact of the COVID-19 pandemic. Several factors must be taken into account when considering the deployment and implementation of vaccines (Khoo et al. 2020).

6.2. DISTRIBUTION OF VACCINE

The equitable allocation of vaccines holds the utmost importance to ensure universal accessibility, irrespective of an individual's socioeconomic stratum or geographical location. Efficient and equitable distribution of vaccines necessitates a synergized collaboration among governmental bodies, international organizations, and vaccine producers (De Boeck et al. 2020).

6.3. PRIORITIZATION OF VACCINE VARIANT

The prioritization of specific demographic segments is imperative to render optimal public health benefits, as a result of scarce vaccine supplies. One notable approach adopted by several nations is the prioritization of healthcare practitioners, aged persons, and individuals with pre-existing medical conditions, as they are inclined to greater risks of severe morbidity and mortality (Taboe et al. 2022).

6.4. PUBLIC DEPENDENCE AND VACCINE ACCEPTANCE

The indispensability of public confidence and vaccine acceptance cannot be overstated in the effective deployment and implementation of vaccinations. It is imperative to convey precise data concerning the safety and effectiveness of vaccines, rectify any doubts and fallacies, and collaborate with societal groups to establish faith (Sallam 2021).

6.5. LOGISTICS AND SUBSTRUCTURE OF VACCINE

It is crucial to guarantee the presence of appropriate infrastructure and logistics to support vaccine storage, transportation, and administration. The immunization process entails a suite of essential components such as reliable cold-chain storage, efficient vaccine tracking systems, and adequately trained personnel proficient in administering vaccines (Szymkuc et al. 2020).

6.6. POST-VACCINATION INVESTIGATION

The establishment of post-vaccination surveillance systems is deemed crucial in monitoring the safety and efficacy of vaccines throughout an extended period. The aforementioned systems possess the capability to discern and pinpoint any unfavorable events that might transpire subsequent to immunization and aid in disseminating vital information that leads to the implementation of required adjustments in vaccination policies (Bamouh et al. 2021).

6.7. GLOBAL COOPERATION FOR THE PRODUCTION OF VARIANT VACCINES

The creation and implementation of diverse vaccines mandate international collaboration and synchronization to establish impartial availability of vaccines and avert transboundary transmission of the virus. The World Health Organization has underscored the importance of a well-coordinated worldwide initiative in response to the COVID-19 outbreak, with a focus on the creation and dissemination of vaccines, as well as the exchange of information and resources among nations (Bajaj et al. 2022).

A critical aspect of promoting worldwide collaboration in the advancement of alternate vaccines is the dissemination of knowledge and technology across nations. Possible academic rewrite: Collaboration among stakeholders in the biomedical industry may encompass diverse activities, ranging from disclosing data derived from clinical trials and exchanging knowledge on manufacturing technology, to furnishing funding resources to facilitate the research and development of alternate vaccines. The World Health Organization (WHO) has established the COVID-19 Technology Access Pool (C-TAP) with the aim of promoting equitable access to intellectual property and technology associated with COVID-19 vaccines and treatments (Pilkington et al. 2022).

6.8. FUTURE GUIDELINESFOR RESEARCH IN THE FIELD OF COVID-19 VARIANT VACCINES

Potential avenues for further investigation and continuing endeavors within the sphere of COVID-19 variant immunizations encompass (Jain et al. 2021).

6.9. PRODUCTION OF MULTIVALENT VACCINES

There is ongoing development of multivalent vaccines aimed at affording protection against various variants of SARS-CoV-2. Recent studies indicate that these vaccines possess the potential to confer wider immunity and exhibit enhanced efficacy against newly emerged variants (Humpierre et al. 2020).

6.10. PLATFORMS FOR VACCINE DELIVERY

Scientists are presently investigating novel avenues for vaccine administration, such as the utilization of self-amplifying RNA vaccines, in order to enhance the potency and longevity of vaccination procedures, specifically in relation to variant strains (Lee at al. 2022).

6.11. ASSESSMENT OF BOOSTER DOSES

Ongoing studies are being conducted to assess the safety and effectiveness of administering booster doses of COVID-19 vaccines, with a particular focus on those designed to target variants of concern (Achrekar et al. 2022).

6.12. OBSERVING OF VACCINE EFFICIENCY

Ongoing studies are being conducted to assess the safety and effectiveness of administering booster doses of COVID-19 vaccines, with a particular focus on those designed to target variants of concern (Walsh et al. 2023).

6.13. ASSOCIATION AMONG INVESTORS

The imperative for the effective development and global dissemination of variant vaccines demands a collaborative effort among a diverse array of stakeholders, including governments, industry, and international organizations (Adil et al. 2022).

7. CONCLUSION

An overview of COVID-19 vaccine status viral variants and variant vaccine development was discussed. New COVID-19 variants concern vaccine effectiveness. Available vaccines vary in type: mRNA, viral vector, and protein subunit. Despite their demonstrated effectiveness and safety, COVID-19 vaccines may be limited when faced with new variants. Advances in vaccine development have led to new technologies. Clinical trials assess vaccine efficacy and safety against Delta and Omicron variants. Deployment involves disseminating, prioritizing, establishing trust, and gaining widespread acceptance. Variant vaccine development requires global collaboration. Research guides strategy. COVID-19 pandemic control requires effective vaccines. New variants and fair vaccine distribution require more research and global cooperation. New SARS-CoV-2 strains emphasize COVID-19 vaccine research. Variant vaccines must stop the pandemic and prevent future outbreaks. Adaptable methods are needed to improve vaccines and manage variants.Genomic sequencing and surveillance are essential for identifying new COVID-19 variants and monitoring vaccine efficacy. Variant vaccines' effectiveness affects distribution, prioritization, and acceptance. Age, occupation, and health determine health priorities. Acceptance mitigates viruses. COVID-19 emphasizes vaccine research and public health policies to prevent outbreaks.

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Transmission Dynamics of Rabies Virus

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ABSTRACT

Rabies, a viral disease that can be transmitted between animals and humans, has a complex transmission pattern involving its natural hosts, carriers, and vulnerable individuals. The rabies virus, part of the Lyssavirus genus, is mainly found in the nerve tissue of mammals, such as bats, raccoons, skunks, foxes, and mongooses, who carry the virus without showing symptoms and act as reservoir hosts. The transmission process starts with an infected animal biting a host, allowing the virus, which is present in saliva, to enter the body and attack muscle cells near the entry point. After entering the body, the virus travels through peripheral nerves using retrograde axonal transport to reach the central nervous system (CNS), which includes the spinal cord and brain. The centrifugal expansion in the nervous system causes quick duplication and resulting inflammation, resulting in distinct clinical signs. As the virus progresses, it invades the salivary glands, increasing its presence in saliva and making the infected person highly contagious. The virus causes changes in behavior, like increased aggression and restlessness, which make it more likely for aggressive interactions to occur and lead to the virus spreading through bites. While the virus is kept in check in wildlife by natural reservoirs, there is a significant threat of transmission between different species. Domestic animals and humans are at risk of contracting rabies from bites or saliva of infected wild animals. Successful prevention relies on the use of vaccines, which are a key component of thorough initiatives that aim to protect both domestic and wild animals. Post-exposure prophylaxis (PEP) is crucial for reducing the impact of potential exposure by using a series of rabies vaccinations. Public health efforts and educational programs are essential for increasing understanding and encouraging responsible pet ownership, which ultimately helps control and prevent the spread of this deadly virus. It is essential to have a deep understanding of the complex transmission patterns of the rabies virus in order to take proactive steps to protect both humans and animals.

Keyword: Rabies virus; Transmission dynamics; Zoonotic disease; Centripetal spread; Post-exposure prophylaxis

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1. INTRODUCTION

Rabies is a viral zoonotic disease that affects the central nervous system. It can be prevented by proper vaccination. Rabies virus is prevalent in more than 150 countries and territories. Every year it causes millions of deaths across the world mostly in Asian and African regions. Mostly it harms the children below 15 years which is 40% of the total cases. The foremost cause of human deaths by rabies virus are stray dogs that contribute about 99% of total rabies spreads in individuals. Rabies virus can also be found in desolate faunae like flaps, raccoons, pigs, and bamboozles (Chhabra and Ichhpujani 2003).

Rabies affects practically all homothermic animals and people and results in severe central nervous system damage (Paweska et al. 2006). About 99% of the human cases in rabies occur in underdeveloped nations in Asia and Africa (Knobel et al. 2005). Several hundred people died from rabies each year between 2015 and 2018 in China, making it a significant public health concern. Rabid dogs are responsible for more than 95% of human rabies cases (Meng et al. 2011).

When clinical signs start, rabies is always deadly in addition to uncalculated psychological trauma for individuals and communities. Worldwide, rabies is thought to cost $8.6 billion annually. Except for Antarctica, all continents have rabies, with Asia and Africa accounting for more than 95% of all fatalities. However, rabies cases are infrequently recorded, and the registered numbers are far lower than the burden estimate. Both domestic and wild animals can are affected by rabies virus (Monroe et al. 2016).

The estimated annual death toll from canine rabies is 59,000 persons globally. Asia is undoubtedly grappling with a significant rabies problem since there are more rabies-related fatalities among humans there than everywhere else in the globe. The Americas account for fewer than 0.05% of all human rabies deaths, with the bulk of rabies-related fatalities occurring in Asia (59.6%), followed by Africa (36.4%). Additionally, India is responsible for 35% of all human rabies fatalities worldwide. The estimated annual cost of postexposure prophylaxis (PEP) for canine rabies in Asia is up to US$1.5 billion and 2.2 million disability-adjusted life years (Organization 2018).

Rabies is completely avoidable in both animals and people with immunization. WHO has suggested pre-exposure prophylaxis for people of those regions where the risk of exposure to rabies virus is high and more frequent (for example, veterinarians and animal handlers). If a wild or rabid animal bite a person, post-exposure prophylaxis (PEP) is acclaimed for the treatment measures as recommended by WHO which includes rapid wound care, immunization and administration of a single dose of Human rabies immunoglobulin (HRIG) and rabies vaccine and then a single dose of vaccine again on 3rd, 7th and 14th days respectively. Nonetheless, canine vaccination is often regarded as the supreme gainful method of averting rabies in people (Ganasegeran and Abdulrahman 2021).

The average cost of rabies post-exposure prophylaxis (PEP) (travel expenses and income loss) is presently estimated to be US$ 108. Managing a rabies exposure can be a crippling financial burden for afflicted households, whose typical daily income may be as low as US$ 1-2 per person. Following a probable rabies exposure, a person should seek immediate medical assistance since the virus can cause damage to the brain that ultimately results in death. By vaccinating pets, staying away from animals, and getting medical help right away after suspected exposures before symptoms occur, rabies can be prevented. A One Health strategy ensures that many sectors and local communities are involved in raising awareness and conducting mass dog vaccination programs (Hemachudha et al. 2013).

2. HOW IS RABIES TRANSMITTED?

Rabies virus can be directly transmitted from the saliva or brain/nervous system tissue of a diseased animal (for example, through injured skin or mucous membranes in the eyes, nose, or mouth). The biting of a rabid animal is the most common way for rabies spread. Scratches, abrasions or open wounds exposed to saliva or other potentially infectious material from a rabid animal can result in non-bite exposure to rabies. Other interactions such as petting a rabid animal or touching its blood, urine or faeces, do not increase the chance of contracting the disease and are not regarded as rabies exposure (Aghahowa and Ogbevoen 2010).

Although transmission is typically local (within one km), rabies can produce fitful and unpredictable behavior with diseased dogs which are capable of running more than 15 kilometers, much beyond the average range of healthiest dogs. As a result, secondary cases are more prevalent due to disease-mediated invasions disseminated from neighboring populations (e.g., nearby human towns within rabid dog movement range). Furthermore, long-distance human-mediated intrusions of incubating dogs can result in spreading of epidemic from previously disconnected communities (Fooks et al. 2014).

According to extensive study on dogs, cats, and ferrets it has been noted that rabies virus may be identified in the saliva of infected animals several days before infection reveals. Before and after the onset of clinical symptoms, viral expulsion might be erratic and the quantity of virus ejected may change significantly over time. The length of time between exposure and the onset of sickness can vary widely depending on a number of circumstances, including the environment in which the exposure occurred, the kind of rabies virus that was present and any immunity present in the affected animal or person (CDC 2017).

3. LIFE CYCLE OF THE LYSSAVIRUS

Non-segmented negative-strand RNA viruses known as lyssaviruses have small genomes of 11–12 kilobases that only include five genes, which are encoded in the conserved gene order of the nucleoprotein (N), phosphoprotein (P), matrix proteins (M), glycoprotein (G) and large polymerase protein (L). A maximum divergence of 60% may be found across the lyssavirus genome, suggesting significant nucleotide conservation throughout (Finke and Conzelmann 2005).

The essential replication process of all the non-segmented negative strand viruses follows a similar theme. Gene sizes and intergenic regions are highly conserved. Completely encapsulated RNA fragments known as genome RNAs are protected from the hazardous intracellular environment by N-protein encapsulation. Messenger RNAs are created by a transcriptase complex that includes the N, P and L proteins along with the RNA. It uses the negative-strand RNA genomes as a template. The simplest viral replicative unit is the ribonucleoprotein complex (RNP), which is a complex of RNA encased in N and linked to P and L proteins (Rupprecht et al. 2002).

Viral proteins are produced via viral mRNA transcription, which is followed by mRNA translation on ribosomes in the host cell. The polymerase produces full-length positive-sense genome strands of RNA that are co-transcriptionally encapsulated as a result of the increase in viral proteins in the cell, which contributes to the change from transcriptive to replicative activity. Following their formation, these replicative intermediates act as templates for the development of nascent genomic negative-sense RNA, which is encapsulated and released from the cell as nascent infectious virions (Miranda and Miranda 2020).

The neurotropic virus prototype known as the rabies virus infects both people and animals and can be fatal. This virus attacks peripheral body parts of the hosts, enters in motor nerves or sensory neurons

and then moves to the central nervous system (CNS) by axonal transference. Later, critical exodus ports like the salivary glands experience centrifugal supper. The behavioral abnormalities caused by the CNS illness enable transmission to additional hosts. The successful completion of the viral infectious cycle is dependent on many virus activities and specific virus proteins. Rabies virus appears to be very crucial for sneaking inside the host without creating obvious host reactions and preservation (Ugolini and Hemachudha 2018).

The advent of reverse genetic technologies for producing engineered recombinant RV has enabled tools for a more complete examination of viral activities relevant to normal RV pathogenesis. Tracking of live fluorescent RV, for example, is expanding the possibilities for determining RV pathogenicity variables. Many elements of RV molecular biology are important to pathogenesis such as precise regulation of RV transcription, gene expression and replication (Finke and Conzelmann 2005).

4. TRANSMISSION DYNAMICS

The transmission dynamics of rabies involve the spread of the virus within populations of animals and in some cases from animals to humans. Severity of disease is dependent on different aspects like species involved, geographical locality, and control measures in place (Yousaf et al. 2012).

Here are some key aspects of the transmission dynamics of rabies:

4.1. RESERVOIR/HOSTS

Certain animal species, known as reservoir hosts are the main reason to affect the spread and transmission of the virus in the certain geographic region. Domestic dogs, for example, are the principal reservoir host for rabies in many regions of the world and contribute to the transmission cycle (Coetzer et al. 2019).

4.2. WILDLIFE RESERVOIRS

Wildlife such as bats, raccoons, foxes and skunks act as reservoir hosts for rabies in many areas. Transmission among wildlife populations can happen through bites but it can also happen through other means, such as contact with infected surfaces or inhalation of aerosolized virus in bat roosts (Lembo et al. 2008).

4.3. TRANSMISSION IN ANIMALS

Rabies is typically transmitted to animals through the bite of an infected animal. The virus can be transferred if a rabies infested animal bites another vulnerable animal. This transmission can occur within a species or across species (Lushasi et al., 2021).

4.4. HUMAN TRANSMISSION

Although it is uncommon but human-to-human rabies transmission can occur by organ donation from infected donors or through extremely intimate contact, such as bites or exposure to contaminated saliva (Lembo et al. 2008).

4.5. INCUBATION PERIOD

Following transmission, the virus replicates within the host's body and transfers to the nervous system from the peripheral parts. The time frame and the duration of the incubation period can vary from several weeks to months (Rupprecht et al. 2017).

4.6. VIRUS SHEDDING

Infected animals can shed the rabies virus in their saliva before clinical indications appear, allowing them to spread the infection to others. This shedding is more common in the latter stages of the illness, when neurological symptoms appear (Hemachudha et al. 2013).
Controlling the transmission of rabies involves measures such as animal vaccination campaigns, responsible pet ownership, surveillance and reporting of cases and timely availability of treatments for persons who have acquired the virus and show the symptoms of the disease. These efforts aim to interrupt the transmission cycle and reduce the incidence of rabies in both animal and human populations (Miranda and Miranda 2020).
The scheme of transmission of rabies infection is shown in Fig. 1.

5. TYPES OF EXPOSURES

Only exposed skin wounds and other mucous membranes like the mouth and eyes can transmit the rabies virus. When assessing a potential rabies exposure, it's also important to take into account the local natural history and current health of the animal that bites the person (such as anomalous behavior or illness symptoms) and the possibility that the animal had previously been exposed to a rabid affected animal. The type and intensity of the exposure affect how likely it is that someone may get rabies (CDC 2017).
There are typically two forms of exposure: bites and non-bite exposure.

6. EXPOSURE WITH BITE

A bite exposure occurs when teeth penetrate the skin. No matter where the bite occurs on the body, there is a chance that rabies might spread. However, the hazard differs depending on the type of animal that bite the victim, where the bite occurred anatomically and how severe the wound was. Some animal bites, like those from bats, might only cause minor damage and are therefore difficult to identify. It’s also important to note that "Was the attack that led to the bite triggered or malicious?” Bites that a person receives while handling or trying to feed a seemingly healthy animal should be regarded as provoked. It is possible that the animal is affected by rabies virus if the attack was uninvited (Acharya Anita et al. 2012).

7. NON-BITE EXPOSURE

Contagion of open lesions, scrapes and other skin tissues that are infested by contagious material from a diseased animal is defined as non-bite exposure. This acquaintance to terrestrial animals seldom results in rabies. However, rabies transmission through these types of exposures suggests that these kinds of exposures should be investigated for prospective post-exposure prophylactic medication. Other types of contact, such as touching a rabid animal's blood, urine, or feces, do not constitute exposure and do not grounds for post-exposure vaccination (Bharadva et al. 2015).

8. OTHER MEANS OF RABIES VIRUS (RV) SPREAD

Injury cases are rare, with the exception of bites and scrapes. One potential non-bite exposure method is inhaling rabies virus through aerosol route. Mostly lab staff comes into contact with rabies virus aerosol. Rabies transmission through corneal and solid organ transplants is extremely uncommon. Only two solid organ donors with rabies are known to have existed in the United States since 2008. It has been claimed that rabies can be acquired through the transplant of infected organs or through the

inhalation of virus-containing aerosols. Transmission from sick animals to humans through raw meat or milk is also possible. There is no link between increased risk of infection by touching a rabies infected individual or coming into contact with urine, blood or other non-infectious fluid or tissue. Contact with a person who has received rabies vaccination does not result in rabies exposure, illness or the need for post-exposure prophylaxis. The rabies virus loses its contagiousness when it is exposed to sunshine and dries out. This virus can be inactivated if the reservoir of the virus is dry and it becomes non-infectious (Gadre et al. 2010).

9. PATHOPHYSIOLOGY OF THE RABIES VIRUS

Rabies virus belongs to the Rhabdoviridae family. The pathophysiology of rabies involves a complex interplay between viral replication, neuronal dysfunction, inflammation and immune responses. It is important to note that rabies virus is highly toxic and it can leads to death. Appearance of clinical signs highlights the urgent need for preventive measures, such as vaccination and prompt medical intervention following exposure (Miranda and Miranda 2020).
The pathophysiology of rabies involves several stages and processes:

9.1. TRANSMISSION

When a rabies infected animal like dogs, bats, foxes, skunks or raccoons bites a human, rabies virus is transmitted. The virus is present in the saliva of the infected animal and enters the body through broken skin (Lembo et al. 2008).

9.2. PERIPHERAL REPLICATION

When the virus enters in the body it starts replication in the peripheral parts and muscle cells at the site of infection, then it travels to the CNS through the peripheral nerves. Time from the start of infection to the onset of symptoms is called the incubation period of the virus that can vary from some days to many years in different individuals (Mazarakis et al. 2001).

9.3. NEUROINVASION

The virus reaches the CNS by traveling along the peripheral nerves. It can enter the nerve endings and spreads to the spinal cord, brainstem and other regions of the brain area. The virus can also enter the CNS directly through mucous membranes or open wounds (Lushasi et al. 2021).

9.4. VIRAL REPLICATION IN THE CNS

Once inside the CNS, the virus starts to replicate rapidly, primarily in the gray matter of the brain, including the limbic system, hypothalamus and brainstem. This leads to inflammation and destruction of neural tissue (Finke and Conzelmann 2005).

9.5. INFLAMMATORY RESPONSE

The presence of the virus in the CNS triggers an immune response, leading to inflammation. This inflammatory response contributes to the clinical manifestations of rabies, including neurological symptoms (Brunker and Mollentze 2018).

9.6. NEURONAL DYSFUNCTION AND ENCEPHALITIS

The rabies virus primarily targets and damages neurons in the CNS. It disrupts normal neuronal function, leading to the development of encephalitis. The affected neurons undergo degeneration and death, causing various neurological symptoms (Jogai et al. 2000).

9.7. ASCENDING PARALYSIS

As the virus spreads within the CNS, it affects motor neurons, leading to muscle weakness and paralysis. This paralysis typically starts at the point of wounds or the bite of the rabid animal or/and progresses towards the head, neck and extremities (Yousaf et al. 2012).

9.8. AUTONOMIC DYSFUNCTION

Rabies can also affect the autonomic nervous system, resulting in abnormalities in heart rate, blood pressure and temperature regulation. This can lead to fluctuations in blood pressure, excessive sweating and salivation (Lembo et al. 2008).

9.9. HYDROPHOBIA AND AEROPHOBIA

One of the characteristic features of rabies is that patient feels fear of water and air and often develops hydrophobia and aerophobia like symptoms. This occurs due to the involvement of the limbic system and brainstem, which control emotions and sensory responses (Brunker and Mollentze 2018).

9.10. COMA AND DEATH

As the disease progresses, individuals with rabies may enter a comatose state due to extensive damage to the CNS. When the infection spreads in the whole body and symptoms of rabies have appeared, mostly it leads to death of the patients within a few weeks because of the cardiovascular arrest and disturbances in central nervous system (Paweska et al. 2006).

10. THE CONTAGIOUS PATH OF VIRUS

Rabies virus passes through different stages:

10.1. INCUBATION PERIOD

After the initial spread of rabies virus by the bite and scratch of a diseased animal, there is an incubation period that typically ranges from weeks to several months. In this phase, the virus duplicates at the site of entry without causing any noticeable symptoms. The rabies virus must move to the brain after exposure before it may cause symptoms. The incubation period is the interval between exposure and the emergence of symptoms. The incubation time for rabies is normally 2-3 months, but can range from 1 week to 1 year depending on factors such as the site of virus entrance and viral burden. It might remain for weeks or months (Hemachudha et al. 2002).
The incubation period may differ depending on the following factors:

- the location of the exposure site (how far away it is from the brain)
- the kind of rabies virus
- Existing immunity (Brunker and Mollentze 2018)

10.2. PRODROMAL PHASE

This stage lasts for 2 to 10 days and is considered by the symptoms that are similar to flu, fever, headache, discontent and gastrointestinal disturbances. The virus starts to invade peripheral nerves and spreads toward the CNS (Colombi et al. 2020).

10.3. NEUROLOGIC PHASE

Once the virus reaches the CNS, it begins to spread rapidly along nerve fibers towards central nervous system (CNS). It is believed that the virus travels within the peripheral nerves using a retrograde axonal transport mechanism. The rabies virus invades peripheral nerves before reaching into the central nervous system (CNS). Viral amplification causes the virus to spread quickly in the rostral grey matter of the spinal cord after the virus has infected the ventral horn of the spinal cord or the dorsal root ganglia. Exoplasmic transport is used to advance material to the brain along a number of ascending and descending fibers where it is first placed in the brainstem and then diffuses into the rest of the brain. In contrast to necrosis or apoptosis, the resulting neurologic symptoms are thought to be predominantly the result of nerve cell malfunction; however, the precise functional impairment involved is unknown (Singh et al. 2017)
This phase is associated with two distinct clinical presentations:

10.3.1. FURIOUS RABIES

This kind accounts for over 80% of cases and is distinguished by hyperactivity, agitation, hallucinations, and unpredictable behavior. Hydrophobia (fear of water) may develop in patients as a result of severe throat spasms and difficult swallowing. As the illness advances, muscle spasms, convulsions and paralysis may occour (Laothamatas et al. 2008).

10.3.2. PARALYTIC (DUMB) RABIES

This variety occurs in around 20% of cases. It is distinguished by muscular weakness, paralysis, and the absence of usual angry signs. The paralysis usually starts in the bitten limb and progresses to other muscle groups gradually. Virus can also move from brain to peripheral parts and other body tissues and also moves out from the body and targets a new host and infect the new host. Following infection of the brainstem nuclei, the facial and glossopharyngeal cranial nerves send the virus to the salivary glands through the ganglia that are connected to them. Viral shedding into salivary secretions is considerable following the infection of glandular epithelia (Mitrabhakdi et al. 2005).
The cornea and retina, as well as the liver, heart and kidneys which are supported by the parasympathetic and sympathetic nervous systems, receive virus transmissions. Additionally, rabies has frequently been spread through corneal transplants. The virus often accumulates in the free sensory nerve endings of nuchal tactile hair, hence a skin tissues biopsy sample taken from this region is used as a routine diagnostic test (Fooks et al. 2014).
The terminal phase is characterized by severe neurologic impairment, which leads to coma, respiratory failure, and death. The autonomic nerve system is disrupted and it can lead to change in heart rates, blood pressure in arteries and temperature of the body can also be increased (Lembo et al. 2008).
The pathophysiology of rabies is mostly linked to the virus's direct effects on neurons and the immune system of the host. Rabies virus can infect and reproduce within neurons, resulting in neuronal damage which causes death. Furthermore, the host’s immune system when tries to manage the infection, causes an inflammatory reaction inside the CNS, which contributes to tissue destruction (Finke and Conzelmann 2005).
The infectious pathways of rabies infection is shown in Fig. 2.

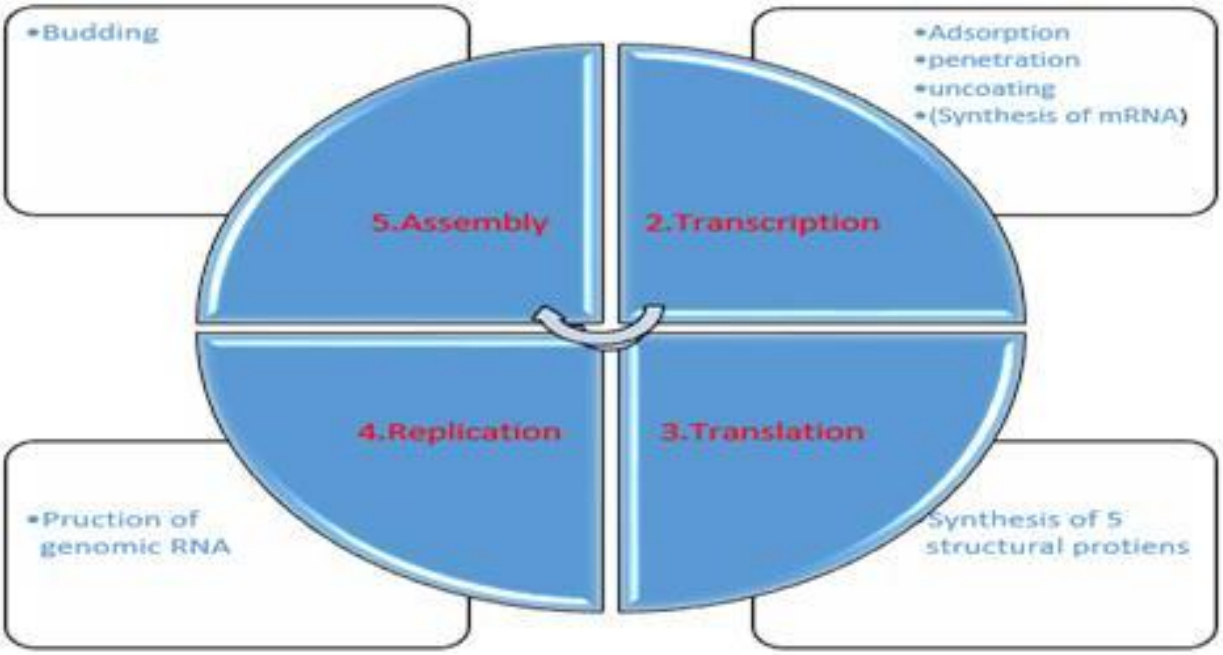

Fig. 2: The Infectious Pathway of the Rabies Virus.

11. SIGNS AND SYMPTOMS OF RABIES

Rabies symptoms, indications and outcomes in animals might vary. Animal symptoms are frequently comparable to human symptoms. These include vague early signs, acute neurologic symptoms and eventually death. Typical rabies symptoms include fever, discomfort, and odd or inexplicable itchy, stabbing or scorching ambiences at cuts or biting sites. When the virus spreads to the brain area or CNS, it causes deadly soreness in brain and spinal cord. Clinically rabies in humans is treatable but rarely cured, and only with significant neurological abnormalities. The initial crests of the disease are common symptoms of fever like flu, body pain, weakness or headache etc (Lushasi K et al. 2021).

Soreness or burning sensations at the location of infection or wound is mostly detected. All these indicators may remain for several days or weeks. The symptoms lead to intellectual damage, nervousness, confusion and distress. The patient may feel hallucination, madness, hydrophobia (fright of water) and sleeplessness as virus spreads in body and the condition worsens (Lembo et al. 2008).

Initial stage of the disease typically remains 2-10 days. When irrefutable indications of rabies ascend, the condition is mostly deadly, and the management is frequently helpful to the patients. Mostly rabies leads to death and chances of survival is very low as only 20 examples of human endurance are reported. Only a few individuals had no prior or postexposure prophylactic history (Susilawathi et al. 2012).

12. DIAGNOSIS OF RABIES

Current diagnostic methods are ineffectual for recognizing the infection before quantifiable illness develops. Mostly rabies is diagnosed by the most prevalent indications of hydrophobia or exposure of the person with a doubted or confirmed rabies affected animal. Different diagnostic techniques are being used to recognize the whole viral genome, antigens in viruses or nucleic acids in septic tissues like saliva, brain tissues or skin tissues that can ratify rabies virus in post- mortem (CDC 2017).

13. RABIES POSTEXPOSURE PROPHYLAXIS (PEP)

The immediate treatment to rabies exposure is post-exposure prophylaxis (PEP). As a result, the virus cannot be able to enter the central nervous system and kill the host. Included in this are a series of rabies vaccinations, an urgent 15-minute soap-and-water wound wash, and, if necessary, the administration of rabies immunoglobulin or monoclonal antibodies, which can save their lives. Every year, PEP is given to about 29 million patients all over the world (Fooks et al. 2014).

Due to the disruption of dog-mediated transmission in the USA, hematophagous bats are currently the main reason of rabies fatality in human. In Australia and Europe, rabies that is caused by bats is also becoming a public health problem. While rabies is regarded as a neglected tropical disease, the cost to human life and the expense of post-exposure preventative resources demand that it should be given high priority. This goal is a part of the Millennium Development Goals, which aim to reduce poverty and preventable deaths of children from transmissible diseases in resource-limited regions of the world (Abela-Ridder et al. 2016).

Following Post-exposure Prophylactic measures should be taken after exposure;

- Comprehensive cleaning with water and soap for at least 15 minutes after a suspected exposure, followed by a local wound care as soon as possible.
- A series of WHO-approved rabies vaccinations that are powerful and effective.
- If required, the wound may be injected with monoclonal antibodies or rabies immunoglobulin (Colombi et al. 2020).

Human rabies immune globulin (HRIG) and rabies vaccination are given as part of PEP on the day following rabies exposure, and then doses of the vaccine are given on days 3, 7 and 14. The administration of both HRIG and the rabies vaccine should always be a part of post-exposure prophylaxis (PEP) for people who have never received rabies vaccination (Yamada et al. 2016).

For bite and non-bite exposures, HRIG in conjunction with immunization is suggested regardless of the interval between exposure and treatment. The only people who should receive the vaccination are those who have already had it or are undergoing pre-exposure immunization for rabies. It is unusual for immune globulin with the rabies vaccine to cause negative reactions. Nowadays, more recent vaccines on the market cause fewer adverse reactions than previous vaccines. The rabies vaccine has been associated with mild local reactions, such as discomfort, redness, swelling, or itching at the injection site (Banyard et al. 2019).

Rarely, reports of symptoms like headaches, nausea, stomachaches, aches in the muscles and dizziness have been reported. Local discomfort and a low-grade fever may appear after receiving rabies immune globulin injection. Unless they are already infected with the illness, people cannot spread rabies to others. Because of the protection by PEP, a person can do his normal activities in an innocuous environment (Prosniak et al. 2003).

14. EXPOSURE RISK AND INDICATIONS FOR PROPHYLAXIS

As rabies is regarded as an ignored tropical malady, the encumbrance on hominid life expectancy and the high cost of post exposure preventative (PEP) resources require it to be a high priority. Administration of a complete PEP course is suggested according to the severity of the suspected rabid animal contact as mentioned in Table 1.

15. CONCLUSION

Rabies is a deserted oppressive ailment that mostly distresses disadvantaged, underprivileged, and susceptible populations. It is transmitted to human and animals when these are bite off or scratched by

Table 1: Types of interactions and suggested prophylaxis measures

Types of interaction with suspicious animal	Post-exposure prophylaxis measures
Type 1: feeding or petting animals; exposure to animal licks on unbroken skin (Exposed)	Only wash the infected skin site and no use of PEP
Type 2: exposed skin pecking, tiny scrapes or scratches without hemorrhage (Exposed)	Instant vaccination and wound washing
Type 3: Saliva of the animal that have contaminated broken skin or mucous membranes, single or many transdermal bites or scratches, and exposures from coming into contact with bats directly (Rigorously exposed)	Vaccination in a right away, application of rabies immunoglobulin and monoclonal antibodies, and wound cleaning

a rabid animal. Because stray dogs and other pets are mostly unvaccinated, it causes increase in rabies prevalence. Other reasons may include occupational menaces, inaccessibility of the proper vaccinations in developing countries and mostly in rural areas. Unawareness about the prominence of getting proper treatment after the animal's bite and unavailability of health facilities can lead to an increase in rate of rabies infection worldwide, predominantly in Asia and Africa. Post-exposure prophylaxis (PEP) is projected to protect human health in millions from rabies every year. Even if Vaccination and protective medicines are available for the prevention of human rabies mostly caused by dogs and other wild animals but these are not always conveniently reachable to the needy people.

Regardless of the accessibility of suggestion and recommendations for rabies prevention and treatment, Southeast Asian states still have difficulties in controlling the disease including a lack of political obligation, insufficient capitals, a privation of strategy agreement, feeble harmonization in different sectors, unresponsive investigation arrangements, restricted access to proper vaccines supply and a lack of community consciousness and collaboration. The large predicted rabies affliction supports the requirement to highlight rabies prevention and control. Different organizations are working to end up the rabies by 2030. These include Food and Agriculture Organization (FAO), World Health Organization (WHO) and Organization for Animal Health (OIE). These all organizations are working for a common objective to decrease scarcity and avertible demises of children by transmissible diseases in under developed countries in the world.

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One-Health Approach to Control Rabies

31

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ABSTRACT

In this chapter, we had focused to control one of the most important and dangerous zoonotic diseases named rabies through one-health approach. Rabies is a viral disease associated with Lyssavirus including the rabies virus and Australian bat virus. Rabies is a threat continues to impose a significant number of risks and dangers to the population worldwide. Many people become affected from this zoonotic disease every year. Therefore, the implementation of one-health approach is need of the hour for the control of rabies knowing the interface of the virus interconnected with humans, animals, and environmental health. This discussion illuminates the origin of the virus and its transmission routes including both less common and most commonly used transmission routes. To better understand the risks and severity of this disease, it is important to know the pathogenesis of the virus in the body. So, the mechanism by which the virus attacks the body, resides in it, and infects the nervous system of the individual leading to the severity of the disease symptoms and high mortality within days is also discussed. Also, diagnostic tools used globally and prophylactic measurements are highlighted along with the control actions that can be taken to avoid the disease spread and transmission. By implementing the holistic one-health perspective, the aims to reduce the occurrence of rabies in humans as well as animals addresses the socioeconomic and environmental aspects to control the prevalence of the zoonotic viral disease.

Keywords: Rabies, One-Health importance, Transmission, Pathogenesis, Control.

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1. INTRODUCTION

Rabies is a well-known zoonotic, fatal viral disease that affects humans and animals through scratches, bites, or contamination of mucous membranes or broken skin with the infected saliva of a rabid animal. Rabies virus primarily affect the brain and spinal cord cause acute progressive inflammation (encephalomyelitis/ encephalitis) and tissue damage develops ultimately resulting in death. There are two types of rabies that exist from a clinical standpoint. The first type is known as furious rabies, two third of infected patients, which is characterized by hyperactivity, hallucinations, lack of coordination, aerophobia (fear of fresh air) and hydrophobia (fear of water). In furious form of rabies, death occurs after a few days. The second type is known as paralytic rabies, one third of infected patients, which is characterized by paralysis of various body parts (Makoto and Naoto 2007). Dogs are the most common reservoirs for human infection, accounting for over 99% of cases worldwide. The infected hosts, like bats, jackals, and foxes, can transmit this infection to humans. In Africa, Asia and Europe, it is linked with dog bite while in America it is associated with bats bites (Thiravat et al. 2013). According to CDC 5000 cases of rabies are reported annually from United States. Rabies is one of the neglected zoonotic diseases despite it has enormous public health importance. The effect of rabies is growing by day even though it can be prevented which is an issue in both industrialized and developing countries.

According to reports, annually, over 55000 individuals are estimated to die from rabies worldwide. Every year, an estimated 1000000 Humans undergo post-exposure therapy after they exposed to animals which are suspected to have rabies. All continents and 150 countries, except for Antarctica, have reported cases of Rabies (Riccardi et al. 2021). The majority of rabies cases occur, after being bitten by a dog particularly in the rural region. Children under 15 years of age account for 40% of cases with Asia and Africa reporting the highest rates of the disease. According to a review, Asia bears a disproportionate share of the public health cost associated with rabies, accounting for an estimated 32,000 fatalities and 96.5% of the disease's economic impact in developing nations, with US$560 million being spent annually mostly on post-exposure prophylaxis (Krishna 2020). There are currently just a few nations that are rabies free, including Singapore, Taiwan, and Japan.

Animals transmit more than 60% of Infectious diseases which are known and 75% of developing infectious illnesses. In terms of public health, Rabies, Because of its lethality, is the most serious of these diseases. The control and management of these zoonotic diseases are complicated because its multifarious nature one-health approach involving multiple sectors could be a superior strategy for dealing with Rabies. Up to date, Rabies prevention and control programs are carried out by mass vaccination of home and communal dogs and cats as well as public awareness campaigns. However, the problem of rabies has not decreased because these techniques failed to integrate animals, humans, and environmental health sectors controlling the disease program (Krishna 2020).

2. ETIOLOGY

The causative agent of rabies disease is a rabies virus. It has a single-stranded RNA genome belonging to the genus *Lyssavirus* and family *Rhabdoviridae* (Rod-shaped viruses). This family is divided into two phylogroups. Rabies lyssa virus (RABV), which is called genotype 1 is included in phylogroup 1. Other genotypes included in phylogroup 1 are: genotype 4 (Duvenhage virus), 5, 6, and 7 (European bat Lyssavirus, EBLV1-2 and Australian bat Lyssavirus). The phylogroup 2 include genotype 2 (Lagos bat virus) and 3 (Mokola virus) (Monroe 2018).

A highly neurotropic virus in the mammalian host, RABV is the cause of the classic form of rabies in both animals and humans. Once the infection is established and has reached the brain, it invariably results in a deadly encephalomyelitis.

Various carnivore and bat species serve as the specialized mammalian reservoir hosts for RABV around the world. There have been 15 different Lyssaviruses discovered that resemble RABV in terms of morphology and structural features.

Only 6 of the 16 Lyssaviruses in the genus of Lyssavirus that are now recognized have been linked to encephalomyelitis like rabies in humans. Of the 16 identified Lyssaviruses, it should be noted that only RABV has numerous host reservoirs, whilst the other Lyssaviruses are only connected to bat reservoirs.

All the viruses belonging to phylogroup "I" are disseminated by bats; only RABV has evolved to employ carnivores as its reservoir host and is spread by them. It is unclear how lyssaviruses transmitted by carnivores and bats developed in connection to one another. Many biological and physicochemical characteristics of other Rhabdoviridae family viruses are shared by *Lyssavirus* species. The morphology of the virus, which has a bullet-like form, the helical nucleocapsid (NC), and the overall arrangement of the viral RNA and structural proteins are some examples. The majority of the biologic roles that these viral proteins perform in other rhabdoviruses are also shared by these lyssavirus proteins (Okumura and Harty 2011). Lyssaviruses, on the other hand, are not spread by insect vectors like all other rhabdoviruses and have evolved to direct transmission. Shortly, Genus *Lyssavirus* contains 16 virus species among all of them rabies virus is the most important and concerning its impact on public health.

2.1. INCUBATION PERIOD

The incubation period of rabies depends upon the site in which the virus is inoculated, it means that incubation period will be shorter if the virus is inoculated near brain or in the area having more nerve proliferation, the degree of the bite and/or damage (a shorter incubation period corresponds to a bite or wound that is deeper and more extensive) and the viral genotype. In most cases, it is 2 to 3 months but may vary from 10 days to month or uncommonly years (Charlton et al. 1997).

3. EPIDEMIOLOGY

- For more than 4,000 years, rabies has been known to exist. It is now present throughout the majority of nations, except for those from which it has not been natively documented, such as several Australian islands or regions that have achieved secondary extinction, like the United Kingdom.
- The bite of a rabid animal is the major source of rabies in humans.
- The likelihood of contracting rabies is highest in those world areas where canine rabies is hyperendemic, such as the majority of Latin America, Africa and Asia.
- In the years 1940 to 1950, the domestic rabies animals were mainly controlled by the America and European countries, now less than 10% of all rabies animal cases reported.
- In United States of America, the wildlife rabies mainly affects the terrestrial predators such as foxes, raccoons, skunks, insectivorous bats etc.
- Almost invariably, a bite is the main cause of human rabies.
- Rabies in humans is mainly brought on by non-bite exposures, which include contamination of an open wound or a mucous membrane by scratches, licks, and aerosol inhalation (Binkley and Gebreyes 2023).
- Rabies is one of the most significant zoonotic diseases in the world, according to the WHO. According to estimates, one in two Americans will experience an animal bite at some point in their lives. It makes sense to divide the world's rabies cases into three geographic epidemiologic regions: (1) nations where

canine rabies is enzootic; (2) nations where wildlife rabies is predominant while canine rabies is under control and (3) Nations where rabies is not an issue (Willoughby 2023).

- Rabies appears to be periodically transmitted in reservoir host populations because of density-dependent transmission. A weak understanding of the ecological elements that increase or decrease rabies' long-term survival in reservoir animals is present.
- It is unknown where terrestrial rabies first emerged. Because the rabies virus kills, most of its infected hosts and lacks any known stages outside of its living host, it defies two of the key principles for effective pathogens. The parameters of the rabies cycle can be affected by human encroachment when reservoir host animals interact near concentrated food sources, such as pet foods, bird feeders, and landfills, and domestic pets are more exposed to wildlife.
- First case of rabies disease is confirmed in domestic fowl in India (Baby et al. 2015). Although solid evidence has only been available for the past 100 years, the Spanish researchers explore the 1st suspect bats as a vector for rabies in South America (Sami and Ennaji 2020).
- There is estimated that the total 10-15 million humans receive rabies post exposure prophylaxis (PEP) a year after being exposed to animals with probable rabies, however, there is no conclusive reporting of these cases (Oertli 2020).
- Serotypes and genotypes of the virus are categorized.
- There are numerous varieties (strains or kinds) of the virus because of genetic evolution, each of which is kept in a distinct reservoir host. The term "viral "strains or variants" refers to viral populations that may be recognized from other strains by their genetic and antigenic properties and are maintained by a specific reservoir host in a specific geographic area.
- The reservoir host is crucial to the virus's ability to spread. For clarification, raccoon rabies in a dog would be used instead of canine rabies to represent rabies in a dog caused by a rabies variety that is still present in raccoons.
- There are so many factors such as natural habitat, home range, the population of the reservoir host, physical barriers, different variants of the rabies virus, other kinds of diseases of the host species, and vaccinated or natural herd immunity status that influence the epidemiology and prevent disease transmission.
- The reservoir host for rabies cases has undergone a significant alteration, except for Africa, Asia, and India. Domestic animals, primarily dogs, used to have the greatest recorded incidence of rabies cases. That would be indicative of the current global scenario, given that dogs have long been thought to be the primary carrier of this zoonosis and continue to be the primary cause of modern-day human fatalities (Streicker and Biek 2020).

3.1. TRANSMISSION

Rabies has two cycles of transmission, one is sylvatic and other is non-sylvatic. The majority of cases of rabies virus transmission happen when an infected animal bites or engraves another vulnerable animal or human. Additionally, people may get rabies if they come into close contact with an infected animal's saliva on their mucosa or skin sores. Although it is very uncommon for the virus to transfer from person to person, but few cases were reported after transplant surgery. Seasons have a major role in the spread of rabies, with late summer and autumn being the seasons with the highest frequency because of the large number of wild animals looking for a mate and food. In emerging nations, it is predicted that it is an urban disease because of the high level of human-domestic animal interaction (Imran 2020).

3.2. COMMON TRANSMISSION ROUTES

- The rabies virus (RV) has been linked to several carnivorous animal species.
- Domestic dogs are the primary carriers of the rabies virus in Asia and Africa.
- Instead of dogs, other animals such as racoons, foxes, skunks, coyotes, possums, and bats carry the virus in the US through bites.
- There are three phases of canine rabies that have been identified. The prodromal stage is the first stage characterized by behavioral changes exists for1 to 3 days. The second stage, which lasts 3 to 4 days, is the excitative stage. This stage of the disease is frequently referred to as "furious rabies" because the infected dog has a propensity to bite when it is overly sensitive to environmental stimuli.
- The paralytic stage, which is the third stage, is brought on by motor neuron injury which causes incoordination because of paralysis of the rear limb, Facial, and throat muscles. Paralysis causes difficulty in swallowing and drooling. Respiratory arrest frequently results in death.
- When a human is bitten by an animal that has the rabies virus in its salivary glands, the disease is transmitted.
- After the initial inoculation, the RV is still cell-free, therefore thorough wound cleansing may lessen the risk of infection.
- Retrograde axonal transport enables RV to infect peripheral nerves and subsequently spread to the CNS. (Müller and Freuling 2020).

3.3. LESS COMMON TRANSMISSION ROUTES:

Less frequent methods of spreading the rabies virus include:

- Mucous membrane contamination, such as that of the mouth, nose, and eyes
- Transmission of aerosols
- Transplantation of the cornea and other organs from an infected donor

4. PATHOGENESIS

- In the pathogenesis of rabies, the virus must get beyond the skin's protective barrier, which is typically accomplished by being bitten by an infected or ill animal. Despite being experimentally proved, other transmission pathways, such as the oral route, are irrelevant to rabies epidemiology.
- Interestingly, the bite of an infected animal is not always cause to development of rabies disease due to intermittent shedding and a species-specific resistance. Muscles or peripheral nerves may initially become directly infected by the virus through infectious saliva.
- The *Lyssavirus* enters a peripheral neuron by receptor-mediated entry and then travels retrogradely in the neuron's axon via endosomal transport vesicles to the spinal cord via either the dorsal root (for sensory neurons) or ventral root (for motor neurons) ganglia.
- Strong immune response activation is something that *Lyssaviruses* successfully suppress and control. Further replication and transsynaptic propagation in the brain cause centrifugal dissemination of numerous infected neurons across the CNS. Clinical indications first appear when neuronal dysfunction worsens.
- The variety of incubation periods recorded with different varying times from virus entry to lead disease in naturally and experimentally infected animals. The clinical stage can last up to 10 days, but it typically concludes with the animal's death following a cardiac arrest and coma.

- Based on experimental results from previous studies, the WHO-recommended 10 days' observation period.
- The biting animal can simply be studied for 10 days if a dog, cat, or ferret exposes a person, or another animal and rabies needs to be ruled in or out. The danger of rabies virus transmission from the prospective exposure to this animal is minimal if it survives these ten days in good health. If there was a chance of viral shedding and transmission, the animal would have displayed clinical rabies symptoms during the monitoring period, perhaps including rapid death.
- Any clinical symptom or unexpected mortality must be verified by laboratory tests. It is interesting to note that before the pathophysiology of the disease was discovered, confinement and observation of questionable animals had already been a veterinary hygiene measure. (Chomel and Sykes 2021).

5. SIGNS AND SYMPTOMS

The majority of rabies' clinical signs are unconditional. The early signs include temperature with pain and tingling and paraesthesia at the site of the bite. Human cases of rabies often present in three stages, prodromal with vague symptoms, acute neurological symptoms, and lastly is coma leading to death. During the acute neurological phase, there are three ways that rabies can manifest clinically i.e., furious, paralytic, and non-classical. When the virus enters the CNS, it greatly causes inflammation in the brain and spinal card. The rabies virus-affected animals exhibit specific CNS neurotic symptoms that vary minimally between species.

5.1. PRODROMAL STAGE

This is the first stage which lasts usually one to three days. In this stage, small behavioral modifications may occur such as rage in household animals, loss of fear from humans in wild animals, and loss of appetite.

5.2. FURIOUS STAGE

In this stage the following signs are present: roaming, sobbing, agitation, assault on other animals and humans. At this stage, animals start consuming foreign objects like stones and firewood. Unusual alertness in cattle is a sign of this stage.

5.3. PARALYTIC STAGE

The paralytic stage of rabies can be identified by gradual paralysis. The primary muscles responsible for swallowing become paralyzed due to which animal may not swallow anything. The hypersalivation is present in this stage. The voice of animal changes and the animal starts bellowing and barking. Hind limbs become paralyzed and then complete body paralysis occurs after which animal dies.

5.4. HYDROPHOBIA

The term hydrophobia means fear of water. This sign is present in all the rabid mammals in advance stage. The animal may struggle to drink water, but because of the paralysis of gullet muscles, it doesn't happen. There is a release of foamy salivation in which virus is present.

6. DIAGNOSIS

The primary factors that determine the diagnosis are the clinical signs and symptoms, the history of the afflicted person, mortality, and immunization prophylaxis. A superior premortem technique to identify the viral antigen is the fluorescent antibody test (FAT). The postmortem diagnosis can be made if negri bodies are found in the brain. FAT is approved by the World Health Organization (WHO) which shows up to 99% accuracy in the result after few hours. More ever ELISA (Enzyme-linked immunosorbent assay), and use of monoclonal antibodies for virus diagnosis, Rabies antibody isolation test can be performed for the accurate diagnosis. The RT-PCR assays is also used to for the confirmation of disease.

7. PROPHYLACTIC MEASUREMENTS

- People who are likely to encounter rabid animals are advised to have pre-exposure to prophylactic immunization.
- Animal handlers, lab workers, and veterinarians should all think about getting routine vaccinations.
- Additionally, those who will not have easy access to medical care while going to locations where dog rabies is widespread should think about getting immunized before leaving.
- A previously inoculated person who may have been exposed to rabies should get two intramuscular doses of the vaccine, the first one as soon as possible after the exposure, and the second one three days later. A booster vaccine should not be followed by routine serologic testing due to the consistency of an antibody response (Del et al. 2020).

7.1. POST-EXPOSURE CARE

- To help lower the risk of bacterial illness, the bite site after an animal bites a person should be thoroughly washed with soap and water. Viral transmission from a bite may be decreased by Povidone solutions or 70% alcohol.
- A bite wound should be evaluated for cosmetic restoration, although closing a wound raises the possibility of bacterial infection.
- It is recommended to get a rabies vaccine. Based on an evaluation of the rabies risk in the animal that bit the person, rabies vaccination should be given.
- The rabies vaccine is 100% effective if given early and still has a chance of success if delivery is delayed.
- There are huge economic losses because of vaccine, more than 15 million people get vaccinated after exposure in the world but vaccines save lives.
- In general, unless the animal exhibits aberrant behavior, a bite from a domestic animal that has been reliably inoculated does not provide a significant risk of contracting rabies and does not call for rabies treatment.
- Low-risk rabies-infected animals can be monitored for 10 days for indications of unusual behavior. The animal should be killed if it exhibits odd behavior, since its saliva might be contagious.
- Domestic animal immunization may not be up to date in poor nations. As a result, whether a dog is domestic or wild, all bites should be regarded as possibly rabid, and treatment should begin right once.
- If an unvaccinated or wild animal bites a person and the animal can be killed and tested for rabies, the patient should get immunized right away, and treatment should continue based on the results of the test.
- Unfortunately, it's difficult to keep an observation on wild animals, therefore; every wild animal bite must be treated as rabid (Gilbert and Chipman 2020).

8. CONTROL

- Routinely visit your veterinarian for a checkup of your dogs and cats and keeps rabies vaccine up to date.
- Always maintain the supervision of your dog, cats and ferrets.
- Neutering and spaying should be done to avoid the unwanted pregnancies because there are difficulties to vaccinate all the animals.
- If you found stray dogs in your neighborhood, please complain to the animals control department.
- No need to adopt wild animals, leave wild animals alone.
- According to WHO, vaccination of 70% or more dog population can reduce the chance of rabies through dog bites. So, need to massive vaccination schedule to control rabies in dogs. Ultimately, they reduce the chances of rabies in dogs as well as in humans.
- Public awareness programs should be adopted to control rabies and for other zoonotic diseases.
- Need to strengthen the laboratories for the diagnosis of diseases as soon as possible.
- Epidemiological studies should be carried out for rabies and other diseases for the identification of different factors involved in diseases.

There should be strong coordination and data sharing among animal doctors, Human doctors and environmental experts etc.

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Monkeypox: An Emerging Global Threat

32

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ABSTRACT

An increase in illegal wildlife trade and deforestation in the past few decades increased the interaction between humans and wild animals, leading to the emergence and spread of several zoonotic diseases, such as “Monkeypox” infection. Monkeypox is a life-threatening disease caused by the Monkeypox virus that belongs to the genus Orthomyxovirus of the Poxviridae family. Monkeypox virus has been isolated from a variety of animal species, including rodents, monkeys, humans, and dogs. Transmission of the infection mostly occurs by direct contact with the infected lesions, body fluid, respiratory droplets, sexual contact, consuming products of the infected animal, or biting by the infected animals. After gaining entry through micropinocytosis, the virus completes its lifecycle within the cytoplasm of the host's cell. The virus starts infection from nasopharynx or oropharynx, leading to viremia and then spread to other organs. The clinical manifestation of the disease exists in the eruptive (characterized by fever, chill, and lymphadenopathy and the pre-eruptive stage (characterized by weakness, fatigue, and headache). After these stages, rashes appear at the mouth and then proceed to the whole face, palms, and soles. The important risk factors of the disease include sexual contact with an infected person, profession, hunting, vaccination against smallpox, etc. For an effective management of the disease, early diagnosis is essential, which can be possible with ELISA, PCR, Immunochemistry, viral culture, and IgG and IgM. There is no specific treatment available for this disease, however, supportive care and some antiviral drugs can be effective.

Keywords: Monkeypox, Year-2022 outbreak, Zoonosis, Viral diseases, Animals.

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1. INTRODUCTION

Due to urbanization, forests are being cut down, increasing the interaction of wildlife and humans. Similarly, the illegal trade of wildlife between countries is increasing day by day, especially in developing countries due to poor legislation. This is resulting in the emergence of new and spread of existing zoonotic diseases such as human monkeypox infection which appeared in 1970, when the world's main focus was eradicating smallpox. A 9-month-old boy was reported with fever, headache, fatigue, lymphadenopathy, and rash on the arms and legs in the Democratic Republic of the Congo (Gessain et al. 2022). These signs were similar to smallpox except for lymphadenopathy, which was not characteristic of the smallpox virus. On investigation, monkeypox was isolated from skin lesions. Later, six new cases were reported in West African countries and most patients were not vaccinated against smallpox (McCollum and Damon 2014). Monkeypox gained more attention in 2003 when the virus was isolated from 71 patients (Center for Disease Control and Prevention 2003). In May 2022, almost 17,300 suspected and confirmed monkeypox cases were identified. Due to the global outbreak, WHO declared a Public Health Emergency of International Concern (PHEIC) in July 2022 (Nuzzo et al. 2022).
Monkeypox infection was first described as the disease of the primate in 1958 when the virus was isolated in the infected cynomolgus monkeys shipped from Singapore to Denmark (Mitjà et al. 2023). Despite the name, the reservoir hosts appear to be rodents especially squirrels, Gambian pouched rats, and dormice (Guarner et al. 2022). In humans, the monkeypox virus starts with a flu-like prodrome and the presence of smallpox-like rashes on the skin (Elsayed et al. 2022). Human-to-human transmission is possible by direct contact with sores, body fluids, bedding, etc., of the infected human or animal (Rizk et al. 2022).

2. ETIOLOGY

Monkeypox virus is a double-stranded DNA virus that belongs to the genus Orthomyxovirus of the Poxviridae family with a genome size of 197kb with 190 genes. Human monkeypox virus is almost 200 to 250 nm large, brick-shaped, and enveloped virus that utilizes glycosaminoglycans to gain entry into the host's cells (Lansiaux et al. 2022). The Monkeypox virus has two important clades: a more virulent Central African/Congo Basin (CA) and a less virulent West African (WA) clade. The CA clade of the monkeypox virus is responsible for 10% mortality in non-vaccinated humans, whereas WA causes a very mild infection (Lansiaux et al. 2022). Due to its larger size, the monkeypox virus finds it more difficult to breach the junction gap to enter the host's cells and replicate rapidly. Their larger size also helps the host's immune response to recognize the virus at early stages of infection. But orthopoxviruses, including the Monkeypox virus, use specific proteins to evade the host's immune response. These proteins include:

- Intracellular Modulatory Proteins.
- Extracellular modulatory proteins (Okyay et al. 2022).

Intracellular proteins include virotransducer proteins and virostealth proteins. Virotransducer proteins lower the ability of the immune cells to respond to infection. Similarly, virostealth proteins help the virus to escape from the host's immune system. Extracellular proteins include viromimic proteins, interfere with the action of cytokines, and help viruses to replicate and spread rapidly (Kaler et al. 2022). Fig. 1 highlights the difference in size between monkeypox virus and other related viruses.

3. EPIDEMIOLOGY

3.1. HOSTS

As already discussed in the previous section, the reservoir hosts of the monkeypox virus include several small mammalian species such as squirrels and dormice, but still more study is needed to recognize other

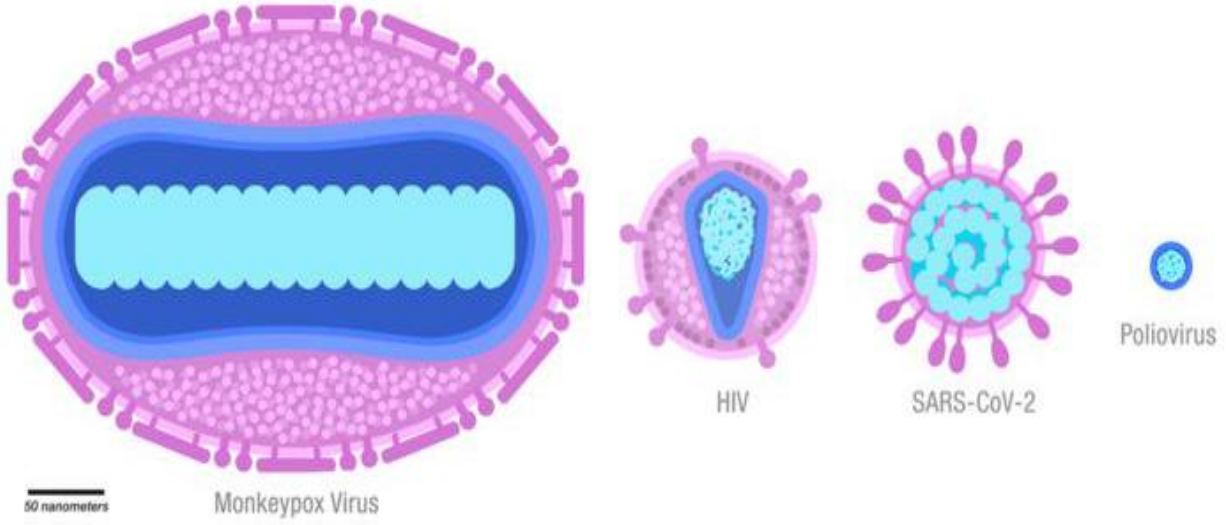

Fig. 1: Monkeypox virus size in comparison with other important viruses

reservoir hosts of the virus. Based on field investigation, viruses have also been identified in a variety of rodents, including rabbits, mice, jerboas, and hamsters (Ullah et al. 2023).

Although the exact reservoir host of the monkeypox virus is still unknown. However, many investigations and research have proved that monkeys are also incidental intermediate hosts of the virus. Dogs, like humans, can also be the fixed or intermediate host of the monkeypox infection. In 2003, a pet prairie dog was found infected with monkeypox infection. Upon further investigation, it was revealed that the dog had contact with other animals which were imported from US to Ghana (Kaler et al. 2022). Another case was reported in dogs in 2022 when a 4-year-old Italian greyhound sick dog was presented with clinical signs of monkeypox infection. On further investigation, it was found that the dog shared the bed with an infected person (Choudhary et al. 2022).

3.2. TRANSMISSION

The transmission of the monkeypox infection can be through direct contact with the lesions, body fluid, respiratory droplets, consuming products of the infected animal, or biting by the infected animals. The virus can gain entry through the respiratory tract or mucus membrane of the skin, eyes, and mouth (Kumar et al. 2022). Human-to-human transmission is a common feature of the monkeypox virus. Mostly, this type of transmission occurs through close contact with the infected patient and contact with the bedding of the infected patient (Huang et al. 2022).

Several studies prove the vertical transmission of the monkeypox virus. A study conducted at the General Hospital of Kole found that two out of four monkeypox-infected women experienced a miscarriage at the early stages of the pregnancy, and another woman experienced miscarriage at 18 weeks of gestation. On further investigation, monkeypox virus DNA was found in the placenta, fetal tissue, and umbilical cord (Fahrni and Choudhary, 2022). The presence of the virus in the seminal fluid of the 29 people indicates that the virus can be transmitted through semen as well (Thornhill et al. 2022). There is more need for the study to check whether the monkeypox virus can be transmitted through breastfeeding or not.

In 2022, most of the monkeypox cases were reported in homosexuals. The presence of rashes on the anogenital and perineal areas suggests that virus can be transmitted through close sexual contact (Martínez et al. 2022). The high occurrence of the infection in homosexuals doesn't describe monkeypox

infection as a sexually transmitted disease, but the disease entered in the homosexual community accidentally and was transmitted due to "close contact" during sexual activities (Thornhill et al. 2022). Fig. 2 and 3 shows the transmission of the monkeypox virus from animal to human and from human to human.

4. PATHOGENESIS

The pathogenicity of the monkeypox virus starts soon after its transmission from an infected animal to a human or from an infected human to an animal (reverse zoonosis as in the case of the Prairie dog). Monkeypox virus (DNA virus) completes its lifecycle in the cytoplasm, which is usually characteristic of RNA virus. For replication, transcription, and packaging, monkeypox utilizes a number of proteins. A virus enters the host's cell by binding through fusion and micropinocytosis. The nasopharynx or oropharynx is the most important host's site from where the virus starts infection and replication before spreading to lymph nodes. Monkeypox virus, just like other orthopoxviruses, needs to cause viremia to spread to other organs and lymph nodes. The incubation period of the monkeypox virus is 7 to 14 days. Some studies suggest the incubation period can be longer up to 21 days (Saied et al. 2022; Anwar et al. 2023).

During pathogenesis, the monkeypox virus, like other members of poxviridae, exhibits two forms: Extracellular Enveloped Viruses and Intracellular Mature viruses. Most of the viruses remain within the cells and lack an envelope (IMV). However, some viruses are transported through microtubes and become enveloped by two Endoplasmic reticulum membranes. These cells sometimes leave the cell cytoplasm and become Extracellular Enveloped Virion (EEV) (Smith et al. 2004).

An increase in the level of cytokines is one of the most common features involved in the pathophysiology of monkeypox infection. Studies found that the level of IL4-, IL-5, and IL-6 increases in monkeypox infection. Similarly, some specific types of tumor necrosis factor (such as TNF-alpha), Interferon-gamma, and levels of IL-2 decrease during the monkeypox infection (Ježek et al. 2015).

During monkeypox infection, the host's epithelial cells show intracytoplasmic eosinophilic inclusions, which is a unique characteristic of the poxviridae family. Similarly, the epithelial cells show hyperplasia, ballooning degeneration, and necrosis of the keratinocytes. The presence of neutrophils, eosinophils, and giant cells can also be seen (Thakur et al. 2023).

5. GEOGRAPHICAL DISTRIBUTION OF INFECTION

The first human monkeypox infection was reported in 1970 in Congo. Since 1970, it was thought that monkeypox is endemic to Central and West Africa. Almost 400 monkeypox cases were reported in the period between 1970 to 1990. Most of these cases were reported in the Democratic Republic of Congo (DRC) (Fig. 4). However, in 1996, a sudden increase in monkeypox cases was seen in DRC with 71 confirmed cases in just six months. Later on, the cases were increasing continuously (Huang et al. 2022). Between 1996 to 1996, the infection rate was 22 cases out of 1000 population (Pal et al. 2017).

5.1. OUTBREAK IN 2003 AND 2017

Monkeypox infection gained the attention of the scientific community in 2003 when an outbreak occurred in the US, with more than 47 confirmed and 10 suspected cases. Investigation suggested that the infection was transmitted from the non-African species, cohoused with the prairie dogs (Reynolds et al. 2006). Most of the infected people had direct and indirect contact with the dog. Some were involved in the handling of the dog, some were bitten by the dog, and few shared rooms with the sick dog. In 2017, Nigeria experienced an outbreak of monkeypox infection with almost 122 confirmed cases in more than 17 states. The mortality rate was 6% during this outbreak (Yinka-Ogunleye et al. 2019).

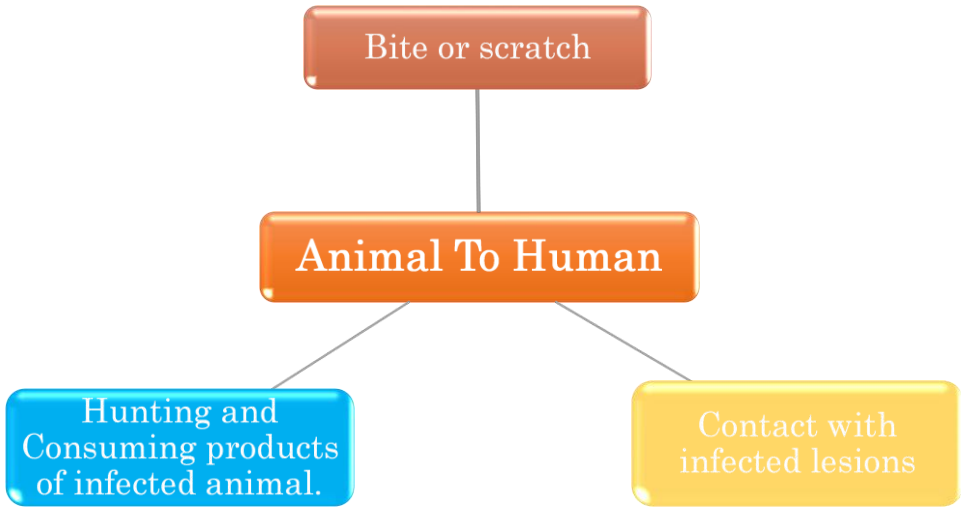

Fig. 2: The sources transmission of MPXV from animal to human.

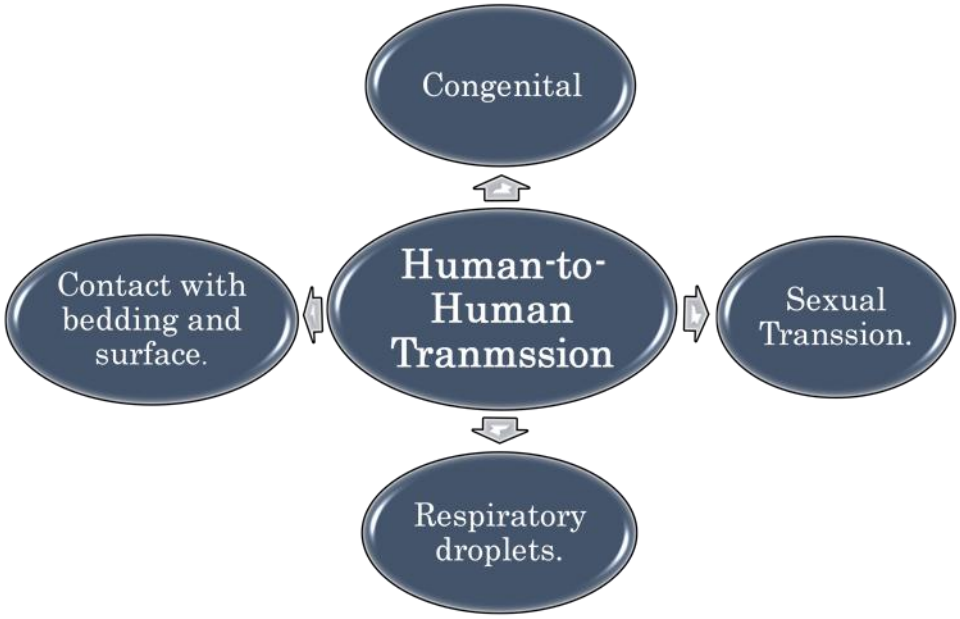

Fig. 3: The sources of transmission of MPXV from Human to human.

5.2. OUTBREAK IN 2022

As already discussed, before the 2022 outbreak, it was thought that monkeypox virus infection was only limited to Central and West Africa because there were few cases reported in other countries. However, in 2022, soon after the emergence of the first case in the United Kingdom, the infection started to increase dramatically and took the shape of endemic in several countries. Upon further investigation, most of the cases have travel history to the UK, Spain, and other countries in which cases were continuously reported (Kraemer et al. 2022). Six cases were reported in the UK between 13 to 16 May 2022 with no travel history to an African country and contact with important animals. However, most of the patients were homosexual. Later on, in September 2022, 24,017 cases were reported in almost 44 European republics (Ullah et al. 2023). Keeping the situation in view, WHO declared monkeypox a "Public Health Emergency of International Concern." Similarly, monkeypox prevention and treatment guidelines have been issued in several countries around the world (Webb et al. 2022). Until September 2022, the total number of

Fig. 4: First outbreaks of Monkey Pox virus.

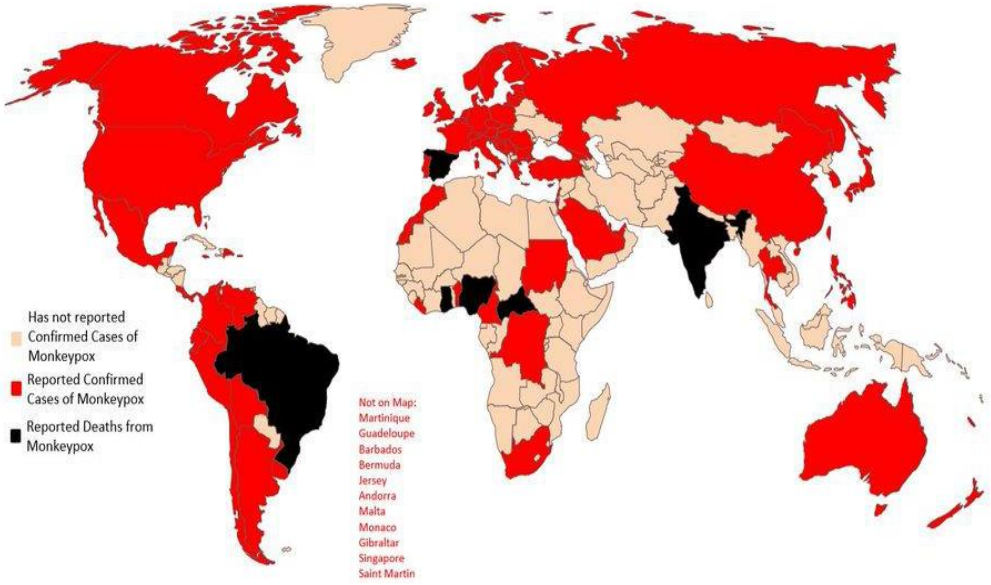

Fig. 5: Map showing spread of the MPX infection in different regions until 06 August 2022

monkeypox cases was 57,995 in more than 100 countries, with 18 mortalities. During the outbreak, youngsters were more affected by the monkeypox infection because of the termination of smallpox immunization after the eradication of smallpox (Ullah et al. 2023). Several factors are responsible for the rise in monkeypox infection during the recent era, including deforestation, illegal trade, climate change, and rapid demographic expansion of the monkeypox endemic regions (Quarleri et al. 2022). Fig. 5 shows the map indicating the spread of MPX in different regions.

6. CLINICAL MANIFESTATION

Resistance against smallpox infection plays a critical role in the onset of monkeypox infection. Several studies proved that monkeypox infection is more common in people younger than 15 years old (Damon 2011). The incidence and the severity of the monkeypox infection depends on a variety of factors including age, sex, and vaccination status of an individual against smallpox. But pre-eruptive and eruptive are the two most important clinical features of the monkeypox illness that are seen in every case (Thakur et al. 2023).

6.1. PRE-ERUPTIVE STAGE

The infection begins with some prodromal symptoms including, fever, chill, and lymphadenopathy (which were not characteristics of smallpox infection). Fever during the pre-eruptive stage of the infection ranges from 38.5 to 40.5℃. Other signs of the pre-eruptive stage include weakness, fatigue, and headache. After these symptoms, rashes appear on different body sites but initially start at the mouth and then proceed to the whole face, palms, and soles (Thakur et al. 2023). Problems associated with the upper respiratory tract and gastrointestinal tract can also be found in monkeypox infection (Reynolds et al. 2006).

6.2. ERUPTIVE STAGE

During this stage of the infection, the lesions start to increase (number varies from 10 to 150) and remain for 4 weeks and then ultimately scab over and fall off (Adler et al. 2022). Lesions turn from macules to papules to vesicles and pustules. Similarly, necrosis, ulceration, and pruritis are other important features of smallpox lesions. Pain can also occur due to secondary bacterial infection. In children, lesions can be 1 to 5 mm in diameter and can be similar to arthropod bite reactions (Pal et al. 2017).
In case of severe infection, the monkeypox virus triggers a robust immune response and ultimately leads to sepsis, an abscess of the deeper tissues, and severe respiratory disease. In monkeypox-mediated immune injury, damage to the other vital organs also occurs and causes tonsillitis, thymitis, myeloid hyperplasia, and splenic injury. Many studies have shown that immunopathogenesis in severe monkeypox infection occurs due to impaired Natural-Killer (NK cells), increased granulocytes and monocytes, immune evasion, and inhibition of the host complement system. Monkeypox-mediated immune injury increases the chances of mortality (Li et al. 2023).

7. RISK FACTORS

Understanding the risk factors associated with the occurrence of any disease in the community is very important. It allows the scientific community to describe the steps that help them to avoid the further spread of the disease. Below are a few important points that can act as risk factors for the transmission of monkeypox infection:

7.1. INDIVIDUAL CHARACTERISTICS

Understanding the risk factors associated with the occurrence of any disease in the community is very important. It allows the scientific community to describe the steps that help them to avoid the further spread of the disease. Below are a few important points that can act as risk factors for the transmission of monkeypox infection:
(21- to 40-year-old) (Antinori et al. 2022).

Table 1: Tests for the detection of the monkeypox infection. (Cheema et al. 2022)

Test	Description.	Sample.
PCR	It is an ideal approach to identifying the monkeypox virus DNA; real-time PCR is perfect.	Fluid from lesions.
Electron microscopy	Help in morphological identification of the virus.	Biopsy specimen, scab material, vesicular fluid
Immunohistochemistry	Confirm the presence of *Orthopoxvirus*-specific antigens	Biopsy specimen.
Viral culture.	The virus can be isolated from the patients and grown in a specific medium.	Fluid from the lesions.
IgG and IgM	Help in the recent exposure to the virus or early detection.	Blood.

7.2. PROFESSION

Occupation of the individual also acts as a risk factor for the transmission of the monkeypox infection. Usually, the infection is most commonly seen in people involved in hunting activities or those who have direct contact with non-human primates. Similarly, farmers are also at higher risk of infection due to their contact with rodents (Quiner et al. 2017).

Monkeypox infection is considered the most important nosocomial infection and is most commonly seen in healthcare workers. The hospital-born occurrence of monkeypox infection is very severe and long-term and demands solid steps to avoid the spread among healthcare workers, who are life saviors for mankind. The most common example of the nosocomial spread was seen in the UK, where a medical employee who was involved in the collection of the dressing and blankets of the monkeypox-infected patients, got monkeypox infection (Vivancos et al. 2022).

7.3. DIRECT CONTACT WITH INFECTED PERSON OR ANIMAL

Direct contact with the lesions, blood, or fluid of the infected person or the animal can also increase the risk of infection. Consuming the uncooked meat of rodents or other reservoir hosts can cause the rapid spread of the disease within the human community. Similarly, people living near the forest have more contact with the animals and their waste and are at higher risks compared to those living in the cities or urban areas. Human-to-human transmission can occur through direct contact with respiratory discharges, skin lesions, or body fluid. However, transmission through aerosol needs a specific distance between the infected and healthy individuals (Petersen et al. 2019; Ullah et al. 2023).

7.4. SEXUAL ACTIVITIES

In 2022, the monkeypox outbreak affected the people who were involved in homosexual activities. The reason behind this is still unknown but it indicates that the LGBTQ community is at higher risk compared to others (Singla et al. 2022).

The common risk factors associated with the monkeypox infection are described in Fig. 6.

8. DIAGNOSIS

The clinical signs of the monkeypox infection have a very close resemblance with chickenpox and smallpox infection. Thus, a definitive diagnosis is essential to prevent the disease from spreading. Although many bovine and caprine diseases, including bovine stomatitis and Orf, cause skin lesions similar to monkeypox, these diseases can be easily distinguished from orthopoxviruses via electron microscopy (Weinstein et al. 2005).

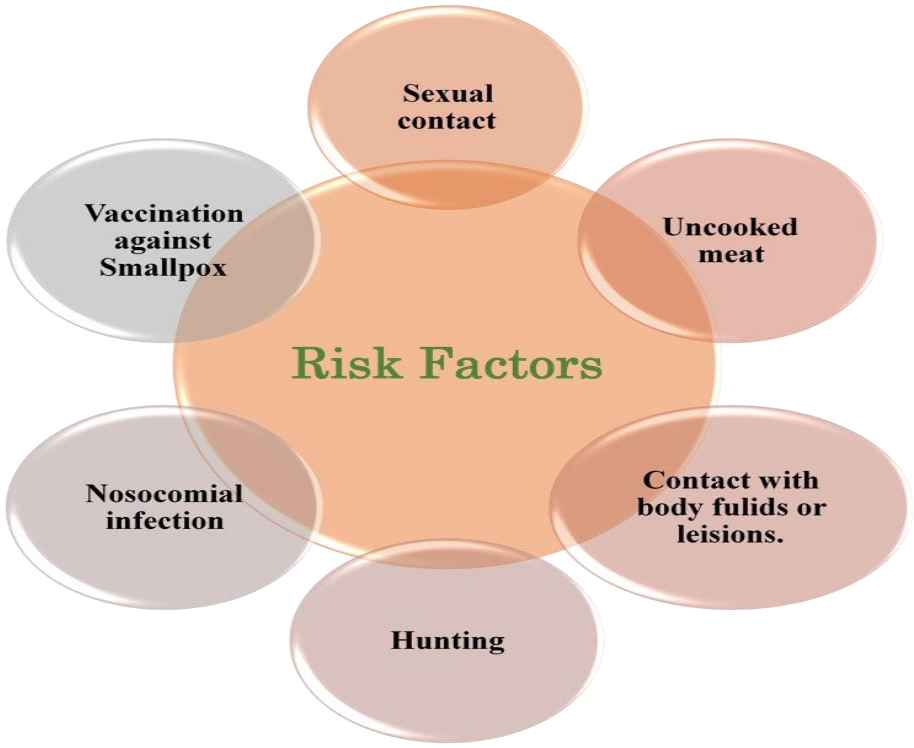

Fig. 6: Common Risk Factors associated with Monkey Pox Virus

Monkeypox infection results in several structural changes in the tissues that can be observed microscopically. Histologically, the lesions seen in the monkeypox infection show similar characteristics as seen in other viral exanthems, such as cowpox infection and herpes simplex infection. Usually, the histology of the monkeypox infection bulla varies from the stage of infection (Schmidle et al. 2023).
Clinical characteristics of the disease can help to differentiate skin lesions from other infections, but laboratory confirmation is essential (Ullah et al. 2023). Table 1 explains the essential laboratory tests along with the samples:

9. TREATMENT

Most monkeypox-infected people show mild symptoms and recover without professional attention or treatment. However, in hospitalized patients, the symptoms of the infection, such as nausea, vomiting, pain etc., can be cured with specific supportive therapy. However, antiviral therapy should be considered in patients with severe illness (Goyal et al. 2022).

9.1. SUPPORTIVE CARE

Patients with gastrointestinal symptoms should be treated with appropriate drugs according to the signs. Multivitamins should be administered to support the body's immune system. Similarly, to avoid secondary infection, antibiotics can also be used (Rizk et al. 2022).

9.2. ANTIVIRAL DRUGS

Antiviral drugs can be used to treat monkeypox infection. Most of these drugs are approved for managing small animals, and many studies have also proved their efficacy against monkeypox infection (Adler et al.

2022). The following are a few of the most important antiviral medicines that can be used against monkeypox infection in severe illness;

9.2.1. TECOVIRIMAT

Tecovirimat is an essential antiviral drug that was first described for the treatment of smallpox. Tecovirimat has activity against the envelope protein p37 and prevents viral release from the infected cells. Although the efficacy of this drug against the monkeypox virus has still not been studied, many researchers have proved that tecovirimat can improve the survival of monkeypox-infected patients. The drug also has an effect against rabbitpox in rabbits (Carvalho 2022).

9.2.2. CIDOFOVIR

Cidofovir is an important antiviral drug that has shown its effect against monkeypox infection during the 2022 outbreak. After administering the drug to monkeypox-infected patients, a significant decrease in the lesions has been reported, along with improved clinical signs, including fever and lymphadenopathy (Raccagni et al. 2023).

9.2.3. VACCINIA IMMUNE GLOBULIN (VIG)

It is an intramuscular preparation of the hyperimmune globulin, prepared from the blood of the individual vaccinated against the smallpox infection. VIG is very effective against infections caused by the vaccinia viruses (Huang et al. 2022). The efficacy of the VIG against monkeypox infection is still being studied, but many researchers have proved that VIG is very effective against vaccination side effects, including eczema vaccinatum and aberrant infections caused by the vaccinia virus. However, VIG is contraindicated in individuals with severe T-cell function immunodeficiency (Chakraborty et al. 2022).
Immunotherapies, including immune-modulating agents, monoclonal antibodies, and NK-based cell therapy, are a few important options that can be considered to treat the monkeypox infection. Human IFN-β inhibits monkeypox infection and can be a safe and novel treatment against human monkeypox infection. Before this, human IFN-β was also effective against other infections, including SARS-CoV-2 and hepatitis viruses (Johnston et al. 2012). NK cells-mediated antibody-dependent cellular cytotoxicity is effective against a variety of infected cells, such as HIV, orthopoxviruses, and SARS-CoV-2 (Fang et al. 2008).

10. FUTURE INTERVENTIONS

The rapid spread of the monkeypox infection soon after COVID-19 made it more dangerous, not only for public health but also for the world's economy. In just three months, almost 10,000 cases were reported in non-endemic countries (May to July 2022) (Kmiec and Kirchhoff 2022). Monkeypox infection can be catastrophic for developing countries. The scientific community needs to generate awareness among the public about the possible consequences of monkeypox infection. The struggling healthcare system of developing countries, including Pakistan, will be on the verge of collapse if monkeypox starts to spread.
To tackle the spread of the infection, awareness among physicians about the general signs, symptoms, and precautions of the monkeypox infection is essential to ensure timely quarantine and nosocomial transmission. Similarly, proper disease surveillance is essential to control and monitor cases effectively. (Mansoor et al. 2022). There is a very close relationship between monkeypox and HIV infection. A study conducted on 528 human monkeypox-infected patients revealed that 41% had a human

immunodeficiency virus infection (Thornhill et al. 2022). Thus, physicians should also focus on HIV diagnosis when monkeypox is suspected or confirmed in an individual. Patients with both HIV and human monkeypox infection have more compromised immune systems; thus, to reduce the severe illness in infected patients, physicians should focus on proper treatment. Tecovirimat is a first-line medication that can be effective against HIV and human monkeypox infection when used in combination with antiviral therapy (O'Laughlin et al. 2022).

Equal access to the vaccine is essential for effective control of the disease globally. Currently, Jynneos (a vaccine against monkeypox infection) is just limited to the US, UK, and other developed countries (Freeman et al. 2022). However, this approach for high-income countries can benefit them in the short term. Many studies have proved that the self-prioritization strategy of the high-income country is an immoral act that has led to the emergence of new variants of concern. Although a mutation within the viruses can occur by chance, the large density population of developing countries can exacerbate the transmission and increase the chances of mutation (Yamin 2022). Thus, high-income countries should support developing countries for equal vaccination access. A survey conducted in 7 developed countries suggests that 70% population of high-income countries supports the donation for equal access to vaccines in developing countries (Clarke et al. 2021).

As already discussed, monkeypox infection is mainly reported in homosexuals. It highly indicates that the virus can be transmitted from one person to another through close contact during sexual activities. Thus, proper physical distance should be maintained during the outbreak. The rodent's meat should be properly cooked, and always avoid direct contact with the animal's lesions and fluid.

Illegal trade is another major factor in the zoonotic transmission of monkeypox and other zoonotic diseases. Unfortunately, regulation and enforcement are still insufficient to control the illegal wildlife trade and demand some extra steps from the government bodies and the general public to avoid the emergence of new zoonotic diseases and the spread of existing diseases, including monkeypox infection. There is more need to empower local communities to value wildlife and support international regulations (Rosen and Smith 2010).

11. CONCLUSION

To sum up, monkeypox poses a growing threat to the world and has to be addressed right now with a coordinated, multinational response. The recent global increase in monkeypox cases have brought attention to the virus's ability to start epidemics, travel across borders, and pose a threat to public health systems. Considering monkeypox as a global health concern requires a multifaceted strategy. International cooperation is crucial beyond everything else. Cooperation among nations is necessary to exchange knowledge, assets, and skills in order to effectively identify, manage, and eradicate monkeypox epidemics. This entails enhancing diagnostic skills, fortifying surveillance systems, and creating potent immunizations and therapies Through collaborative efforts, prioritizing research, and increasing public awareness, we can effectively tackle this dilemma and mitigate its effects on worldwide health.

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Hepatitis A: An Overview

33

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ABSTRACT

Hepatitis A, caused by the hepatitis A virus (HAV), remains a consequential global public health concern. This chapter provides a comprehensive overview of the virology, pathogenicity, zoonotic transmission, epidemiology, clinical manifestations, and prevention strategies associated with hepatitis A. Hepatitis A is caused by non-enveloped virus belongs to the family Picornaviridae. It has a limited scope for zoonotic transmission, but it is widely distributed in human population with varying prevalence rates across different regions. Factors such as contaminated food and water sources, and crowded living conditions with poor sanitation contribute to the transmission of the virus. The disease predominantly affects low and middle-income countries, emphasizing the understanding of its socio-economic implications. Clinical features of hepatitis A range from asymptomatic infections to severe liver disease. The virus primarily targets the liver, leading to symptoms such as jaundice, fatigue, nausea, and abdominal pain. Vulnerable populations, including young children and older adults, are at a higher risk of getting severe complications. Timely diagnosis through serological testing is crucial for proper public health management and interventions. Prevention strategies play a pivotal role in controlling the spread of hepatitis A. Vaccination campaigns targeting high-risk populations have proven to be effective in reducing the incidence of infection rate. In conclusion, hepatitis A remains a significant challenge with diverse clinical presentations and global distribution. By fostering a deeper comprehension of the virus and its modes of transmission, healthcare professionals, policymakers, and researchers can contribute to the development of effective strategies to mitigate the impact of Hepatitis A on public health. Ongoing efforts to enhance vaccination coverage, improve sanitation infrastructure on individual and public level, and raise awareness about hygienic practices are crucial for reducing the burden of hepatitis A and preventing its associated complications.

Keywords: Hepatitis A, Infectious Hepatitis, Enterovirus, Jaundice, Fulminant Liver.

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1. INTRODUCTION

Hepatitis is a contagious systemic illness that infects the liver. Initially, only two patterns of hepatitis were noted, named "infectious hepatitis" for clinically apparent infection and "serum hepatitis" for clinically inapparent infection, respectively. These two early forms of hepatitis got differentiation when the Australian antigen was discovered on the surface of the hepatitis B virus. Serum hepatitis was called hepatitis B, and infectious hepatitis was called Hepatitis A (Blumberg et al. 1967). Now, hepatitis has many types; Hepatitis A, B, C, D and E. Hepatitis B and C are the leading cause of chronic illness, while other viruses cause acute illness (Gholizadeh et al. 2023). The hepatitis A virus was characterized in 1973 from human fecal material using an electron microscope by Feinstone and his colleagues (Feinstone et al. 1973; Koff et al. 2002). Complete hepatitis A viral culture was studied a few years later than its discovery (Fig. 1) (Martin and Lemon 2006).

The causative agent of hepatitis A is a non-enveloped hepatitis A virus (HAV). It is an enterovirus (positive single-stranded RNA virus) that belongs to the family Picornaviridae (Fox et al. 2015).

Primarily, hepatitis A (formerly called "infectious hepatitis") is an acute viral disease that affects humans, but in rare cases, it has also been associated with zoonotic transmission. Hepatitis A virus (HAV) is highly contagious that can cause mild to severe illness, ranging from imperceptible anicteric infection to fulminant liver (acute liver failure), and can cause death. Its transmission mode is the feco-oral route via contact with contaminated water, food, and an infected person (Acheson and Fiore 2004). HAV enters the body through ingestion and replicates itself in the patient's liver. Its incubation period is usually from 15-50 days, during which it replicates and remains present in blood and excretes via the biliary system into feces (Foster et al. 2021).

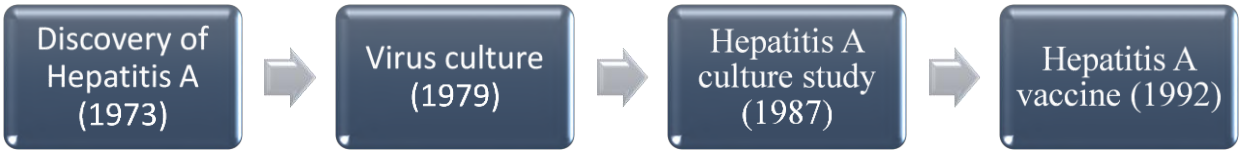

Fig. 1: Series of events after the discovery of the hepatitis virus

HAV can persist in the environment and spread epidemically and sporadically worldwide. Improper personal hygiene, inadequate sanitation, international traveling, oral-anal sex, and lack of safe food and water are the primary cause of getting the infection (WHO 2023). Every year HAV results in millions of cases globally. Based on HAV seroprevalence types, the globe can be divided into high, intermediate, low, and very low endemicity rates (Jacobsen 2018). Its outbreak and illness have lessened due to immunization and adopting health measures, but underdeveloped countries are still struggling with this virus. In highly endemic countries, inhabitants acquire hepatitis in their early childhood and become immune to it for the rest of their lives (Jacobsen 2009).

On the contrary, in less-endemic countries, inhabitants get this infection due to exposure to that environment or engaging in risky health behaviors (Aggarwal and Goel 2015). HAV has an asymptomatic appearance in small children. In developing countries, adults usually do not show clinical symptoms due to partial immunity, but in developed countries, adults show early symptoms. Humans are naturally

more susceptible to HAV and are the reservoir for infection than non-human primates. HAV circulation is limited to primates and is very rare in other vertebrates (Lanford et al. 2019). HAV has been reported in captive non-human primates like monkeys, chimpanzees, etc., where humans have close contact with these animals (Balayan 1992; Chichester et al. 2018). In this chapter, we will discuss virology, epidemiology, zoonotic transmission, clinical complications, and treatment of hepatitis A based on the latest available data.

2. VIROLOGY

Hepatitis A virus is a naked (non-enveloped) RNA virus, 27 nm in diameter, belonging to the genus Hepatovirus and family, Picornaviridae (Fig. 2). The Hepatovirus genus is specifically known to infect small mammals (Drexler et al. 2015). HAV is a very tough virion that can survive in the environment for at least one month and temperatures up to 85℃. Chlorine inactivation and heat-resistant properties make it intact against physical treatment (Lemon 1992; Cromeans et al. 2001).

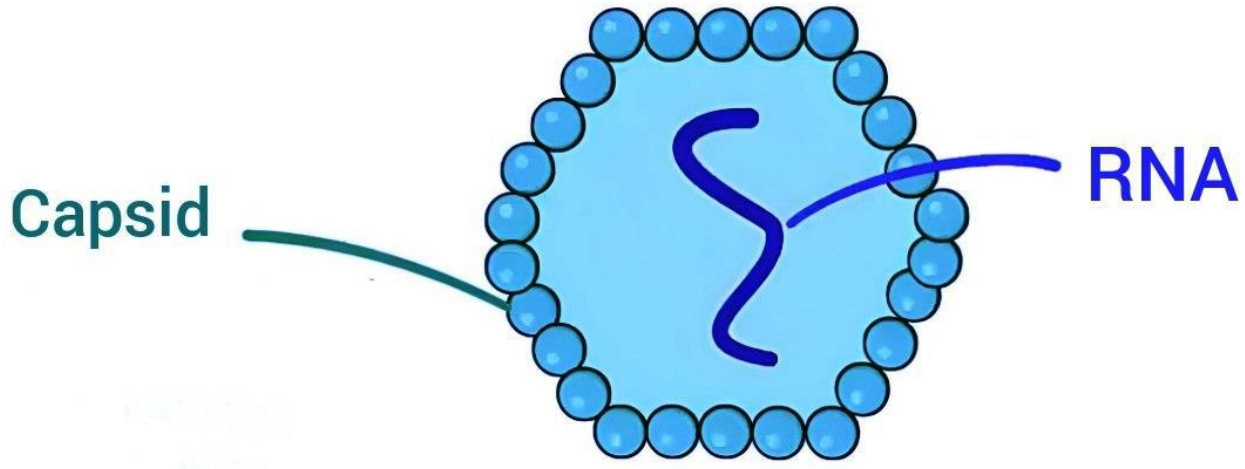

Fig. 2: Structure of Hepatitis A virus; non-enveloped, single-strand RNA genome (Retrieved from Paint)

2.1. SEROTYPE

Hepatitis A virus has only one serotype across the globe. Although it has nucleotide heterogeneity in its genome, this high preservation of nucleotides to hold a single serotype is due to the antigenic structure of the capsid. A person is fully protected from reinfection by other serotypes of HAV, even from different parts of the world. Anti-HAV preparations of immune globulin can give protection against disease irrespective of the geographic region because of the one serotype of HAV (Desbois et al. 2010).

2.2. GENETIC ORGANIZATION

HAV is a positive-polarity (i.e., translatable), single-stranded virus having 7470-7478 nucleotides in its RNA genome (Lin et al. 2017). It has two noncoding regions, a 5' region with ~734 nucleotides and a 3' region with 40-80 nucleotides, respectively. 5' end of the genome has no cap and is attached to a genome-linked viral protein (VPg), a protein primer for the synthesis of RNA (Weitz et al. 1986; McKnight and Lemon 2018). On the contrary, the 3' end terminates with a tail of poly A chain (Baroudy et al. 1985; McKnight

and Lemon 2018). A coding region of ~2225 nucleotides is present in the center of both terminals, which codes for viral proteins (Hollinger et al. 1996; Gholizadeh et al. 2023).

2.3. PROTEIN ARRANGEMENTS

The hepatitis A virus has 3 protein units (P1, P2, P3) as shown in Fig. 3. The structural proteins of the virus derive from the P1 region, and nonstructural proteins involved in the reproduction of the virus translate

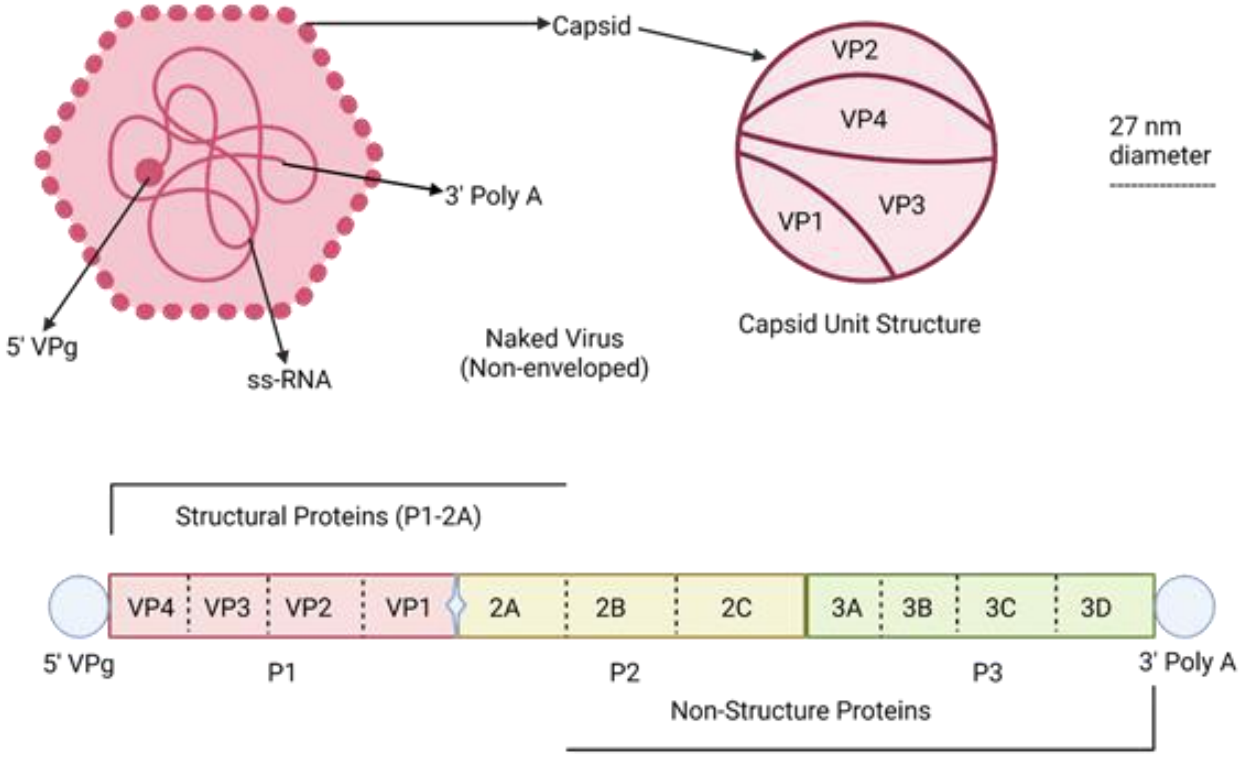

Fig. 3: Hepatitis A virus with its RNA structure having protein units (Retrieved from BioRender)

from P2 and P3 regions. P1 region forms the main proteins of the capsid, i.e., VP1-pX (VP1-2A), VP2, and VP3, along with VP4, which is necessary for virion maturation. These proteins are involved in capsid formation. VP4 protein is not detected in viral culture but only in mature viral particles (Cuthbert 2001). P2 and P3 regions have seven proteins, of which six mature proteins (2B, 2C, 3A, 3B, 3C, 3D) involved in RNA synthesis have nonstructural characteristics (Nainan et al. 2006). Several studies revealed a unique contribution of 2A protein in HAV morphology, but most of its characteristics are still unknown (Morace et al. 2008; Lemon et al. 2018).

2.4. GENOMIC DIVERSITY

HAV shows several genotypes and subgenotypes, although it has a very high degree of nucleotides and amino acids conservation (Robertson et al. 1992). According to the early classification, which facilitates the understanding of the zoonotic aspect, HAV has seven genotypes; four of which (I, II, III, VII) share a

human origin, and three of which (IV, V, VI) have the simian origin (Ching et al. 2002). In 1991, some scientists extracted and reported the simian origin serotypes as mentioned in Table 1.
All three simian genotypes have unique sequences of nucleotides on the P1 region, derived from the species of Old-World monkeys. Early studies showed that these three genotypes have unique signature sequences of nucleotides on capsid protein at VP1/VP3 junction, differentiating them from the human HAV strains (Brown et al. 1989). It has also been studied that non-human primates, i.e., bats, rodents, and shrews, have HAV strains that appear to share antigenicity with the hepatitis A virus of human illness (Williford and Lemon 2016).

Table 1: Non-human primates' strains of HAV, isolated from non-human primates

HAV genotype	Animal	Scientific Name	Imported	Reference
IV	cynomolgus macaque	*Macaca fasicularis*	Philippines	(Nainan et al. 1991)
V	African green monkey	*Cercopithecus aethiops*	Kenya	(Tsarev et al. 1991)
VI	cynomolgus macaque	*Macaca fasicularis*	Indonesia	(Nainan et al. 1991)

3. PATHOGENICITY

The pathogenicity of HAV generally depends upon the severity of the infection and the physiology of infected persons (Rezende et al. 2003; Belkaya et al. 2019). Some pathological events of HAV are described below.

3.1. VIRAL REPLICATION

The entrance route of the HAV in the body is the oral pathway. It replicates only in the targeted host cells. Primarily, it attacks the hepatocytes and binds with its cellular receptors. A recent study revealed that gangliosides are the promoting molecules of HAV entrance into the host cell (Nain et al. 2022). HAV enters the cell by receptor-mediated endocytosis. The viral capsid gets dissimilated, and its genome releases out of the capsid. The viral RNA serves as the messenger RNA for the host cell ribosomes and forms a polypeptide unit by translation. It is cleaved by viral protease (3C unit of the 3P region in the viral genome) to manufacture additional viral protein components (Feng and Lemon 2014; Yang and Zhang 2015). Henceforth, this cellular activity initiates the 3D unit in the P3 region of the viral genome to work as RNA-dependent polymerase (Enzyme) and replicates the RNA to make several copies as shown in Fig. 4. Newly synthesized viral proteins and a viral genome assemble to form a new virus, which releases the infected cell by exocytosis (Lemon 2010).

3.2. HEPATIC CYTOPATHY

Acute hepatitis A cause severe cytopathic effects. The liver, infected with the hepatitis A virus, gets inflammation and destruction of hepatocytes. The hepatitis A virus does not cause hepatic cell death, but the immune-mediated mechanism induces cytopathy of hepatocytes. After replication, a single HAV clones into multiple infectious virions. Activated immune cells, i.e., natural killer cells and macrophages, infiltrate the liver to combat the infection (Chen et al. 2018). T lymphocytes, cytokines, and chemokines play an essential role during hepatitis. T cells coincide with HAV-infected hepatic cells during this viremic phase. Virus-specific $CD8^+$ T cells contribute to the virus control and cause HAV-infected cell injury, thus increasing the ALT level in the blood. T cells also combat hepatitis A virus and control its proliferation in the blood. T cells, cytokines, and chemokines also increase the interferon level in the blood. These cells cause the hepatocytes to release INF-γ, which triggers the natural killer cells, and T cells to release

granzyme molecules. Granzymes are protease enzymes that induce programmed cell death in virus-affected hepatocytes. These hepatic cell deaths due to the hepatitis A virus ultimately result in liver inflammation (Maier 1988; Fleischer et al. 1990; Shojaie et al. 2020).

3.3. DUAL PHENOTYPES

HAV is recently discovered in two phenotypical forms, naked virion and quasi-enveloped virion (eHAV) (Feng et al. 2013). The quasi-enveloped virion is actually a naked virion, membraned by an exosome-like vesicle (McKnight et al. 2017). HAV exists in the bloodstream as a quasi-enveloped virus. eHAV is immature in the lipid-membraned exosome, containing VP1-pX protein. This form of HAV is responsible for the cell-to-cell transmission of virion. In the liver, the detergent-like action of bile salts in the biliary canaliculi releases the naked virion out of the exosome. The naked virion passes from the bile duct to small intestine and is shed into the feces (Hirai-Yuki et al. 2016). This form is the ultimate source of human-to-human viral transmission through feces (Fig. 5). The naked form of HAV is mature and has completely processed VP1 and 2A proteins in its genome (Feng et al. 2014).

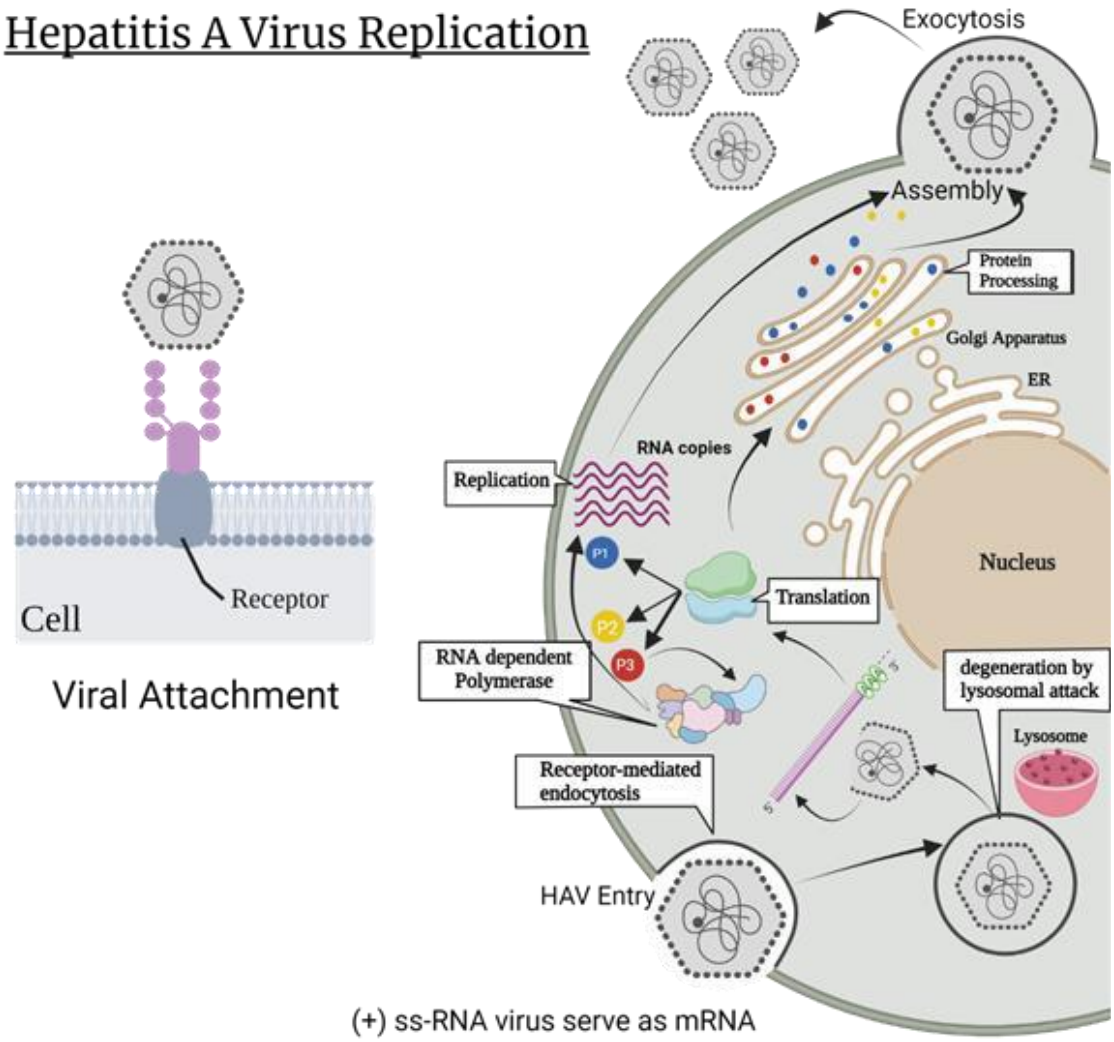

Fig. 4: Generalized replication process of HAV in the host cell of infected patient (Retrieved from BioRender).

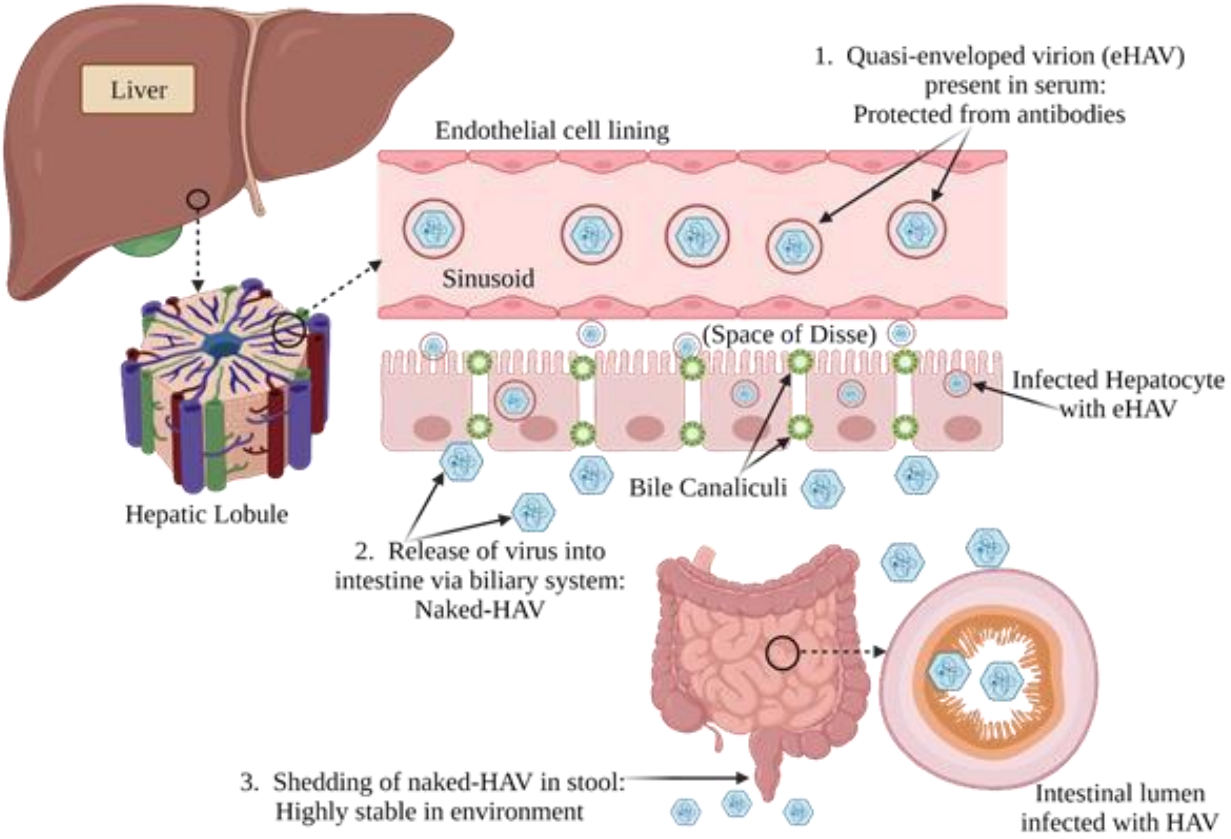

Fig. 5: Two morphological forms of infectious hepatitis A virus (HAV); Quasi-enveloped HAV exists in blood plasma, and naked HAV exists in feces (Retrieved from BioRender).

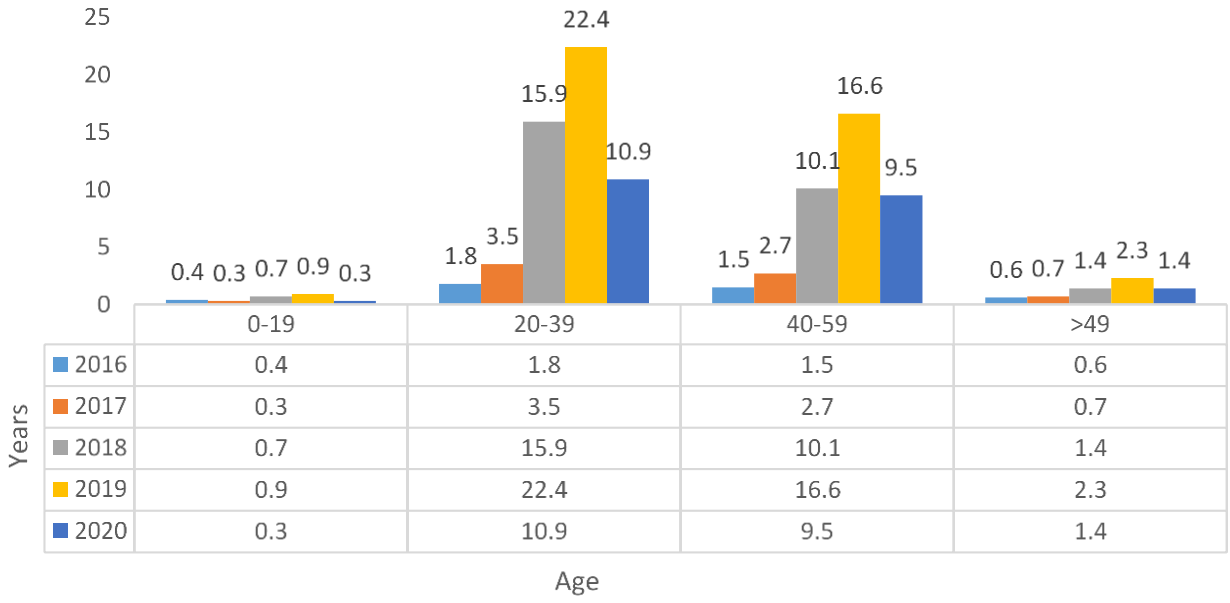

Fig. 6: Rate of HAV distribution per 1 lac population on the basis of CDC report.

4. TRANSMISSION

Hepatitis A virus is exceedingly transmitted through the feco-oral route. The virus is passed either through the ingestion of contaminated food or water materials or through direct contact from one infected person to another. Other potential transmission sources include travel to HAV-endemic countries, sexual contact, men having sex with men (MSM), occupational or nosocomial exposure, and infrequent parenteral transmission. Transmission of the Hepatitis A virus through blood transfusion is exceedingly rare due to the short persistence of viremia (Jeong and Lee 2010).

4.1. CONTAMINATED FOOD AND WATER

Drinking contaminated water, whether caused by poor irrigation infrastructure or inappropriate chlorination, is the potential source of HAV transmission in developing countries. Hepatitis A virus mostly persists in water bodies. It infects vegetative eating and defiles the drinkable water reserves of animals and humans (Ahmad et al. 2018). Many fruits, vegetables, fish, and other edible food become infected if they come into contact with this contaminated water during irrigation or cultivation. HAV transmission through eating improper food and water also includes public food-service workers. They neither sanitize their hands nor wash off serving glasses or plates properly (Schwarz et al. 2008). Sharing this contaminated silverware on public food courts or homes transmits the hepatitis A virus to a large community (Ahmad et al. 2018).

4.2. PERSON-TO-PERSON TRANSMISSION

An infected patient having direct contact with a healthy person causes the transmission of the hepatitis virus. Children are most likely to transmit the infection to their parents due to less scrupulous hygiene (Klevens et al. 2010). Some crowded living communities with less sanitation are also involved in the transmission due to their low standard of living. Moreover, sexual contact, particularly MSM and anal sex, is also a dramatic cause of HAV transmission in Europe and America (Bruisten et al. 2001; Nainan et al. 2005; Tanaka et al. 2019).

4.3. INTERNATIONAL TRAVEL

A healthy person traveling to regions of high HAV endemicity may acquire hepatitis infection because of the unsanitary environment and unhygienic local food of that region. On the contrary, one HAV-infected person can be the vector of this disease to an area with a low HAV rate. It is advisable to get one dose of HAV vaccination before your trip to that infected region (Steffen et al. 2004).

5. EPIDEMIOLOGY

The endemicity of HAV depends upon the hygienic and socioeconomic standards of a region. Hepatitis A has a higher sporadic and endemic rate than all other types of hepatitis. Around the globe, millions of cases are reported, and thousands of people die annually due to hepatitis A. Its prevalence rate is higher in low-income countries than in developed countries (Jacobsen 2018). Its illness rate over the years is described in Fig. 6 (CDC 2020). Hepatitis A infected countries and regions can be classified into high, intermediate, low, and very low HAV endemicity presenting areas as shown in Fig. 7.

5.1. HIGH ENDEMICITY

The high incidence of HAV persists in most developing countries. The highest infection rate of HAV occurs in regions with the lowest living standards. Hyperendemic countries are in African (Sub-Saharan) and

South Asian regions (Jacobsen 2018). Pakistan is also one of the highly infected countries with hepatitis A. Although these regions have a high rate of hepatitis, the surveillance of reported cases is very low due to the asymptomatic behavior of local populations. However, this asymptomatic illness confers even long-term immunity to infected patients. Seroprevalence survey in high endemicity regions shows that nearly 100% of adults and older children have IgG (anti-HAV immunoglobulin) levels in their blood, indicating past viral exposure. These statistics provide evidence of the high incidence rate and adaptive immunity of individuals in low-income countries (Jacobsen 2009).

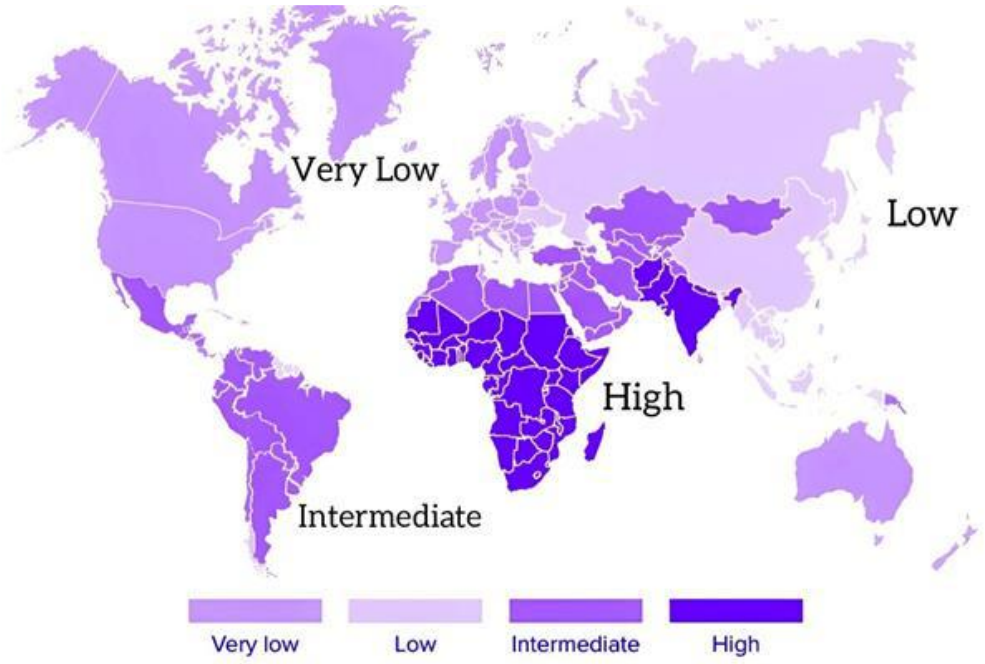

Fig. 7: Worldwide map of HAV seroprevalence (Retrieved from Paintmap)

5.2. INTERMEDIATE ENDEMICITY

These regions have a medium level of hepatitis A incidence. The sanitation and hygienic conditions are improved to facilitate the individuals and decrease the HAV incidence rate; however, populations are still susceptible to HAV due to the low vaccinations and immunity development. Eastern Europe, Middle Asia, and South American countries are on the hit list of intermediate incidences of HAV (Jacobsen and Koopman 2004).

5.3. LOW ENDEMICITY

These areas have a relatively low incidence rate of HAV, primarily due to vaccination efforts, improved hygienic norms, and better sanitation. HAV infection is unusual in these regions and often invades individuals during traveling or immigration from high or intermediate-susceptible countries. East Asian and East European regions mainly include in this category (Jacobsen and Wiersma 2010).

5.4. VERY LOW ENDEMICITY

These regions have a minimal incidence of HAV. Viral infection is sporadic due to universal vaccination, advanced research, high hygienic measures, and promising sanitation. Although these regions have a

negligible rate of HAV, very severe cases of HAV-infected children and adults have been reported due to less innate immunity and local exposure to this virus. That's why many adults and children remain susceptible to this disease (Carrillo-Santisteve et al. 2017). Australia, North America, and Western Europe fall in this category (Koff 2004).

6. ZOONOTIC FACET

Hepatitis A is a host-limited viral disease that principally affects humans. Unlike hepatitis E, it does not have a wide range of infected host transmission; however, there are some instances where it has been transmitted from animals to humans and holds zoonotic importance. The main animals implicated in the zoonosis of hepatitis A are non-human primates, i.e., new-world monkeys, old-world monkeys, and Apes (Lanford et al. 2019). The zoonotic relevance of hepatitis A is very uncommon and is associated with close contact between humans and infected animals. These animals carry and shed the virus in their feces. Humans get this infection from animals related to their life activities. People who toil directly with these primates, such as veterinarians, researchers, animal handlers, and zookeepers, are at a high risk of acquiring zoonotic infection (Smith et al. 2017).

These non-human primates share genetic relevancy with human DNA; thus, pathological sequences of the viral infection in hepatocytes are similar in these primates as in humans. Zoonotic transmission of HAV has significant importance in low-income countries due to the typical habitat of humans living with these primates. In developed countries, it has zoonotic significance because biomedical research centers and zoos provide direct exposure to these primates. Seafood also plays a crucial role in zoonotic complications of hepatitis A (Halliday et al. 1991; Pintó et al. 2009). In China, bivalve shellfish, i.e., oysters, cockles, and calms, are a leading cause of HAV transmission to the human population. Shellfish are filter feeders that can live in contaminated water and concentrate the virus in their bodies. Thus, shellfish eating causes the infection of hepatitis A in humans (Xu 1992; CFS 2000). The susceptibility of HAV in mice with some genetic depletion and modification in the virion has also been observed. The basic theme of this study was permitting experimental broadness of the host range, zoonotic mode, and interferon-mediated responses on viral prevalence (Hirai-Yuki et al. 2018).

7. CLINICAL SIGNS AND SYMPTOMS

HAV has a broad range of clinical manifestations, from severe liver damage to mild instances of disease with no signs and symptoms. Clinical interventions are mainly dependent upon the age of the infected patient. In children under 6 years of age, HAV usually remains asymptomatic, and illness remains anicteric, but in adults, it is symptomatic in 70% of cases (Hadler et al. 1980; Abutaleb and Kottilil 2020). There are two types of clinical manifestations based on the duration of the illness.

7.1. TYPICAL MANIFESTATIONS

It includes the prodromal and icteric phase symptoms of the disease that start after the incubation period of HAV, about one-month following exposure to the viral attack (Fig. 8). The prodromal phase includes the very first nonspecific symptoms of HAV that last for 5-7 days. This phase is the onset of cytopathic effects in the liver, resulting in the initial change in the body functions. Fever, anorexia, fatigue, malaise, and vomiting are the common complaints of adults during the prodromal phase of HAV infection, but small children usually don't show any such signs or symptoms (Martin and Lemon 2006; Van Damme 2017).

The icteric phase starts after the prodromal phase. It is the severe stage of hepatitis A and has clinical importance due to the jaundice manifestation. During the icteric phase, there is inflammation of the liver

due to immune-mediated attacks on the hepatic cells. The hepatocytes become dysfunctional, and their structure changes leading to hepatocellular injury. This inflammation disrupts the breakdown of red blood cells and produces nonconjugated bilirubin. Jaundice is characterized by the paleness (yellowing) of the skin, especially on the hands and feet, sclera of the eyes (icterus), and mucous membranes of the body due to the accumulation of bilirubin in these tissues (Hoofnagle and Seeff 2006; Dienstag 2019). Accumulation of conjugated bilirubin in the kidney also leads to dark urine production during the very onset of this phase. ALT and AST levels increase in serum due to hepatic dysfunction and inflammation. There is severe upper right-quadrant abdominal pain due to hepatomegaly (inflamed liver). Less common symptoms include diarrhea, skin rashes, and pruritis, which may also appear during the icteric phase (Khan et al. 2012).

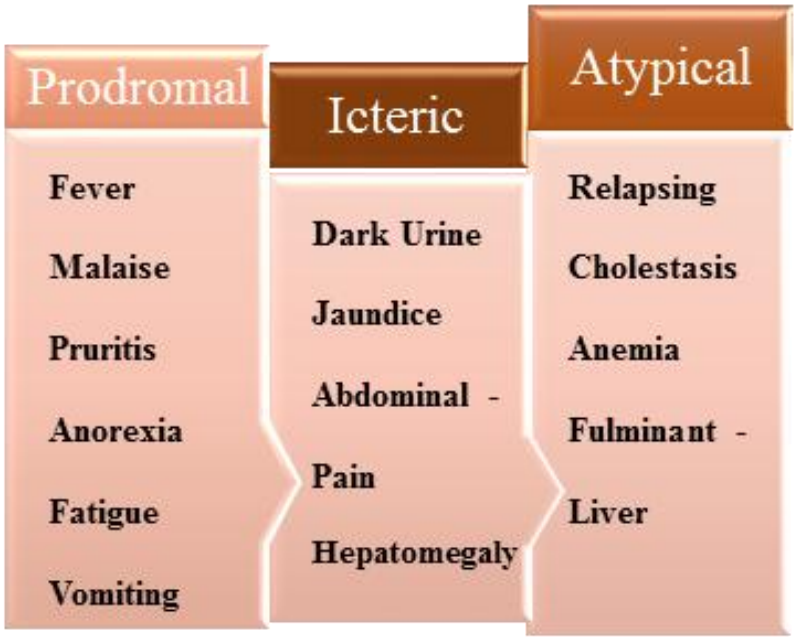

Fig. 8: Symptoms of HAV during the initial and late stages of infection

7.2. ATYPICAL MANIFESTATIONS

HAV cannot establish long-persistent infection in humans or non-human primates and cannot induce chronic infection even in significantly immunocompromised patients. It is a self-limited disease and does not prolong to chronicity. Typically, the illness persists for less than 2 months; however, many atypical complications can occur in 10 to 15% of the patients. These symptoms include relapsing hepatitis, prolonged cholestasis, acute liver failure (fulminant liver failure), and other extrahepatic manifestations (Jeong and Lee 2010). Relapse of disease occurs after 2 to 6 months of the initial viremia, but it does not cause such a severe form of hepatitis as the initial one accomplishes (Glikson et al. 1992).

Prolonged cholestasis (accumulation of bile elements in the liver) causes the impairment of bile flow and lasts up to 6 months, resulting in intense pruritis, malabsorption, and fatigue (Sherman 2015). The severe form of hepatitis A is fulminant hepatitis, characterized by the rapid progression of liver failure. Fulminant hepatitis occurs in less than 1% of HAV-infected patients. The risk of fulminant hepatic failure is more targeted in adults over 40 years of age with chronic liver disorders (Murphy et al. 2016). It develops in scarce situations of HAV but is potentially characterized by life-threatening complications. Higher viral concentrations in aged patients cause viremia that is impatient to recover

due to immunosuppression, ultimately leading to acute hepatic failure (Lee et al. 2015; Moon et al. 2018). It has a high mortality rate, and a liver transplant can be the only option for survival (Uchida et al. 2018).

8. HAV DIAGNOSIS

HAV infection cannot be clinically diagnosed because it may include similar reaction symptoms to other types of hepatitis. Due to the single serotype, detection of the anti-HAV antibodies in the blood is very easy. It can be differentiated from other types of hepatitis by examining the humoral immune response of the patient's body. These antibodies are detected by serological testing. There are different techniques to determine HAV positivity in the infected patient (Tennant and Post 2016; Medscape 2021).

8.1. ANTIBODIES EXAMINATION

In this method, IgM antibodies against hepatitis A are examined (Park et al. 2009). IgM antibodies mainly detect the capsid proteins of HAV. These antibodies start proliferating about 1-2 weeks after exposure to infection and persist for several months. Before the onset of clinical symptoms, anti-HAV IgM antibodies start proliferating in the blood. However, IgM levels can report false results due to autoimmune hepatitis or rheumatoid factors, which cause cross-reactivity of antibodies. Therefore, it is not advisable to rely only upon this antibody detection test (Lee et al. 2013; Tennant and Post 2016).
After one week of IgM production, IgG antibodies produce in the convalescent period of infection and persist in the body for the whole life to secure a person against relapsing of the infection (Fig. 9). IgG antibodies remain in feces, urine, serum, and saliva even post-exposure to the disease (Chitambar and Chadha 2000; Oba et al. 2000). Enzyme-linked immunosorbent assay (ELISA) is preferable to distinguish between IgM and IgG antibodies in the blood. The comparison between these two antibiotics gives enough data to detect the previous infection or ongoing viremia in the patient's body (Crum-Cianflone et al. 2011). These antibodies can be easily collected from saliva and used for anti-HAV saliva analysis. Saliva examination is more feasible in outbreaks and epidemiological testing due to the simplicity of sample collection from a large number of individuals (Augustine et al. 2020).

8.2. LIVER ENZYMES EXAMINATION

HAV causes liver inflammation, which results in elevated levels of several enzymes, i.e., alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and aspartate aminotransferase (AST). Their level becomes 5-50 times increased in the blood. This test indicates the infection complexity during the onset of HAV symptoms. Increased level of these enzymes in the blood helps to measure the infection rate of the liver by comparing it with standard enzyme values (Medscape 2021).

8.3. ANTIGEN EXAMINATION

The nucleic acid of HAV is detected in the infected samples of patients through Nucleic acid testing (NAT). It is the more sensitive and accurate method for examination. This technique includes Southern blotting (Buti et al. 2001; Calder et al. 2003), single-strand conformational polymorphism (Goswami et al. 1997; Fujiwara et al. 2000), real-time PCR (Costa-Mattioli et al. 2002) and reverse transcription-PCR (Polish et al. 1999; Cromeans et al. 2001). The most sensitive, precise, and extensively used method for HAV-RNA detection is RT-PCR. This method is a low-cost HAV detection test with the gold standard of specificity (Kozak et al. 2022).

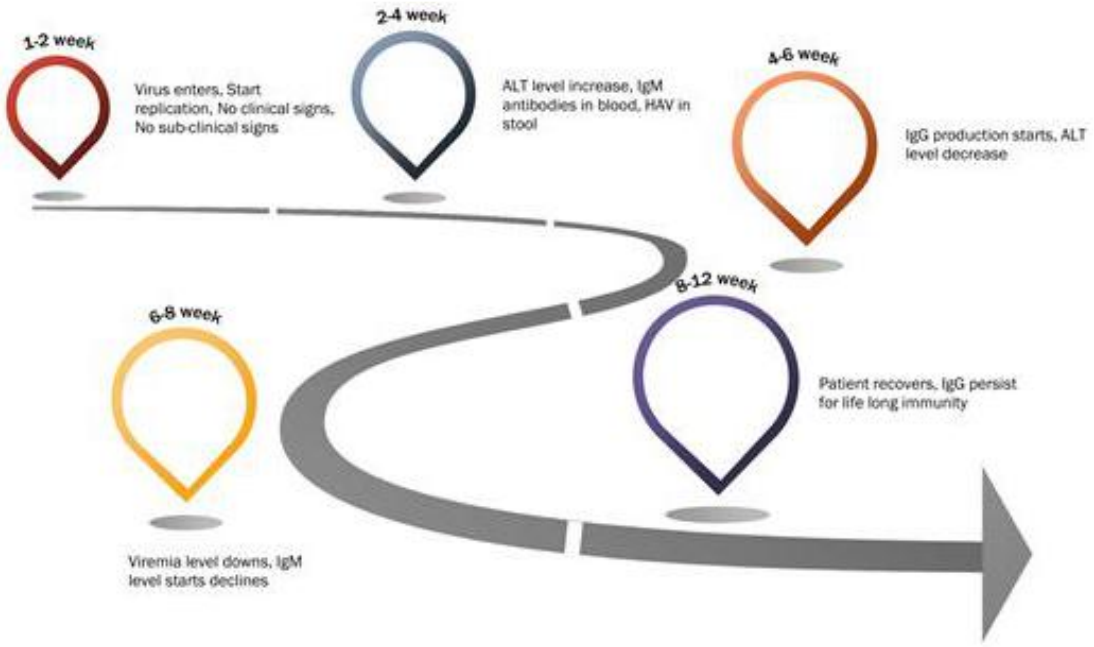

Fig. 9: Antibodies production sequence and their levels in the body after exposure to the HAV

9. TREATMENT & PREVENTION

Hepatitis A has no specific treatment. The infected patient is given supportive treatment against the disease. In most cases, patients recover on their own without any medication or assistance. Proper rest is required to conserve body energy during the acute stage of illness. Fresh water and juices are recommended to maintain the body's electrolytes during vomiting and diarrhea. Antiemetics and antipyretics can be used to control vomiting and fever (Lanford et al. 2011). In fulminant hepatitis, hospitalization is required for proper monitoring of liver functions and supportive therapy. Anti-viral drugs are used briefly, but it is advisable to refrain from any drug intake during the acute phase of HAV (Migueres et al. 2021). Recovery usually takes 3-7 weeks. Auxiliary care and better nutritional therapy are effective for treatment. Interferon treatment for acute hepatitis was previously effective in some HAV-infected patients, but results remained limited and unclear (Crance et al. 1995). Further quality research is required to investigate and discover suitable medication against HAV.

Complete sanitation and self-hygiene, such as regular handwashing, sanitizing hands before meals and after using the toilet, proper vaccination, proper cooking of food at high temperatures, water chlorination, and use of disposable plates or glasses on public water and food courts, can help to prevent the HAV infection. Preventive techniques for the sexual transmission of HAV should be adopted using safe sex methods (Ndumbi et al. 2018). Despite vaccination availability, a challenge to developing anti-viral treatment still has space to discover more in this field to shorten the period of symptoms, limit the outbreaks, reduce drug ineffectiveness, and treat atypical complications like fulminant liver (Thomas et al. 2012; Migueres et al. 2021).

9.1. PASSIVE IMMUNIZATION

Passive immunization against HAV is provided to the infected patient by administering immunoglobin. It provides the immediate source of antibodies against HAV. Immune globulin is recommended in patients

with severe HAV infection. It is provided as a post-exposure prophylaxis to immunocompromised patients, the elderly, and patients with chronic liver diseases. In the modern era, immune globulin is now being replaced by inactivated vaccines due to its short time action and large dose requirement (Victor et al. 2007).

9.2. ACTIVE IMMUNIZATION / VACCINATION

Vaccination in the whole community is a strategic approach toward eliminating and preventing the hepatitis A virus (Bell and Feinstone 2004). Developed countries have adopted the universal vaccination program, resulting in the control of HAV. Two vaccine forms are available against HAV: live-attenuated and inactivated (Patterson et al. 2019). Inactivated vaccines are the most commonly used in developing and some developed countries. These are effective for pre-exposure prophylaxis but require multiple doses over time to obtain ongoing HAV immunity. In China, an attenuated vaccine against HAV has been developed with a weekend virus form and provides long-lasting immunity than inactivated vaccine (WHO 2019). Vaccines have several advantages over immune globulin, including long-term immunity, pre-exposure prophylaxis, and easy availability in market. Usually, two main doses of the HAV vaccine are administered to individuals. The first dose is given after 1 year, and the second booster dose is given after 6 months following the first dose. Routine vaccines with an additional single dose are provided against HAV before international traveling, patients with chronic liver failure, HIV-infected patients, and people who use injection drugs (CDC 2021).

10. CONCLUSIONS

Hepatitis A has the most viremic prevalence among all other forms of hepatitis. It is a pervasive disease of humans, which has become a global curse affecting developed and developing countries every year. The primary mode of person-to-person transmission of HAV has more importance than its zoonotic mode of animal-to-human transmission. However, its zoonotic aspects highlight the need for precautions and safety measures to follow while handling and working with these animals. Personal hygiene, proper nutritional equipoise, along with immunization are the best strategies to adopt during incipient and prophylactic cures against this disease.

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Pathological Events of Lassa Fever Infection

34

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ABSTRACT

This chapter discusses the morphology, epidemiology, pathology, mortality risk factors, clinical manifestations, diagnosis, treatment, and prevention of Lassa virus (LASV) with a main focus on pathological events associated with the infection caused by LASV. Lassa fever (LF) also known as the viral hemorrhagic illness is caused by the LASV. It belongs to the family Arenaviridea. It is an animal-borne ailment spread by the common African rat. It is endemic in West Africa. It is a medium-sized virion that measures between 70 and 150 nm and is spherical. It is composed of two ambisense RNA segments. The natural reservoir of this virus is the Mastomys natalensis which is a common rat found in rural West Africa. Humans generally get an infection when they come into contact with the urine, feces, and respiratory secretions of the rats as the virus is shed in the secretions of the rats and also found in the blood. The prevalence of the antibodies to the lassa virus is 21% in Nigeria, 8 to 52% in Sierra Leone, and 4 to 55% in Guinea. LASV primarily affects the endothelial cells and utilizes the alpha-dystroglycan receptors. LASV suppresses the cells of the immune system and prevents the secretion of proinflammatory cytokines. Almost 80% of the patients do not show any kind of symptoms so LF is difficult to diagnose. Infected individuals may show acute to severe LF followed by multiple organ failure that can be seen in the spleen, kidney, and liver. The similarity of symptoms with other diseases is quite challenging in the recognition of the infected ones. Supportive treatment is the basis for the management of LF. Ribavirin is a broad-spectrum antiviral drug that is a guanosine analogue and owes a fine activity against LASV. In conclusion, LF is a crucial rodent-borne (zoonotic) illness. Suitable training of medical personnel and health care workers is essential in the treatment and prevention of infection. Vaccine development, preventive measures, and the development of drugs other than ribavirin or the modification of the existing drugs are the major suggestions to diminish LF.

Keywords: Viral hemorrhagic illness, Lassa virus (LASV), Ambisense RNA, Mastomys natalensis, Rodent-borne

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1. INTRODUCTION

The viral hemorrhagic illness known as Lassa fever (LF), caused by the Lassa virus (LASV). It is an arenavirus endemic in West Africa. Generally, it is spread by the common African rat and it is an animal-borne ailment. Lassa fever's first documented case occurred in Borno state of Nigeria in 1969 where two missionary nurses died because of LF and is named after the Nigerian town (Lassa), the virus is then isolated by Buckley and Cabals in 1970 (CDC 2022). It is noteworthy that nosocomial infections can affect healthcare workers as well (Chevalier et al. 2014). Throughout West Africa, it is endemic with a higher incidence in Sierra Leone, Liberia, Guinea, and Nigeria since *Mastomys natalensis*, the animal reservoir and vector of the virus is widely spread (Asogun et al. 2019). The endemic areas suffer considerably from the economic burden of this disease and public health officials around the world are concerned about potential importation (Garnett and Strong 2019; Kofman et al. 2019).

As the disease starts, it usually causes fever, general weakness, and malaise. Incubation period of LF ranges from 6 to 21 days. Flu-like symptoms may follow in a few days, including headache, chest pain, sore throat, cough, nausea, vomiting, diarrhea, and abdominal pain. Aside from facial swelling, there may also be pleural amd pericardial effusions, low blood pressure, and bleeding from the nose, mouth, vagina, or intestines in severe cases (Buckley and Cabals 1970; Asogun et al. 2019). Mortality and morbidity rates are considerably high in pregnant women suffering from lassa fever infection (Akpede et al. 2019; Kayem et al. 2020). Exposure to the excreta of the rodents and even butchering/hunting of the infected rodents can transmit disease to humans (McCormick et al. 1987; Ter Meulen et al. 1996; Newman 2021). Study findings from recent years (Lo Iacono et al. 2015) suggested that outbreaks are primarily driven by independent zoonotic transmission, whereas approximately 20% of cases result from secondary transmission, usually through spreading events in hospitals. Splenic, hepatocellular and adrenal necrosis and other histopathological changes in kidneys, lungs, and heart were observed on pathological examinations (Winn and Walker 1975; Walker et al. 1982; Hensley et al. 2011; Stein et al. 2021).

Even though Lassa fever gets its diagnosis from clinical criteria, laboratory confirmation is essential to confirm the diagnosis. Lassa fever is commonly diagnosed by enzyme-linked immunosorbent assays (ELISAs), which detect IgM and IgG antibodies and also LASV antigens. The best method for the early diagnosis of the disease is the reverse transcription polymerase chain reaction (RT-PCR) (Wiley et al. 2019) For treatment purposes, ribavirin is used. It is an antiviral drug with a broad spectrum of activity against LASV (Bausch et al. 2010). Oral and intravenous routes of transmission are used but the most preferred method is intravenous treatment as it shows a stronger effect in higher-risk cases. Control of rodents, avoiding direct contact, and consumption of rats are the main preventive measures against LASV (Ogbu et al. 2007).

This chapter aims to discuss the structure of the LASV, its epidemiology and prevalence in different regions, replication strategy, pathological events, complications caused by the virus, diagnostic approaches, zoonotic importance and mechanism of its transmission, current and developing methods of treatment of the infection, and the strategies to prevent and control the virus.

2. VIRUS MORPHOLOGY

This medium-sized virion measures between 70 and 150 nm and is spherical. A single-stranded RNA virus known as the LASV belongs to the Arenaviridae family (AV). All members of the family are composed of

two segments of ambisense RNA (genome that is used in both negative and positive sense capacities) and a nucleoprotein. This nucleoprotein is surrounded by a lipid envelope, which in turn contains a glycoprotein (Fig. 1). A sand-like particle inside the virus is traceable to ribosomes from the host, that is why it gets its name (Arena = sandy) via electron microscopy. The AV is classified based on their geographical distribution. They include the worldwide leukocytic choriomeningitis virus (LCMV), as well as the African LASV and Lujo viruses, all of which are not known to cause human disease. In particular, a new world virus is a group of viruses that are distributed across specific areas of the American continents, including the Junin, Guanarito, Machupo, and Sabia viruses, as well as other non-pathogenic strains (Yun and Walker 2012). As it contains two segments of single-stranded RNA the smaller RNA encodes the immature glycoprotein precursor and the nucleoprotein while the larger RNA segment encodes the Z protein and RNA polymerase which is RNA-dependant (Salvato et al. 1989; Eichler et al. 2003; Andersen et al. 2015).

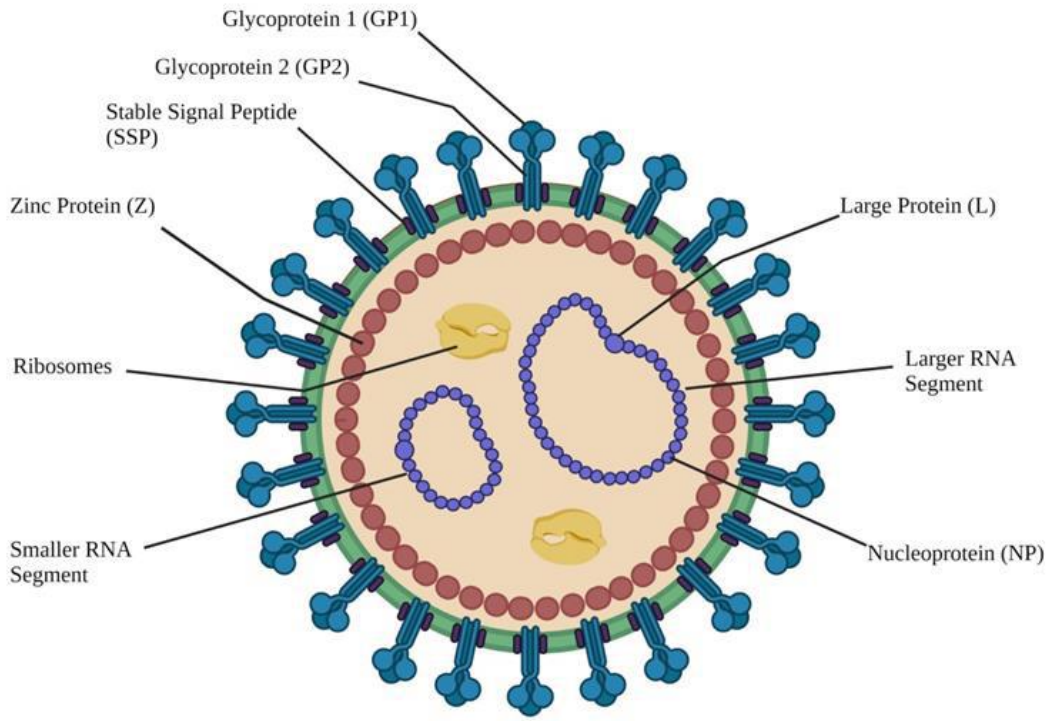

Fig. 1: Structure of Lassa Virus (Retrieved from BioRender)

3. EPIDEMIOLOGY

The virus is sustained in the environment by the rats that are chronically infected. The natural reservoir of this virus is the *Mastomys natalensis* which is a common rat found in rural West Africa. Humans generally get an infection when they come into contact with the urine, feces, and respiratory secretions of the rats as the virus is shed in the secretions of the rats and also found in the blood. Inhaling the dust contaminated with the virus or eating rats is also a source of infection (CDC 2015; Seregin et al. 2015). The virus may be shed in urine for 21-42 days and in semen for 3 months with a considerable risk of sexual transmission inspiring the survivors to use condoms (Richmond et al. 2003; CDC 2015; Seregin et al. 2015; WHO 2015). The regions in which the disease is endemic are Nigeria, Sierra Leone, and Liberia with seroprevalence rates of about 7% or more than 20% (Ogbu et al. 2007; Yun and Walker 2012). Confirmed cases were reported in Guinea, Mali, Senegal, Congo, Cote d'Ivoire, and Central African Republic (Fig. 2) (Richmond and Baglole 2003). Annually there is an incidence of about 100,000 to 300,000 cases out of these almost 5000 cases are fatal. In 2014 and 2015 two cases were reported in the United States (CDC 2015).

Fig. 2: Lassa fever: Outbreaks and Serological evidence of human infection (BMJ 2003) (Retrieved from BioRender).

The prevalence of the antibodies to the lassa virus is 21% in Nigeria, 8 to 52% in Sierra Leone, and 4 to 55% in Guinea (McCormick et al. 1987; Tomori et al. 1988; Lukashevich et al. 1993). The case fatality rate of lassa fever in the general population in Sierra Leone is about 70% and it is 20% in other developing countries (Keïta et al. 2019; Koch et al. 2021). Nigeria is also an endemic country. There is an increase in the number of cases that are confirmed because of poor sanitation, the presence of rodents that carry disease, and a lack of education and awareness among healthcare workers and the public (Fig. 3) (WHO 2023). So, the countries in which *Mastomys natalensis* is not commonly present generally have a less prevalence of the lassa virus. To stop the transmission of the virus in the prevailing countries people should avoid contact with the *Mastomys* rodents, keep the food in the containers that are rodent-proof, and by cleaning the houses to discourage the entry of rodents (Africa CDC 2019).

4. PATHOGENESIS OF LASSA FEVER

Lassa virus primarily affects the endothelial cells and utilizes the alpha-dystroglycan receptors to establish itself in the cells like macrophages, endothelial cells, and dendritic cells and these are the sites where the virus replicates. Lassa virus inhibits the manufacturing of interferons by the cells with the help of nucleoproteins (Fig. 4). Moreover, the LASV suppresses the cells of the immune system and prevents the secretion of the proinflammatory cytokines which include IL-8β, IL-6, and tumor necrosis factor (TNF-α) (Brosh-Nissimov 2016).

Receptors (alpha-dystroglycan) on the cell surface helps the virus to enter into the host cell. Alpha-dystroglycan is a very versatile receptor. LASV adopts a specific replication strategy called as “Ambisense” and it is very rapid. The early transcription of mRNA makes enough deposition of viral proteins that are required for the upcoming stage of replication. NP and L proteins are translated by the mRNA. Positive sense gene makes the copies of viral complementary RNA (vcRNA). Templates of RNA make the Negative-sense progeny. The mRNAs that are produced from the vcRNA are utilized to synthesize glycoproteins (GPs) and zinc (Z) proteins. At last temporal controls intensify the formation of spikes (Morin et al. 2010).

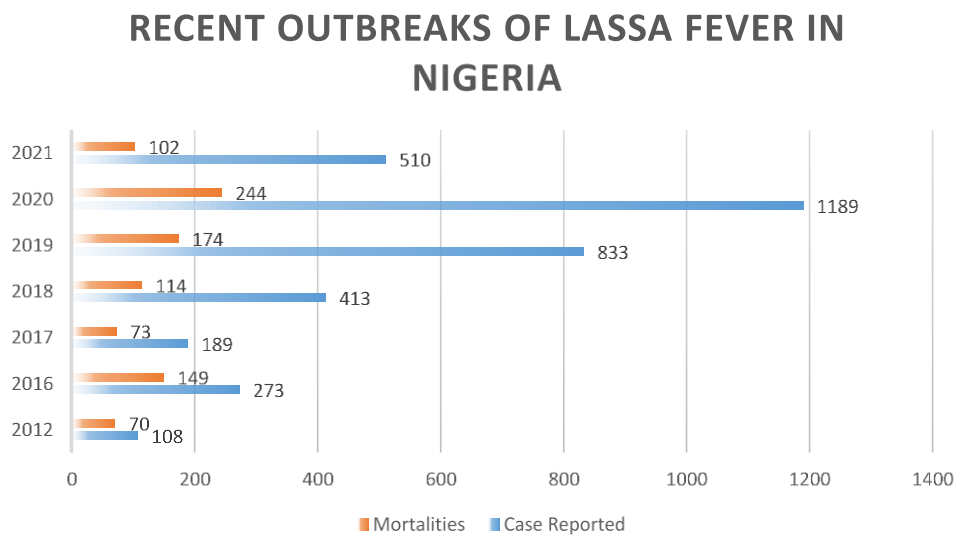

Fig. 3: Recent Outbreaks in Nigeria (Africa CDC 2019)

Initiation of the lassa fever infection occurs when an individual comes in contact with the excreta like respiratory secretions, urine, and saliva of the rat that carries the LASV. Antigen-presenting cells work as the focal points for the virus as it gets entry into the host cell. Most tissues of humans are infected by the virus causing multi-systemic complications, and stoppage of translocation of interferon regulatory factor-3 (IRF-3) (Rojek and Kunz 2008; Hastie et al. 2012). LASV halts the responses of interferon (IFN) as it has exonuclease activity. LASV utilizes pathogen-associated molecular patterns (PAMP) to find a way around the host's immune response (Azeez-Akande 2016). LASV mostly affects the blood vessels and cells of the reticuloendothelial system that are the sites of its replication and injures the capillaries. Bleeding in the lungs, brain, intestine, and myocardium can be observed (Günther et al. 2001; Ogbu et al. 2007).

Free expression of cytokines induced by the LASV is considered as the feasible mechanism of lassa fever pathogenesis. There is reported evidence of the fatal lassa fever in Germany in 2000 (Schmitz et al. 2002). The patient died because of multiple organ failure and development of shock which is because of hemorrhage and clinical findings showed that there is a high level of the interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and proinflammatory cytokines. Although, no elevation in cytokines can be seen in another case study of lethal LF. This indicates that the concentrations of TNF-α and IFN-γ increased for a brief duration or in a few patients (Mahanty et al. 2001; Yun and Walker 2012). Therefore, LF does not exhibit a "cytokine storm" as it is apparent in other hemorrhagic fevers (Ogbu et al. 2007; McLay et al. 2014).

Additionally, the organized suppression of the immune system by the virus is somehow related to the pathogenesis of the LF (Lukashevich et al. 1999). When there is an infection of LASV, the dendritic cells (DC) and macrophages (MP) fail to activate. Infected DC shows malfunctioning and is unable to produce the proinflammatory cytokines (Mahanty et al. 2003; Baize et al. 2004). Mopeia virus which is a non-pathogenic arenavirus, also affects the DC and has a 75% amino acid sequence resemblance with the LASV and has the same rat reservoir (Bowen et al. 1997). Mopeia virus can cause stronger responses of T-cells (Pannetier et al. 2011).

The principal pathological change is in the capillary permeability, along with the development of hypovolemic shock and edema, necrosis of the liver, adrenals and spleen, and hepatitis is also observable (Ogbu et al. 2007; McLay et al. 2014). Immune response against the LASV is not thoroughly acknowledged. Cell-based immunity is very essential with efficient responses of T-cells in the survivors (Yun and Walker 2012). Responses of antibodies are less essential, however, there is an early production of the antibodies, and neutralizing antibodies emerge after weeks or months and have low avidity and titers (Seregin et al. 2015).

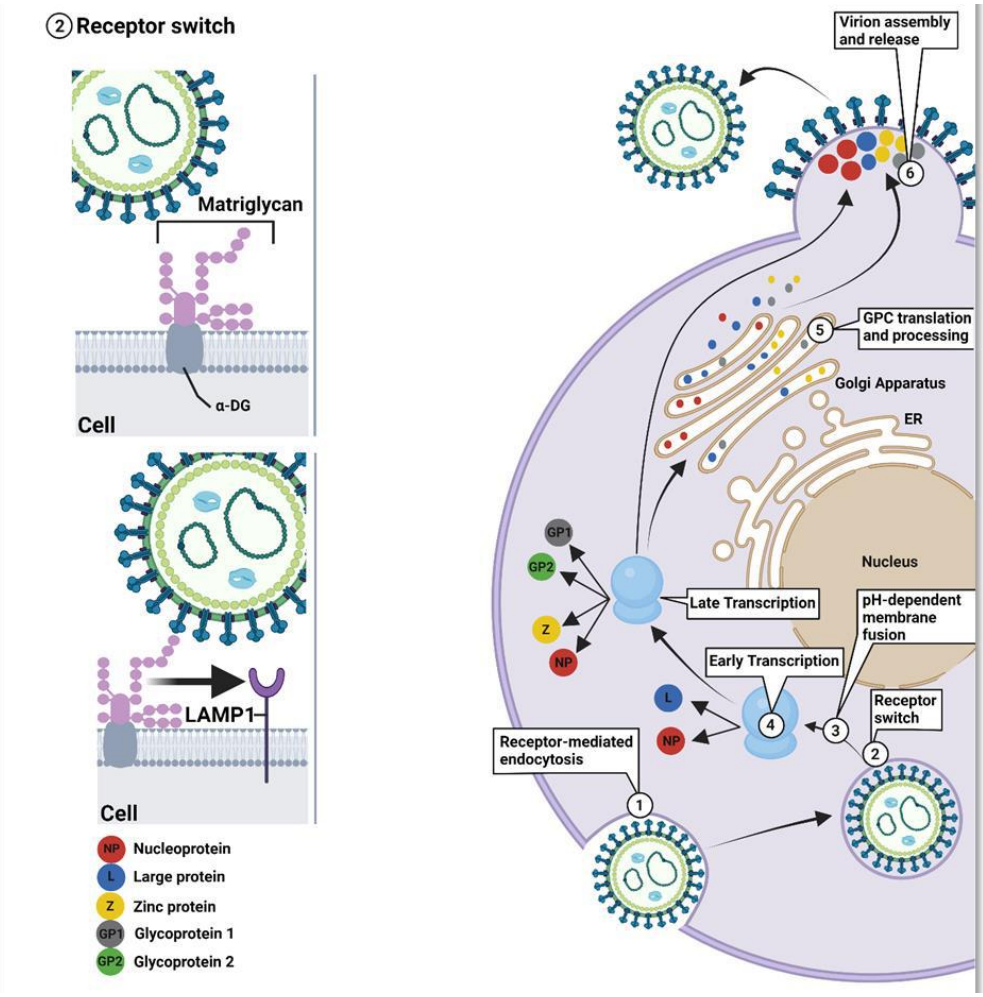

Fig. 4: Replication strategy of Lassa virus (Retreived from BioRender)

5. ZOONOTIC PERSPECTIVE AND TRANSMISSION OF LASSA VIRUS

Lassa fever (LF) is a zoonotic disease (McCormick and Fischer-Hoch 2002; Günther and Lenz 2004; Fichet-Calvet and Rogers 2009). The primary reservoir of LASV is *Mastomys natalensis* which is a multimammate mouse. Some other reservoirs (*Hylomyscus pamfi* and *Mastomys erythroleucus*) have also been currently recognized (Olayemi et al. 2016). The participation of these two species in human infections is still unknown. LASV can spread between *Mastomys natalensis* via vertical or horizontal routes (Fichet-Calvet et al. 2008; Fichet-Calvet et al. 2014).

Transmission through rodents into humans generally occurs due to direct contact with the fluids like blood, saliva, and urine and indirectly via foodstuffs and surfaces polluted with these fluids (McCormick 1999; Ogbu et al. 2007). Urine may exhibit a certain threat of infections in humans as the *Mastomys natalensis* can cast LASV in the urine at any time of their age (Walker et al. 1975; Borremans et al. 2015). LASV can be converted into a fine mist in the laboratory (Stephenson et al. 1984). In living areas and hospitals, contact with the fluids of the human body is a common source of infection transmission and approximately occurs in 20% of the cases (Fig. 5). Chances of disease development because of zoonotic transmission are generally connected with the consumption and hunting of rodents (Ter Meulen et al. 1996; Bonner et al. 2007; Bonwitt et al. 2016). While shaking hands, hugging, and sitting together are not a source of LASV transmission (WHO 2015).

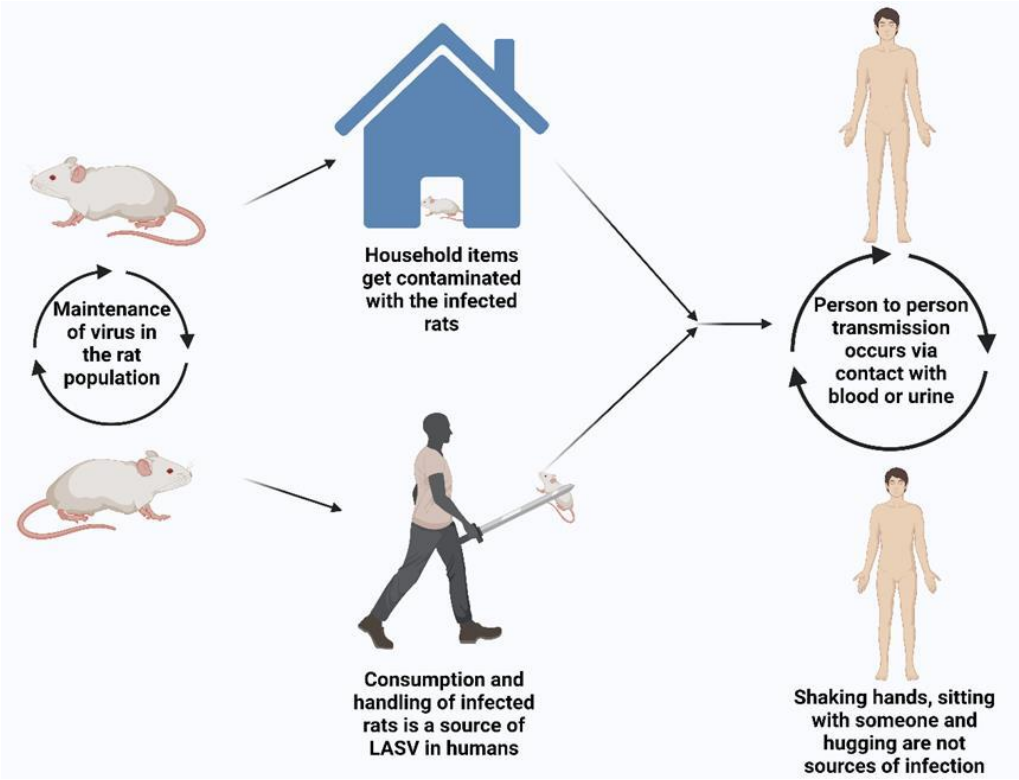

Fig. 5: Transmission of Lassa virus (Retrieved from BioRender)

6. MORTALITY RISK FACTORS

The rate of case fatality in patients is almost 30%, who are presented to the health care environments (Kenmoe et al. 2020; Merson et al. 2021). Chances of death are greater in pregnant women and even higher in the third trimester (Price et al. 1988; Kenmoe et al. 2020). About 90% of total pregnancies can be lost in pregnant women infected with LF (Wauquier et al. 2020). Children infected with LF and who have positive antigen tests confront high mortality (63%) (Samuels et al. 2021). The mortality rate in severe cases of LF is generally between 1 to 15% (WHO 2023). The possible risk factors for high mortality rate are enlisted in Fig. 6.

7. CLINICAL MANIFESTATIONS OF LASSA FEVER

The way of clinical indications is not specific and this creates difficulties for clinical examination. The rats that are zoonotic hosts carry the virus and do not show any symptoms of disease but they shed the virus in their feces, urine, and other secretions. Almost 80% of the patients do not show any kind of symptoms (Richmond and Baglole 2003; Johnson et al. 2019). Infected individuals may show acute to severe LF followed by multiple organ failure that can be seen in the spleen, kidney, and liver (McCormick et al. 1987; WHO 2021). Duration of clinical symptoms is 1 to 4 weeks. The indications of LF are similar to other diseases like typhoid and malaria which may be confusing. The similarity of symptoms with other diseases is quite challenging in the recognition of the infected ones (Akhuemokhan et al. 2017; Okokhere et al. 2018). Evolution of LF symptoms is given below (Table 1).

Death of the infected individual may occur in 14 days if there is multiple organ failure (CDC 2019). Long-term after-effects like hearing loss is a major social and economic burden in West Africa. In Nigeria, $43 million are used annually for aid programs (Mateer et al. 2018).

Table 1: Evolution of LF symptoms (WHO 2018).

Infectivity	
Days	Symptoms
1-3	Fever Extreme fatigue General weakness Headache
3-6	Severe throat Diarrhea Vomiting Face swelling
6-9	Low blood pressure Nose bleeding

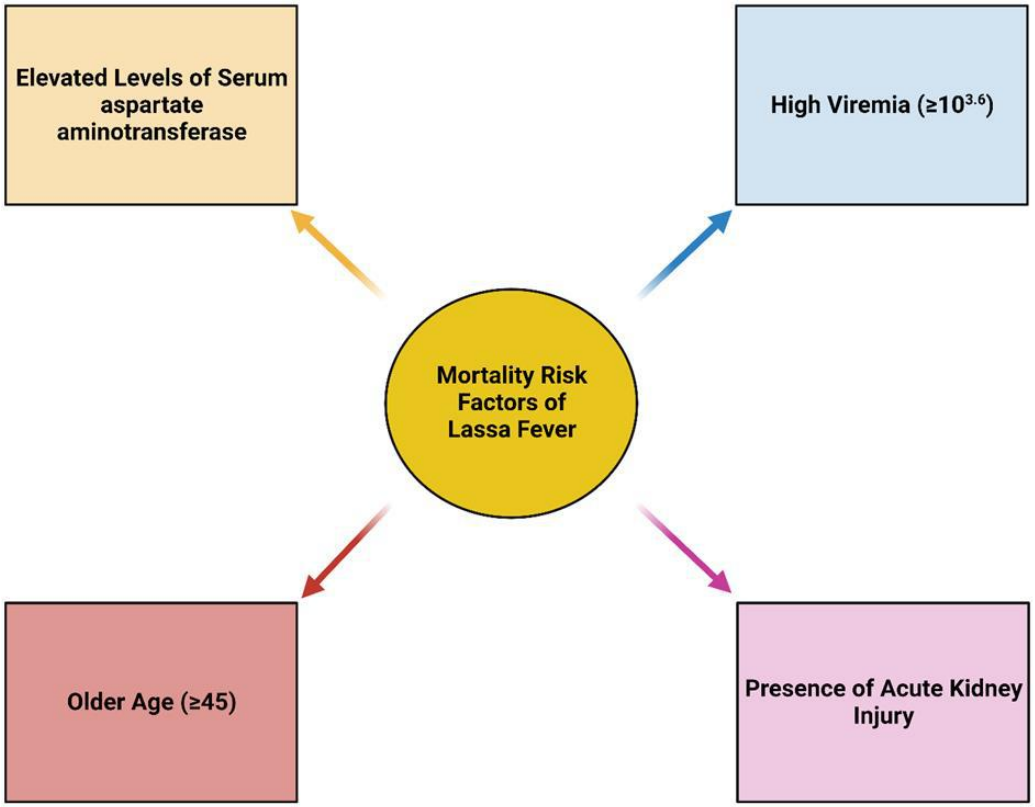

Fig. 6: Mortality Risk Factors of LF (McCormick et al. 1986; Okokhere et al. 2018; Adetunji et al. 2021) (Retrieved from BioRender).

There is an indication of exudative pharyngitis on the clinical inspection of the throat of the patients that are infected with the LASV and the inspection of the urine samples generally shows the presence of the proteins. There is also a decrease in the number of neutrophils. Meningitis, tremors, and convulsions are neurological signs that are not generally visible. Strong evidence from the 441 infected individuals showed that the prime indication of LF is pharyngitis, proteinuria, aggregation of fever, and retrosternal pain. Vomiting and sore throat are also observable (McCormick et al. 1987; CDC 2019). In addition to these conditions, effusion of pericardia, the 8th nerve deafness, and bleeding of mucosa were described as 2%, 4%, and 17%, respectively. Nausea, diarrhea, pleural effusion, and facial edema are also visible in the lassa fever. Factors like poor sanitation and bad social habits are considered as alarming components that can increase the dissemination of the ailment (Okokhere et al. 2009).

Individuals infected with LF generally show no visible symptoms and may remain unrecognized. People of this category and the survivors of acute LF infection may develop loss of hearing to various extents. Bilateral loss of hearing is most common and can affect all extents of hearing (Ibekwe et al. 2011). Around 25% of individuals are at risk of infection upon exposure to LASV (WHO 2000). The development and origin of this diminution in hearing are postulated to arise because of an immunological reaction among the plasma membrane and circulating LASV immunoglobins in the cell at its basal side (Okokhere et al. 2009). Yun and his colleagues in 2016 accustomed a model from muridae (the largest family of rodents and mammals) which exhibits several features of LF that are also visible in humans (Yun et al. 2016). The virus isolated from lethal cases was extremely virulent and the virus that is isolated from the non-lethal cases showed mild disease and low mortality but, in both cases, the surviving ones developed a condition called sensorineural hearing loss (any cause of hearing loss due to pathology of the cochlea, auditory nerve, or central nervous system). Recently, Maruyama and his colleagues conducted an evaluation of the auditory function engaging the distortion product otoacoustic emissions (DPOAE) (generated by cochlea when the ear is dispensed with the two concurrent pure tones) and auditory brainstem response (ABR) (that generally checks the brain's response to the sound) in determining the mechanism of the LASV-prompted hearing loss. They calculated the values of the above-mentioned tests in some rodents and deduced that the exhaustion of CD4 T-cells plays an important role in hearing loss prompted by LASV and CD8 T-cells take part in acute phase and pathogenicity of LASV (Maruyama et al. 2022).

8. DIAGNOSIS

Lassa fever is difficult to recognize especially in the early stages as 80% of the patients are asymptomatic, so laboratory diagnosis is essential in such cases for the initiation of the specific treatment. Commercial and laboratory-made assays are available but the testing of LASV is still restricted to the West African laboratories (Asogun et al. 2012; Akhuemokhan et al. 2017). The best way for the diagnosis of LASV is the polymerase chain reaction (PCR) out of the blood. 1st day of hospitalization reports 79% sensitivity, escalating to 100% on the third day (Richmond and Baglole 2003; Ogbu et al. 2007; Seregin et al. 2015). Variation in the genetic strains hardly guides to false negative outcomes (Panning et al. 2010). Different serological tests are being utilized which include direct nucleoprotein antigen testing and IgM and IgG antibodies against nucleoproteins (NP) and glycoproteins (GP). A mixed IgM and NP enzyme-linked immunosorbent assay (ELISA) has a specificity of 90% and a sensitivity of 88% (Richmond and Baglole 2003). The persistence of IgM is for months or even years, and IgG can persist for decades (Bond et al. 2013). There is the existence of cross-reactivity with the lymphocytic choriomeningitis virus (LCMV) which is also a member of the Arenaviridae family and its primary host is, *Mus musculus,* the common house mouse (Haas et al. 2003). A qualitative quick indicative test (rapid diagnostic test) (RDT) that requires no instrumentation is also available and is perceptibly elucidated by the user (Boisen et al. 2018; Boisen et al. 2020). Clinical samples from the patients of LF are hazardous to the laboratory personnel because contact with the mucosal surfaces and the percutaneous inoculations are the main risk factors of the infection. So higher level of safety for the processing and collection of samples is required. Isolation of LASV requires extreme biosafety conditions (CDC and NIH 2009).

9. TREATMENT

Supportive treatment is the basis for the management of LF. The main aim is the rejuvenation of the volume that accounts for third spacing (too much fluid movement from blood vessels towards the

interstitial space) as the overload of volume can cause pulmonary edema. Respiratory support and electrolyte balance are the other goals of treatment (McCormick et al. 1986; Ölschläger and Flatz 2013).
Ribavirin is a broad-spectrum antiviral drug that is a guanosine analogue and owes a fine activity against LASV. Plasma concentration is considerably higher in case of intravenous treatment with standard doses as compared to minimal inhibitory concentration (lowest concentration of drug that inhibits the visible growth of microorganisms) but the oral treatment is limited because of 50% bioavailability and has considerable side effects (Bausch et al. 2010). Controlled clinical trials were performed by CDC in the 1980s in Sierra Leone in which they assessed the gains of oral and intravenous ribavirin (McCormick et al. 1986). Both intravenous and oral ribavirin are beneficial. Recommended intravenous dose is 2.4 g followed by a 1g dose every 6 hours for almost 10 days (recommended in average-weight adults). Ribavirin is not effective if it is administered after physiological dysregulation or viremia peak (McCormick et al. 1986).
A major adverse effect of ribavirin is dose-dependent hemolysis (a blood disorder in which a medicine triggers the immune system to kill the red blood cells) appearing in almost 20% of the patients and decreasing the hematocrit level (proportion of red blood cells in the blood) (McCormick et al. 1986; Duvignaud et al. 2021). There are many other adverse effects associated with the oral treatment like diarrhea, vomiting, nausea, dry mouth, fatigue, myalgia, metal taste, headache, rashes, thrombocytosis, insomnia, mood changes, jaundice, and increased lipase level but no mortality was declared after treatment with the ribavirin (Bausch et al. 2010). Ribavirin is embryotoxic and teratogenic in rodents. It is generally contraindicated during lactation and pregnancy (Sinclair et al. 2017).
For the treatment of lassa fever some other small molecular drugs are under consideration (Hansen et al. 2021). A small molecular purine analogue Favipiravir (T-705) is considered more efficient than ribavirin in the treatment of LASV (Gowen et al. 2010; Mendenhall et al. 2011; Safronetz et al. 2015; Oestereich et al. 2016; Rosenke et al. 2018; Lingas et al. 2021). Currently, no approved vaccine for LASV is available but there are many vaccine platforms that show efficacy in animal models that have been developed and some have recently entered the first phase of human clinical trials (Salami et al. 2019).

10. PREVENTION AND CONTROL

The important preventive measure in endemic areas is the control of rodents in and around the residences and avoiding contact and consumption of the rats (Ogbu et al. 2007). Avoid contact with infected persons and health care workers if the maintenance of infection control practices is poor. Acquisition and transmission of LASV can also be controlled and prevented by implementing some measures that include the establishment of a task force, policy formulation, reducing the LF at the national and state level, and the formation of committees for monitoring. Additionally, there should be awareness among the general public and healthcare workers about the transmission, symptoms, disease dynamics, and preventive measures. This disease can be controlled by prohibiting the spread of zoonotic host and by shunning rat hunting and consumption, obstruction of the hiding places of rodents, and use of the snares in the homes to diminish their number. Other preventive measures comprise healthy and good personal hygiene, proper disposal of waste, good environmental sanitation, and shunning of food scattering by the roadside or in areas where rats can gain access to this food and also storing the food items in rat-proof containers (Ogoina 2013). General strategy to control LF outbreaks is given in Table 2.
Control of hospital infection is the main focus when dealing the imported cases in the Western world as there are many nosocomial outbreaks of LF in Africa. Inhibiting the use of contaminated needles and avoiding the direct contact with the blood and secretions of patients can also prevent the transmission of the virus. Lack of personal protective equipment, reuse of needles, and surgery performance in poor hygienic conditions are major sources of disease in endemic areas (Fisher-Hoch et al. 1995; Yun and Walker 2012). Hospitals in Africa where preventive measures are followed, have less seroprevalence for LASV as compared to the neighboring rural community (Helmick et al. 1986).

Table 2: General strategy to control lassa fever outbreaks (WHO 2018).

Coordination			
Psycho-social support		Control of reservoirs and vectors in nature	
Social and behavioral interventions	Clinical case management	Logistics	Epidemiological investigation and surveillance
Conduct cultural and social assessments	Triage in/out	Security, police	Active case-finding
Formal and informal connections	Barrier nursing	Lodging, food	Follow-up of contacts
Address community concerns	Infection control	Epidemiological and	Specimens
Engage with influencers: traditional	Organize funerals	social mobile teams	Laboratory testing
healers, local authorities & religious	Clinical trials	Finances, salaries	Database analysis
leaders	Ethics committee	Transport vehicles	Search for source

11. CONCLUSIONS

LF is a crucial rodent-borne (zoonotic) illness that has validated the epidemiological progression and proportion in the sub-region of West Africa. International travels considerably increase the possibilities of transmission of LASV to several other zones of Africa. An unstable economy and limited resources are the major factors that hinder the management of current and emerging contagious diseases in the region. Suitable training of medical personnel and health care workers is essential in the treatment and prevention of infection. The transmission of LASV is very simple and can easily be prevented. Majority of the infected individuals are asymptomatic and the general symptoms of the disease are correlated with several other ailments, so the diagnosis is difficult in the initial stages. In endemic areas, ribavirin is provided in health care centers and hospitals particularly at the onset of the disease because it is very effective in the progressive stages of the disease. Vaccine development, preventive measures, and the development of drugs other than ribavirin or the modification of the existing drugs are the major suggestions to diminish LF.

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The Black Death: A Historical Overview of Zoonotic Plague

35

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ABSTRACT

This comprehensive review explores the socioeconomic effects, types, outbreaks, historical background, and transmission of the Yersinia pestis which caused the zoonotic plague. One of the deadliest pandemics in human history, the Black Death, is reviewed, with special attention to how it affected the Europe in the fourteenth century. The three known forms of plague—pneumonic, septicemic, and bubonic—are described in depth, emphasizing the various ways in which they spread and the symptoms that go along with them. Significant plague outbreaks throughout history are also discussed in the study, including the Justinian Plague to the 19th-century revival, and some recent cases. The study focuses particular emphasis on the spread of Y. pestis over the world today, the role fleas play in its transmission, and prior incidents of the plague being used as a biological weapon. The discussion of socio-economic repercussions serves to shed light on the plague's significant social effects, including labor shortages, economic downturns, and the scapegoating of communities like the Jewish community. Moreover, historical and modern contexts are discussed which includes the response to plague outbreaks and the mechanisms used to manage them, such as isolation and quarantine. The document additionally examines the medical side, discussing further about the signs, symptoms, and medications for each kind of plague, including antibiotics like gentamycin and streptomycin. It also explains the precautions to be taken, highlighting the significance of isolation and quarantine in halting the disease's spread. The review finishes with an emphasis on vaccination initiatives, recognizing the lack of a completely effective vaccine but focusing on previous and ongoing efforts for the development of live-attenuated vaccines. In conclusion, this review offers an in-depth examination of the zoonotic plague, covering its historical causes, dynamics of transmission, socioeconomic effects, and current initiatives for treatment and prevention of this renowned infectious disease.

Key words: Zoonotic plague, Yersinia pestis, Black Death, transmission, bubonic plague, pneumonic plague, septicemic plague, outbreaks, socio-economic consequences, quarantine, antibiotics, vaccination.

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1. INTRODUCTION

The plague, often known as the Black Death, was recorded as one of the worst pandemics (Green 2015). It refers to a contagious sickness caused by the bacteria *Yersinia (Y.) pestisa*, a gram-negative bacterium belonging to the Enterobacteriaceae family (Bhagat et al. 2023). Body fluids of living plague patients, dead bodies of diseased people and animal carcasses, and body fluids of infected dead bodies were discovered to be potential sources of infection. It was found that pneumonic plague can be spread by intense handling of the dead bodies of infected humans and animals, primarily by inhalation of respiratory droplets, and that bubonic plague can be transmitted through being in contact with the blood of a corpse or carcass's body fluids (Jullien 2021). The symptoms of the plague depend upon how the patient got exposed to the plague bacterium (Halabi 2020). Many plague complications occur quickly and are dangerous to life, which include tissue death and limb loss from gangrene, inflammation of the brain lining (meningitis), organ failure, and respiratory distress (Kasper et al. 20l5, Chung et al. 2020, Glatter and Finkelman 2021)

The bacteria *Y. pestis* is the cause of many large-scale economic and social destructions, unrivaled by many other infectious microbial diseases or military wars over the previous 2000 years (Callinicos 2023). It is widely assumed that three global pandemics of plague have occurred, indicating that these have resulted in 200 million deaths (Perry and Fetherston 1997).

Three types of plague reported are bubonic, septicemic, and pneumonic plague, among which only one spread while others do not. Coughing, sneezing, and close touch have been assumed to cause the spread of pneumonic plague (Ansari et al. 2020).

A wide range of negative consequences of the Black Death has been reported (Yimer et al. 2019). Sometimes, the trade was affected, conflicts were delayed, and many workers perished, which caused personal pain and economic issues for families. Additionally, it affected landowners who hired workers as tenant farmers. The landowners who have been able to maintain their tenants due to the scarcity of exertions did so via paying wages or cash rents rather than exertion offerings, which was advantageous for the tenants who have been alive. As Jews have been blamed for the spread of the Black Death and numerous Jews were killed in crowds or massacred with the aid of being put on fire, anti-Semitism remarkably accelerated all through Europe (Gupta et al. 2020; Hanna-Wakim et al. 2023).

Significant plague outbreaks have occurred throughout history, with the most infamous in the 14th century (DeWitte 2015; Gómez 2022). World Health Organization (WHO) has received reports of 100-200 deaths and 1000-5000 human cases of plague annually for the last 20 years. Several features of the Black Death shock are critical to understanding its impact. Jedwab et al. (2019) reported that 40% of Europe's population was killed by plague between 1347 and 1352. It was the greatest solitary demographic catastrophe in European history as 50% to 60% of England, France, Italy, and Spain's population was lost in two years.

The plague has an extended history of being used as a biological weapon (Mussap 2019). Historical reports from ancient China and medieval Europe describe the Xiongnu/Huns, Mongols, Turks, and other groups contaminating enemy water supplies with infectious animal carcasses such as cows or horses and human remains. General Huo Qubing of the Han Dynasty was said to have perished from similar contamination while fighting the Xiongnu. Plague victims were also said to have been catapulted into

besieged cities (Schama 2000). The plague primarily affected people in a few African countries, but cases are documented in Asia and America annually (Barbieri et al. 2020). Madagascar and Congo are most affected. In the United States, plague is more common in rural areas of western states. If you deal with animals where plague is present, you are at a higher risk (Park et al. 2020; Glatter and Finkelman 2021). A sub-unit vaccination effective against bubonic and pneumonic plague has also been developed (Richard et al. 2015).

2. TRANSMISSION

Fleas transmit *Y. pestis,* but the other two species *Y. enterocolitica* and *Y. pseudotuberculosis* are considered dangerous for humans and are transmitted through faeces and cause mild intestinal symptoms (Hordofa 2022). It is thought that *Y. pestis* is a mutant of *Y. pseudotuberculosis,* first seen between 1500 to 2000 years ago (Achtman et al. 1999; Achtman et al. 2004). The fleas are believed to be the primary cause of the Black Death. Infected fleas' esophagus becomes obstructed, and they attack rats and humans, transferring the causative agent into the bite wound. Human-to-human transmission is less observed (Mordechai et al. 2019).

Transmission among rats and flies has been associated with epidemics in urban areas. Sick rats (for example, delivered by ships) enter a new city in this typical urban plague scenario and spread the disease to house rats in the area and their fleas, which served as a source of human plague. At times, individuals develop a pneumonic plague, passed from person to person by sneezing, coughing, and respiratory droplets (Mwengee et al. 2006, Vallès et al. 2020). The majority of the time, rodents carry the plague by consuming infected fleas, but it can also spread through contact with sick people or animals. Plague is also transmitted by inhalation of infectious respiratory droplets. As a zoonosis, it primarily affects rodents and has complicated zoonotic/epizootic cycles, as depicted in Fig. 1. When it infects people, it can lead to sporadic instances, outbreaks, or even sizable epidemics (Vallès 2020).

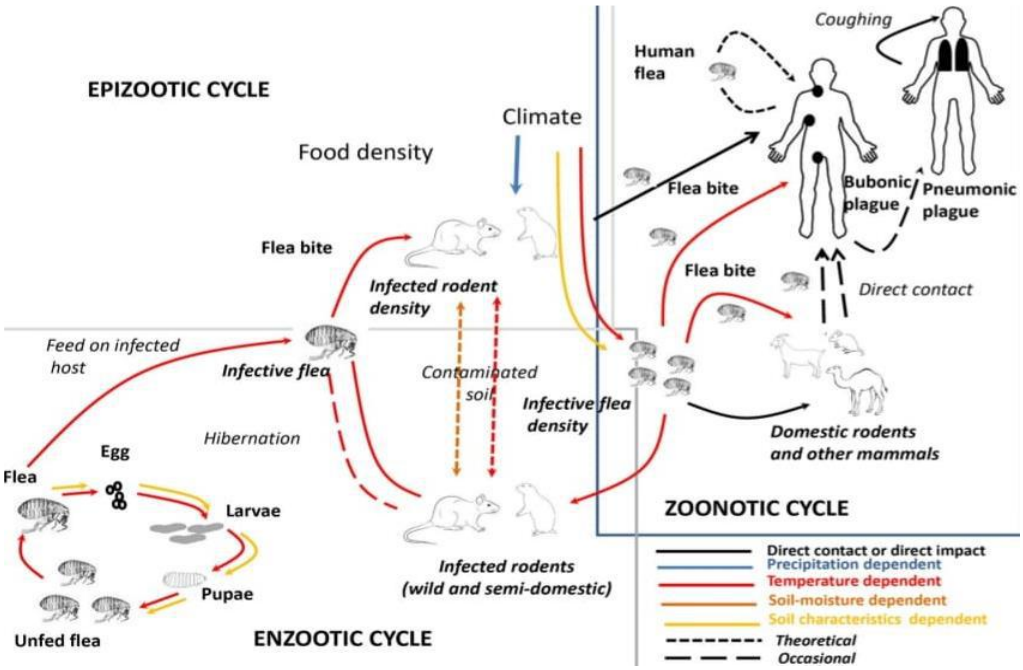

Fig. 1: Epizootic/enzootic cycle of *Y. pestis* (Vallès et al. 2020).

3. TYPES OF PLAGUE

3.1. BUBONIC PLAGUE (BLACK DEATH)

The Black Death, also called the bubonic plague, is one of the deadliest pandemics in recorded human history, which killed almost more than 25 million people or about a third of Europe's population during the fourteenth century, which draws immediate analogies to the recent coronavirus "modern plague" (Zietz and Dunkelberg 2004).

The major carriers of the bubonic plague are infected fleas from small animals. It can also happen if the person comes into contact with the carcass of an animal that had a plague. Animals affected by bubonic plague, such as rabbits, hares, and many cat species, often die (CDC, 2019).

When a flea bite causes bubonic plague, the bacteria enter the skin and move to the lymph node through the lymphatic system, where they cause the enlargement of the lymph node (Sebbane et al. 2006).

The symptoms include fever, headaches, nausea, and enlargement of the lymph nodes in the area closest to the region from where the bacteria gained entry into the skin. Another sign is acral necrosis, which is a darkening of the skin. Sometimes, the enlarged lymph nodes called "buboes" may burst open (Aberth 2016). The bubonic plague can be treated with a variety of antibiotics (Uddin et al. 2021). These include tetracyclines (particularly doxycycline), fluoroquinolone ciprofloxacin, and aminoglycosides like streptomycin and gentamycin (Nelson et al. 2020).

Many rodents died during the plague outbreaks, leaving fleas to seek alternative blood supplies (Anstead 2020). People and animals living where plague-affected rats have recently died are in danger of getting the disease through flea bites. Cats and dogs may introduce the infected fleas into the home (Kugeler et al. 2015).

3.2. PNEUMONIC PLAGUE

The bacterium *Y. pestis* causes pneumonic plague, a severe lung infection. Some major symptoms include fever, headache, difficulty breathing, chest pain, coughing, *etc*. The signs usually appear within seven days following exposure (Dennis et al.1999).

Pneumonic plague can be caused by inhaling infected droplets or by the untreated bubonic or septicemic plague that has progressed to the lungs (Theriot et al. 2023). Pneumonia can result in respiratory failure and shock (Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Vector-Borne Diseases (DVBD). In most cases, the disease begins with the patient having the bubonic form of the disease, which then spreads from the lymphatic system into the respiratory system (Armstrong 2022).

The disease progresses quickly unless discovered and treated quickly enough, often within a few hours. The death can occur in one to six days. In untreated instances, mortality is about 100% (Hoffman 1980; Ryan 2004).

3.3. SEPTICEMIC PLAGUE

Septicemic plague happens when *Y. pestis* enters the bloodstream and multiples (Zhou and Guo 2020). Fever, chills, abdominal pain, weakness, shock, and bleeding beneath the skin or other organs are caused by septicemic plague. Disseminated intravascular coagulation (DIC), necrosis of small blood

vessels, and purpura are also caused by septicemic plague. Sometimes, fingers, toes, and nose can have gangrene, giving rise to the name "black death" (Purba et al. 2019).
Person-to-person transmission of septicemic plague is rare, but it can become so if the disease progresses to the pneumonic stage or is associated with buboes (Sherman, 2009).

4. OUTBREAKS AND IMPACT

4.1. FIRST OUTBREAK

The Justinian plague happened between AD 542 and AD 750. The plague was entitled after Byzantine Emperor Justinian I (r. 527-565), who got the disease and regained health in 542, at the height of the pandemic that killed nearly a fifth of the imperial capital's inhabitants, according to his court historian Procopius (Arrizabalaga and Larraz-Andía 2010; Stathakopoulos 2018).
At the height of the pandemic, some new-age researchers believe that the plague killed more or less 5,000 people every day in Constantinople. According to one theory, the original epidemic killed up to 40% of the city's residents and killed up to a quarter of the Eastern Mediterranean's human population (Mango 1990; Mordechai et al. 2019).

4.2. SECOND OUTBREAK (1347-1351)

The other wave, the Black Death in Europe, happened between 1347 and 1351 and spread from Asia to Europe (Koulesser 2020). It had high mortality rates (estimated 25-50%). It wiped away an estimated one to two-thirds of Europe's population. Venetian authorities kept The ships isolated for 30 days at the seaport in 1347 to guarantee they were not exposed. The quarantine period was extended up to 40 days, and the term quarantine was also derived from 40, which means quarantine in Italian (Perry and Fetherston 1997). This epidemic should have started in Central Africa and expanded over the Mediterranean basin (Perry and Fetherston 1997). In Europe, 25 million deaths were caused by the plague, which lasted hundreds of years, leading to the Great Plague of London in 166 (Dennis 1994).
Because plague is predominantly a zoonotic disease of rodents, it has been widely considered that when the Black Death arrived in Europe from Asia, the bacteria developed in European wildlife and urban rodent reservoirs (Slavin 2021). The sickness would have spread from these reservoirs to humans until the bacterium vanished from Europe in the early nineteenth century (Keeling and Gilligan 2000).

4.3. THIRD OUTBREAK

Between 1899 to 1947, there were 1692 cases of plague reported in Europe, with 457 deaths. In the Beed District of Maharashtra and Surat in Gujarat, other plague outbreaks occurred in India between August and October 1994, one bubonic and the other pneumonic, respectively (Das and Deobhankar 2022). In the five impacted Indian states and the Union Territory of Delhi, 693 suspected cases and 56 deaths were observed. These instances originated in Maharashtra (488), Gujarat (77), Karnataka (46), Uttar Pradesh (10), Madhya Pradesh (4), and New Delhi (68). There have been no reports of cases being transferred to other nations, as per data from the Centers for Disease Control and Prevention (CDC 1994).
Based on available materials, the 1993 earthquake became the main factor, which led to the loss of food grains in many residences. Due to the destabilization of both domestic and wild rat populations, where

the plague was widespread, the disease could travel from wild rats to house rats and eventually to people (Evans et al. 2018).

4.4. CURRENT INCIDENCE OF PLAGUE

According to World Health Organization (WHO) statistics, plague is still a public health threat, particularly in numerous countries like Africa, Asia, and South America. Fig. 2 shows the global distribution of Plague. The plague, cholera, and yellow fever are internationally quarantinable infections (World Health Organization 1994).

These primarily included cases of the bubonic form of plague (84%), septicemic plague (13%), and pneumonic plague (2%) (koirala 2006). There is a risk of human plague wherever there are coexisting human populations and plague natural foci. As a result, plague epidemics frequently occur across Africa, Asia, and North and South America. However, more recently, the most endemic countries were the Democratic Republic of the Congo, Madagascar, and Peru (WHO 2017). The plague-causing *Y. pestis* is endemic in Madagascar, specifically in the central highlands (Pandey et al. 2023). Although there have not been any prior reports of plague in northern Madagascar, a pneumonic plague outbreak happened there in 2011. Within 27 days, 17 suspected, 2 probable, and 3 confirmed human occurrences were found, and all 20 untreated people died. Using molecular typing, it was possible to identify 4 clustered regularly interspaced short palindromic repeat patterns and the 1. ORI3-k unmarried-nucleotide polymorphism genotype that is rare for Madagascar in *Y. pestis* was isolated from 2 survivors and five Rattus samples. The case-fatality rate for this outbreak was 100% for those who went untreated (Richard et al. 2015).

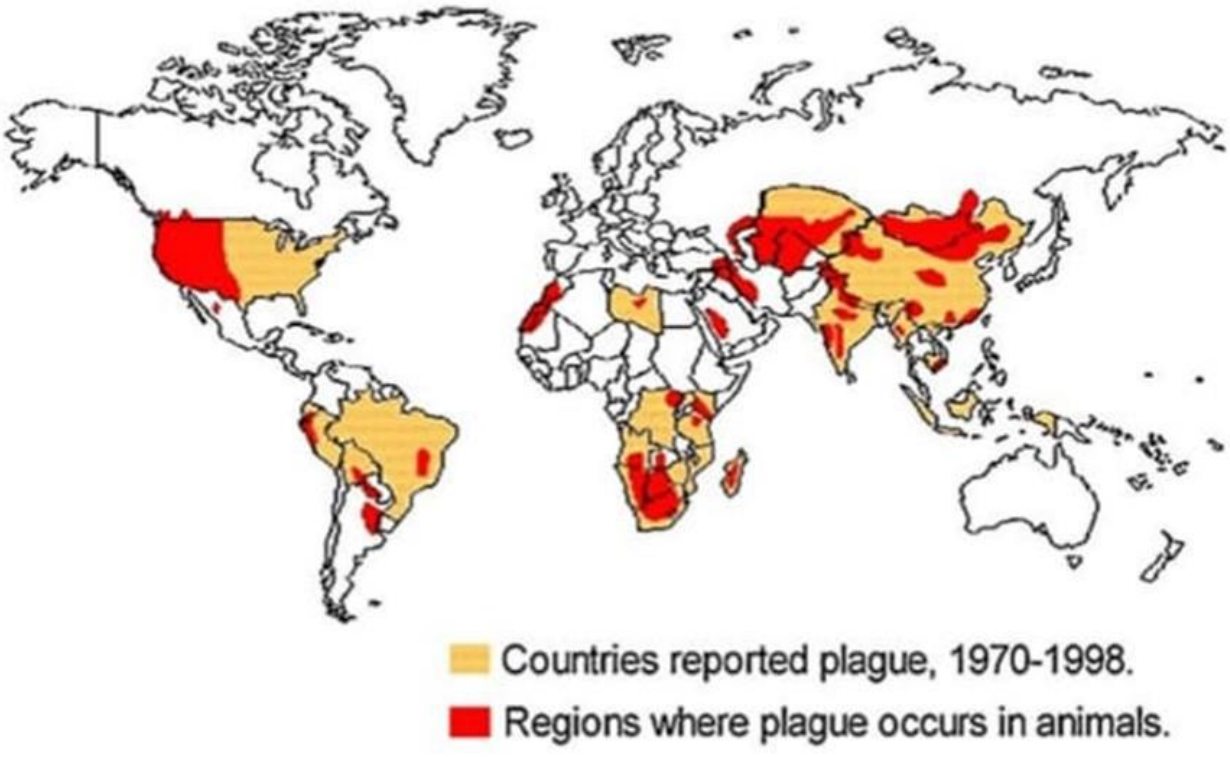

Fig. 2: Global distribution of plague, 1970 to 1998 (Centers for Disease Control and Prevention).

5. SOCIAL AND ECONOMIC CONSEQUENCES

Justinian's Plague of 421-540 AD, which is thought to have killed 25–50 million people in Europe and the Mediterranean, and the Black Death Pandemic of 1347–52 AD, which killed up to 50 million people in those same regions, as well as untold numbers in the Middle East, Central Asia and some areas of China, were two of the three pandemics in human history (Wuk 2020). It killed roughly half of the people in Europe and the Mediterranean (estimates range from 35 to 60%). Black death was a pure population and economic shock to society. As a result, it is not surprising that the Black Death is widely regarded as having had the most significant economic impact (Alfani et al. 2023). The loss of skilled and unskilled laborers was the most visible and immediate result of the first wave of the Black Death. In the arts, productivity usually decreased, artistic traditions were streamlined, and much more attention was devoted to phenomena such as the danse macabre and the memento mori tradition (Armstrong 2022). When the plague struck England in 1348, the immediate result was a 20% reduction in real income over the ensuing years for both professional and unskilled workers (Horrell et al. 2020). The estimated constant per capita GDP decreased by 6% between 1348 to 1349. Similarly, in Spain, where the Black Death occurred in 1348, real income decreased by 9% in 1350 and anticipated per capita GDP fell by 3.3% (Hatcher and Dunn 2011; Jedwab et al. 2019).

A termination of wars and an abrupt decline in exchange instantly started. The deaths of many labourers had a large and disastrous impact on the quantity of land, which became below cultivation, resulting in a large decline in the area under cultivation. Many landlords have been ruined because of this mess. Because of a body of workers scarcity, they have been obliged to substitute pay or cash rents in place of help and employment offerings to maintain their tenants. In general, wages for artisans and peasants were also increased. These revolutions provided a new fluidity to society's formerly strict stratification. The instant effects of the 1349 outbreak seem to have been lived for a quick period in England, and the economic downturn that reached a low within the mid-15th century can also probably be attributed to the pandemic recurrence of the plague (Hanna-Wakim et al. 2023).

The richest 10 percent of the population experienced a 15–20% decline in overall wealth due to the outbreak. Since the richest 10% did not regain control of typical wealth until the second half of the 17th century, this fall in inequality persisted for a very long time (Alfani et al. 2023).

People evacuated to different areas of the arena, abandoned their friends and family, and fled their towns. Work ceased, and funeral rituals either became ceremonial or disappeared altogether. Some humans had the self-belief that God's vengeance was falling on them, so they confronted the disorder with prayer. Some felt they should follow the adage, "Eat, drink, and be merry, for tomorrow you can die." Faith in faith began reducing after the plague, as a result of the deaths of so many clergy, in addition to the failure of prayer to save you from the occurrence of disorder and deaths (Bollet et al. 2004).

It also had religious impacts on society along with social and economic effects. The scapegoating of Jews was a well-studied initial effect of the pandemic. Pogroms, expulsions, and violence against Jews have become more common since the 12th century. The Black Death, on the other hand, resulted in the most heinous persecution in medieval European history. There were at least 363 cities in Europe with Jewish communities on the eve of the Black Death. During the Black Death pandemic, half of these Jewish communities were either slaughtered or evicted. Jews were accused of spreading the illness, and municipalities took advantage of the chaos and shock of the plague to expropriate populations who had long faced antisemitic animosity (Jedwab et al. 2019).

6. RESPONSE AND MEASURES

6.1. ISOLATION AND QUARANTINE

The pillars of preventive and control measures include surveillance, environmental management, and personal protective measures. A mandatory method of separating people, animals, and objects that may have been exposed to a dangerous illness is called quarantine (from the Italian "quaranta," which signifies 40). Since the fourteenth century, quarantine has been the central part of a complete plan of action for controlling the spread of disease. It includes isolation, sanitary cordons, health certificates, fumigation, disinfection, and control of populations considered to be the source of the infection (Matovinovic 1969.

When the plague first arrived in Sicily from the eastern Mediterranean, it was carried by sailors, rats, and goods. It swiftly moved throughout Italy and wiped out the populations of significant city-states like Florence, Venice, and Genoa. The disease then spread from Italian ports to French and Spanish ports. The disease spread over the Alps from northern Italy to Austria and central Europe. The epidemic had subsided but not stopped by the end of the fourteenth century for the next 350 years as many cities saw pneumonic and septicemic plague outbreaks. The presence or establishment of robust healthcare systems, defined by collaboration between governmental, non-governmental, and academic partners as well as long-term commitments, is necessary for plague management. The plague, Ebola, and other possible threats that might (re-)emerge in nations with few resources and deficient healthcare systems are all examples of this (Tognotti 2013).

7. PREVENTION AND MEDICAL TREATMENT OF PLAGUE

The chances of infecting close contacts is very low for a patient with bubonic plague but do not have secondary and septicemic plague. *Y Pestis* transmitted to individuals by mean of coughing and respiratory droplets from the patients with primary and secondary plague. The patient has a high fever and increased heartbeat with the beginning of pneumonic plague, but there is no coughing or expectorating blood in sputum. This time frame is not contagious (Kool 2005). Sputum that a patient has expectorated is extremely infectious. However, Nishiura et al. (2006) stated that the transmissibility of pneumonic plague via this pathway is not strong. Because pneumonic plague is efficiently prevented through covering mouth using a face mask, prevention is relatively simple (Wang et al. 2011). A person suspected of suffering septicemic plague, bubonic plague, or pneumonic plague should be isolated (Wang et al. 2011).

Aside from physical protection, the WHO Expert Committee on Plague (1970) (WHO 1970) suggested antibiotics for treating plague patients using tetracycline, streptomycin, and chloramphenicol. Historically, streptomycin has been the drug of choice for treating plague patients, especially the pneumonic type. Adults are advised to take a daily dose of 2g intramuscularly for up to 10 days. Since streptomycin is bacteriolytic, caution must be used to prevent the induction of endotoxic shock. Gentamycin is also used for treating plague patients, typically considered adequate to streptomycin. Gentamycin is widely accessible than streptomycin, and a study has shown that it may effectively cure human plague infections when given intramuscularly at a dose of 2.5 mg per kg every 12 hours (Mwengee et al. 2006). Three days after their temperature has returned to normal, patients are often switched to another antibiotic, usually tetracycline, due to the toxicity of streptomycin. Tetracycline is bacteriostatic; however, it works well to cure simple plague. Tetracyclines can also be taken orally, but they shouldn't be used by anybody pregnant, breastfeeding, or under the age of seven. The treatment of

choice for plague meningitis is chloramphenicol because of its capacity to enter tissue. For 10 days, 50 mg per kg per day can be given parenterally or orally. Although fluoroquinolones like ciprofloxacin, gatifloxacin, and moxifloxacin have been demonstrated to be effective in treating laboratory animals, sometimes this class of antibiotic has been used to treat human plague (Kuberski 2003). Ciprofloxacin is now included in CDC recommendations with a recommended dose of 400 mg given intravenously or 500 mg orally twice a day (Inglesby et al. 2000). Based on its effectiveness in African Green monkeys, the fluoroquinolone antibiotic levofloxacin was licensed by the US FDA in 2012 for the treatment or prevention of plague infections (Layton et al. 2011). Penicillin, cephalosporin, and macrolides are a few more antibiotics demonstrated ineffective in treating plague. It should be emphasized that late medication decreased antibiotic efficiency, especially with powerful antibiotics such as gentamycin and doxycycline (Mwengee et al. 2006). In rats, mice, and primates other than human models of pneumonic plague (less commonly), the effectiveness of aminoglycosides, tetracyclines, fluoroquinolones, β-lactams, rifamycin, chloramphenicol, sulfonamides, ketolides has been examined (Sebbane and Lemaître 2021) From one animal research to the next, the resulting level of protection against plague frequently differs.

For instance, based on data calculated with the *Y. pestis* strains, which were generally used in models of animals distinguished by the synthesis of a protein capsule (F1), a therapy based on doxycycline, ampicillin, or cefoperazone may be advised. However, mice who get infected with a strain lacking an F1 capsule respond poorly to treatment with either of these three antibiotics (Samokhodkina et al. 1994)

8. VACCINATION

Plague caused by *Y. pestis* is one of the most dangerous infectious diseases (Wang et al. 2013). There is currently no effective vaccination to protect from the plague, but several live-attenuated vaccines have been available. Live bacterial vaccinations offer protection and frequently include almost all natural antigens, lowering the risk of developing resistant diseases. However, live attenuated vaccines are also thought to be more reactogenic than other vaccination approaches, and they may raise safety concerns in some groups of the community (such as older people or immune-compromised). It also elicits only temporary immunity depending on the vaccination strategy (Sun and Singh 2019; Rosario-Acevedo et al. 2021). Recombinant *Y. pestis, Y. pseudotuberculosis,* and Salmonella strains have all been used as potential live vaccines (Branger et al. 2009; Branger et al. 2010).

9. CONCLUSION

Three types of plague have been reported, the bubonic plague (one of worst pandemics of human history), the pneumonic plague caused by the bacterium *Yersinia pestis* results in respiratory failure and shock, and Septicemic plague occurs when *Y. pestis* gains entry in the blood and starts multiplying. Over three types of plague (bubonic, septicemic and pneumonic plague), only pneumonic plague spread by coughing, sneezing, and close touch. In human history, Black Death appeared to be a significant loss by causing the death of about 5 million people and resulted in population and economic shock to society. Quarantine has served as the main part of a complete plan of action for controlling the spread of disease, including isolation, sanitary cordons, health certificates, fumigation, disinfection, and managing the populations of people considered to be the source of the infection. WHO suggests the antibiotics tetracycline, streptomycin and chloramphenicol for treating plague patients. Streptomycin has historically been the drug of choice to treat plague patients, especially pneumonic patients. Gentamycin, which is typically regarded as more effective than streptomycin, has also been used to treat plague

patients. Further, live bacterial vaccinations offer protection and frequently include almost all natural antigens, lowering the risk of developing resistant diseases.

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Middle East Respiratory Syndrome (MERS): An Overview

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ABSTRACT

Middle East respiratory syndrome coronavirus (MERS-CoV) is a zoonotic disease that can cause mild pneumonia to severe respiratory infections in humans. The virus only produces a little infection in dromedary camels, but it transmits quickly amongst them. The behavior of the virus varies from person to person and between humans and dromedary camels, which emphasizes the part played by host variables in MERS-CoV pathogenesis and transmission. It results in a high temperature, cough, acute respiratory tract infection, and multiorgan dysfunction that may ultimately cause the infection victims to pass away In order to control MERS-CoV infection, no medication has yet received clinical approval. To avoid the negative effects of future epidemics like this one, a number of sensible precautions should be implemented. The development of efficient therapeutic and preventative anti-MERS-CoV infections, as well as further research into the epidemiology and pathogenesis of the virus, are all required.

Keywords: MERS-CoV, zoonotic importance, virus, respiratory disease

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1. INTRODUCTION

A virus is a microscopic organism that only reproduces within the living cells of plants, animals and humans. The Nucleic acid (DNA or RNA) and proteins constitute the viruses (Hyman and Abedon 2012). About 64% of identified human diseases come from vertebrate hosts apart from humans or zoonotic pathogens (Heeney 2006). Emerging infections are primarily caused by viruses of zoonotic importance.; These viruses include the Ebolavirus, human immunodeficiency virus (HIV), Hantavirus, Middle East Syndrome coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome (SARS), and Influenza A viruses (Mandl et al. 2015). Different infectious diseases arise and spread through a variety of environmental factors, including people, animals, and the environment (Wang and Crameri 2014). Animals are the primary source of the majority of respiratory diseases that infect humans. These zoonotic diseases are transmitted naturally from vertebrate animals to humans and from one individual to another (Rahman et al. 2020). One of the three zoonotic coronaviruses to infect people and cause severe pneumonia since 2002 is the MERS- CoV (Peiris and Perlman 2022). The infectious respiratory disease known as MERS was initially identified in the Kingdome of Saudi Arabia in September 2012 (Al-Tawfiq et al. 2014). MERS-CoV, known for its high pathogenicity, causes the disease in humans (Hui et al. 2021). People who have MERS-CoV infection maybe asymptomatic, or they may have mild, severe, or even fatal respiratory illness (Baharoon and Memish 2019). It is a new viral respiratory illness with a focus on the lungs and breathing airways (Durai et al. 2015). It is a novel, fatal, zoonotic human viral disease that resides entirely in the Middle East.

Patients with MERS-CoV caught this fatal disease from a variety of sources, including infected humans, camels, bats, other farmed animals, and pets (Ramadan and Shaib 2019). Clinical manifestation includes acute respiratory distress syndrome, influenza, pneumonia, and asymptomatic MERS. Occasionally, pneumonia develops, which advances to acute respiratory distress syndrome. Human coronavirus-EMC was the original name for the virus before it was universally agreed upon to be known as MERS-CoV (Kane and Gao 2023).

It was found in a pulmonary specimen from a patient who had died at the age of 60, from respiratory distress in Jeddah, Saudi Arabia, in 2012 (Abdel-Moneim 2014). Following, this respiratory distress in Jeddah, Saudi Arabia, MERS cases were found in other places throughout the globe. Travelling or residing in the Middle East countries played a role in the vast majority of these cases, either directly or indirectly (Fehr et al. 2017). The prevalence of these respiratory disorders are increasing in both adults and children, causing worldwide mortality and morbidity (Leung 2021). Respiratory conditions affect the lungs and airway, leading to difficult breathing and gas exchange. These airway systems leave the nose and proceed through the large and small windpipes before reaching the lungs (Lombardi et al. 2021). In general, respiratory conditions are often categorized as contagious (communicable) disorders like bronchitis and tuberculosis (Sencio et al. 2021). The morbidity and mortality caused by deadly viruses like MERS-CoV is significantly influenced by their epidemiology and transmission mechanism (Naz et al. 2023).

According to the WHO, a primary MERS-CoV infection is one that occurred outside of a clinic or medical facility and was likely caused by contact with dromedary camels, which serve as a reservoir host (Durai et al. 2015). MERS-CoV infections exist in two types, primary MERS-CoV infections are those that have been confirmed in the lab and have no known direct epidemiological link to human infections (Goyal et al. 2022). Whereas, a secondary MERS-CoV infection is a lab-proven that has an apparent clinical interaction to a person who has a confirmed or likely MERS-CoV infection (Al-Ahmadi et al. 2019). Where and how MERS-CoV spreads to humans are both unknowns. Preliminary studies revealed that MERS-CoV originated in bats since MERS-related sequences have been identified in a number of bat species (Tai et al. 2022). MERS CoV was initially recognized in people in the Middle East in 2012 and then spread to many European countries (Azhar et al. 2023). Epidemiological research had specifically

indicated that MERS was spreading from person to person and was on the verge of becoming a pandemic (Tai et al. 2022). CoV strains recovered from camels were nearly identical to human CoVs, dromedary camels were engaged in the MERS-CoV's emergence. Saudi Arabia, Jordan, Qatar, the United Arab Emirates, France, the United Kingdom, Germany, Tunisia, and Italy all reported cases of MERS-CoV that had been proven by lab testing (WHO 2022, Johari et al. 2023). The MERS-CoV is the most recent example to emerge from bats, and it is considered that all human CoVs originate from animal reservoirs (Alsafi 2022). This animal species is most likely to begin the zoonotic transmission, and it is predicted that it will do so for a very long time (Everard et al. 2020). MERS-CoV has not appeared to spread well from one individual to another, although reports of hospital outbreaks and individuals departing Middle Eastern countries and their close contacts have been made (Dawson et al. 2019). Currently, there are no medications available on the market that are specifically for treating MERS-CoV in humans (Bleibtreu et al. 2020). Currently, clinical management of MERS concentrates on symptoms, providing supportive care in addition to managing pain and fever, promoting the function of essential organs, and treating secondary or concomitant bacterial infections. The prevention of the transmission of zoonotic diseases depends on early detection, identification of potential and verified cases, and continuous monitoring. In most diagnostic laboratories, MERS-COV diagnosis remains a serious concern. Currently, the most common method employed for the diagnosis of MERS-CoV is the Real time Polymerase Chain Reaction (RT-PCR). Therefore, several intervention strategies, such as transmission control, are required to treat MERS patients (Mackay and Arden 2015). Since its emergence in 2012, researchers have been working on the development of a MERS vaccine (Zhang et al. 2014). To develop an efficient vaccine, extensive research is being done using multiple resources like viruses, antibodies, and protein. The MERS coronavirus spike (S) protein's receptor-bound area was discovered to be the focus for vaccine development in a prior investigation. The development of vaccine is being taken up by numerous organizations, some of which have demonstrated efficacy in animal models (Tai et al. 2022).

2. VIROLOGY of MERS

The β-coronavirus family includes MERS-CoV. It has four main surface proteins, including the envelope protein (E), spike protein (S), nucleocapsid protein (N), and membrane protein (M). These proteins help in the virus's ability to penetrate cells. The spike (S) protein is a transmembrane glycoprotein consisting of the S1 and S2 sub-units. According to recent research, these viral structural and nonstructural proteins can be used as potential therapeutic targets (Abdi and Javanshir 2022).

The MERS-CoV basic protein (S), (E), and (M), and (N) contaminated individuals' bronchial cells screened for MERS-CoV as a viral antigen (Durai et al. 2015) are shown in Fig. 1. MERS-CoV is an enveloped Nidovirus that enables entrance into host cells and is adorned with homotrimers of the spike (S) glycoprotein. The primary antigen at the viral surface, S, is the focus of vaccine development and the target of neutralizing antibodies during infection (Baharoon and Memish 2019). MERS-CoV binds to the dipeptidyl peptidase 4 receptor via receptor-binding domain (RBD) in spike (S) protein S1 subunit and then mediates virus entry into target cells via S2 subunit. Therefore, for merging of viruses as well as cells genomic RNA infusion into the cytol, protease cleavage of the S protein is necessary (Xia et al. 2014). The endoplasmic reticulum derived from double membrane compartments and additional membrane-like structures serve as the sites for the transcription and replication of viral RNA (Comar et al. 2022).

Structural proteins of MERS-CoV, their stability, function, or effect on the host is shown in Table 1. The genomic structure of MERS-CoV also consists of accessory proteins like ORF3 and ORF4a that help in replication of virus (Joshi et al. 2023).

3. EPIDEMIOLOGY of MERS

The epidemiology and transmission method of MERS-CoV significantly impact the morbidity and mortality caused by these viruses. There are numerous established methods that spread MERS-CoV. Cattle to man, dogs to man, cats to man, bats to man, dromedary camel to the human method, bats to camels, among camels, cattle to man, and lastly man to man transmission are included (Xie and Chen 2020). In close quarters and congested environments, human-to-human transmission is very effective and frequent. In addition, nosocomial infection has also been reported (Assiri et al. 2013). There have been instances where patients have transferred diseases to healthcare professionals. Dromedary camels are crucial to the epidemiology of MERS-CoV because they serve as reservoir hosts. Additionally, dromedary camels serve as "gene mixing vessels". A new subtype of MERS-CoV develops when two distinct MERS-CoV strains from two different sources infect dromedary camels. This happens because the two genetically distinct MERS-CoV swap their ssRNA. These unique virulence genes and novel antigens are the striking characteristics of these new MERS-CoV subtypes. Possible incidences of human transmission via consuming camel milk have been reported in Saudi Arabia. However, no incidences of transmission to humans by consumption of camel flesh have been reported (Widagdo et al. 2019).

Table 1: Structural proteins of MERS-CoV, their functions, and stability

Protein	Function and effect on host	Stability	References
PL protease	Viral replication, membrane proliferation	Stable	(Naz et al. 2023)
3CL protease	Survival of viruses	Stable	(Li et al. 2019)
Helicase	Viral replication, effect tropism	Stable	(Li et al. 2019)
Spike	Receptor binding, virus entry	Stable	(Li et al. 2019)
ORF3	Pathogenesis and replication	Stable	(Naz et al. 2023)
ORF4a	Viral replication and IFN antagonism	Unstable	(Li et al. 2019)
sssORF5	Mediated inflammation	Unstable	(Naz et al. 2023)
Envelope	Virion assemblage	Stable	(Li et al. 2019)
Membrane	IFN antagonism, virion assembly	Unstable	(Naz et al. 2023)
Nucleocapsid	Replication and assembly	Unstable	(Li et al. 2019)

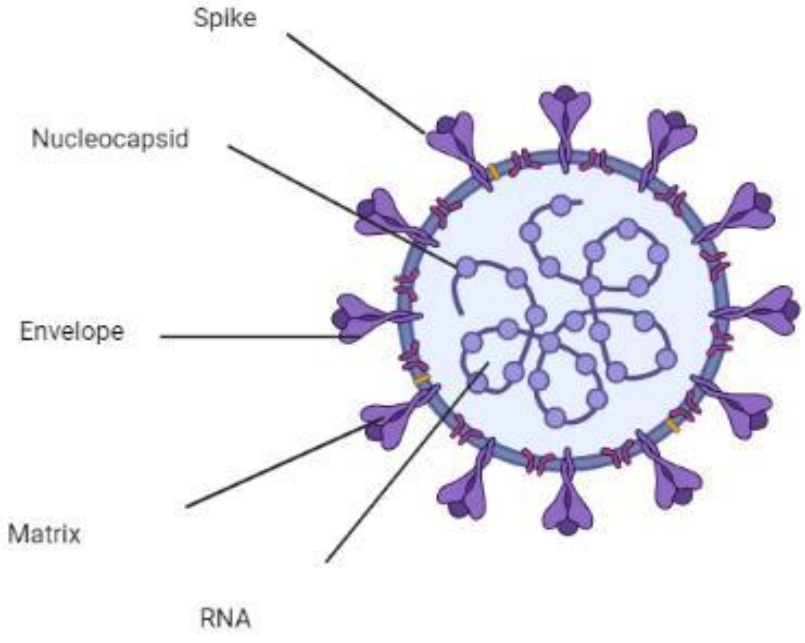

Fig. 1: Genomic structure of MERS-CoV (Retrieved from biorender)

4. PATHOGENESIS AND TRANSMISSION

According to the host, MERS-CoV manifests to a different extent of pathogenicity. Particularly in humans, it stimulates the highest level of pathogenic potential. This because the bronchial non-ciliated epithelia exhibit significant MERS-CoV tropism (Killerby et al. 2020). MERS-CoV infects and replicates in the human airway epithelial cells and suppresses the production of interferons. MERS virus interacts with the host DPP4 receptor through its spike (S) protein after entering the respiratory tract. DPP4 receptors are present on the epithelial surface of various human organs such as, the lungs, kidneys, liver, bone marrow, thymus and intestines. The systemic distribution of DPP4 facilitates the dissemination of virus in the human body (Choudhry et al. 2019).

4.1. ANIMALS TO HUMAN TRANSMISSION

The MERS-CoV transmission mechanism and route continue to be a mystery. The most likely method of camel to human transmission may be droplet transmission or direct contact with infected camels shown in Fig. 2 (Hemida et al. 2017). Other potential pathways include ingestion of unpasteurized camel milk, close contact with intermediate hosts, urinalysis for medical purposes, or intake of raw meat. Foodborne transmission via uncooked meat or unpasteurized camel milk is also a possibility (Widagdo et al. 2019).

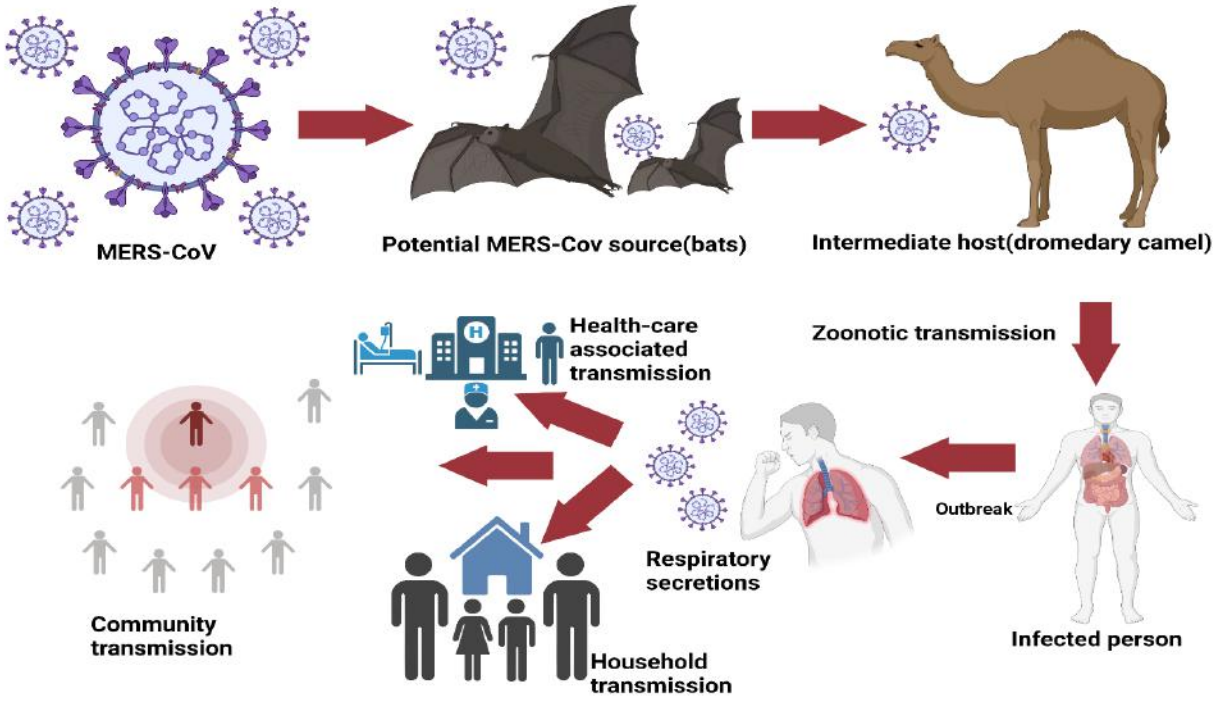

Fig. 2: Potential routes of emergence and transmission of MERS-CoV

4.2. HUMAN-HUMAN TRANSMISSION

MERS-CoV is mostly spread from person to person by nosocomial transmission. Despite the possibilities of airborne or fomite transmission, it was considered that transmission would primarily occur by contact and big droplets. Since MERS- CoV have been isolated from such excretions,

transmission by other bodily fluids such as diarrhea, the stool, and vomit are also potentially probable. The majority of infections were passed from person to person, highlighting the significance of taking the proper protection for aerosols and communication to stop spreading to additional affected persons, healthcare professionals, as well as relatives (Raj et al. 2014). Communities, homes, and, most dramatically, hospital settings are all places where human to human transmission occurs (De Wit et al. 2016).

4.3. TRANSMISSION FROM BATS

Numerous viruses, including Henipaviruses, Lyssaviruses, and SARS-CoVs, have been identified to be reservoir hosts in bats. Although it was just recently discovered, the virus may have been spread to humans in antiquity. Therefore, limiting initial and ongoing interaction among bats and individuals, would be one potential future strategy to prevent infection. Knowing these methods of spreading can aid us stop prospective occurrences of recognized and possibly undiscovered diseases that spread from bats to people either directly or through intermediary animals. MERS-CoV significant sequence similarity to viruses found in bats suggests that bats may have been the virus's source, even though its natural reservoir has not yet been identified (Mohd et al. 2016).

5. CLINICAL FEATURES

Any infection has specific symptoms that help with diagnosis and differential diagnosis with other viral infections. However, this effort is quite difficult due to the lack of distinct clinical characteristics for MERS-CoV infection. This causes delays in implementing the safety measures necessary to avoid subsequent contamination. Additionally, it may lead to improper patient management and medical ambiguity. MERS has no defined signs or symptoms; however, it typically manifests as respiratory symptoms. Through asymptomatic manifestations to moderate to severe illness including ARDS, multi organ dysfunction, and mortality, clinical presentation might vary. In the beginning, these individuals only exhibit minor symptoms such as shivers, headache, fatigue, a stuffy nose, coughing, throat discomfort, drowsiness and a mild fever. MERS-CoV might manifest clinically as anything from asymptomatic infections to severe respiratory conditions. Patients who are infected frequently display hemoptysis; a difficulty of breath, coughing, throat discomfort, a high body temperature and additional symptoms of digestion like vomiting and diarrhea (Mann et al.2020).

6. TREATMENT

Currently, there is no MERS-CoV vaccine or medication available (Ramadan and Shaib 2019). Clinical treatment for mild cases of MERS focuses mostly on symptom relief and supportive care, including pain and fever-relieving drugs, plus resting at home. Severe instances necessitate hospital inpatient care for supportive therapy with the goal of lowering the risk of consequences like organ failure and subsequent infections. Additionally, pharmaceutical companies have little incentive to develop the MERS-CoV vaccine because clinical trials are exceedingly expensive and it can take at least 10 years for the vaccine to be authorized for use (Ying et al. 2015).

Patients primarily get supportive treatment, which is frequently augmented by various medication combinations as given in Table 2, in the absence of an antiviral therapy against MERS-CoV that has been clinically demonstrated to be successful. Supportive care is required to maintain renal and hepatic function, assist the respiratory and circulatory systems, and to avoid subsequent infections (Li et al. 2019).

Table 2: Potential therapeutics for MERS-CoV

Treatments	Stage of development	References
Host protease inhibitors	In-vitro inhibition	(Alyami et al. 2020)
Viral protease inhibitors	In-vitro inhibition	(Alyami et al. 2020)
Repurposed FDA-approved drugs	In-vitro inhibition	(De Wit et al. 2016)
Monoclonal and polyclonal antibodies	Efficient in nonhuman primate, mice, and rabbit models.	(Memish et al. 2020)
Convalescent plasma	Efficient in a mice model; clinical study approved	(Alyami et al. 2020)
Interferons	Excellent in nonhuman primate studies; illegally used in patients	(Memish et al. 2020)
Ribavirin	Excellent in nonhuman primate studies; illegally used in patients	(Memish et al. 2020)
Mycophenolic acid	In the nonhuman primate model, protection was ineffective	(Azhar et al. 2019)
Lopinavir and ritonavir	Excellent in nonhuman primate studies; illegally used in patients	(Azhar et al. 2019)

7. PREVENTION AND CONTROL

From the SARS epidemic, the primary infection prevention and management techniques for treating MERS affected individuals are well established. The prevention of nosocomial spread requires continual observation, early detection of suspected or confirmed infections, and isolation of those people. It is necessary to use higher levels of personal protective equipment (a greater protection, stronger types of respiratory immunity), air circulation (more oxygen changes, more ventilation,), and more intensive efforts to stop airflow from spreading past the origination point (enclosure, capture ventilation). In order to prevent MERS infection in hospitals an adequate room air circulation efficiency of twelve air turnovers every hour within one room or a minimum of 161L/s per receptive in establishments via ventilation from the outdoors is recommended to minimize room contaminants in the healthcare environment while taking care for patients obtaining ventilatory therapy along with aerosol-generating processes (Subbaram and Gatasheh 2017). Other preventive strategies included;

7.1. PHYSICAL DISTANCING

An effective and powerful strategy to reduce viral transmission among people and the number of people dying from sickness during the pandemic is to engage in forceful physical distance-creating activities to reduce direct interaction between persons. Absolute containment was used in several countries around the world and showed positive results, most notably reducing the increase in the number of cases. Activities that isolate affected people, quarantine close connections, allow people to work for virtually, close schools, and prohibit large gatherings have all proven effective social distancing measures (Zinn 2021).

7.2. DECREASING THE RISK OF TRANSMISSION

To stop transmission, especially in hospitals, proper infection control measures must be put in place as soon as the diagnosis is taken into account. Primary instances of people with MERS-CoV infection are challenging to diagnose because the symptoms and indications are nonspecific (Ezhilan et al. 2021). It's crucial to take actions for preventing infection and management to stop the transmission of MERS-CoV in homes, communities, and healthcare facilities (Alslamah and Abalkhail 2022).

7.3. PREVENTION OF HEALTHCARE FACILITY TRANSMISSION

The fundamental tenets of MERS-CoV prevention revolve around implementing organizational and environmental events to guarantee initial detection and use of personal protective equipment to avoid cross transmission. To ensure the effective implementation of all administrative measures, healthcare facilities should actively invest in infrastructure for infection prevention and control in addition to developing policies and procedures. All healthcare workers must receive assistance, adequate resources, and training, and all policies must be subject to regular inspection (Behnke et al. 2021). Healthcare institutions must have a sufficient and reliable supply of these supplies. They consist of a robe, gloves, a mask that is very effective, goggles, or a face shield. Demand for PPE may expand significantly, but supply should always be sufficient. PPE use protocols, ongoing training, and auditing are required, especially in settings with significant personnel turnover rates (Kim et al. 2015).

7.4. HEALTH CARE WORKERS AND COMMUNITY EDUCATION

Education about MERS-CoV and MERS preventive strategies may lessen the potential for spreading within the home and avoid community cases in MERS-CoV endemic areas wherever MERS-CoV cases can arise within communities and homes. It is advisable to regularly wash your hands before and after handling camels and to stay away from ill ones (Aleebrahim-Dehkordi et al. 2021). It is not recommended for people to consume uncooked camel meat or to drink raw camel milk or urine. People who suffer from illnesses such as diabetes, cancer, persistent lung condition, or renal illness, who suffer from illnesses such as diabetes, melanoma, persistent lung condition, or renal illness, or who are receiving immunosuppressant therapy must keep distance from bats and camels because they run a significant threat of acquiring severe MERS-CoV illness (Aldohyan et al. 2019).

7.5. GUIDANCE FOR TRAVEL

Travelers should be warned not to go to areas where MERS has been found, per the WHO and CDC's recommendations, in order to avoid MERS infections (Errett et al. 2020). The suggestion is to provide travelers with up-to-date information about MERS coupled with advice on how to prevent illnesses, particularly respiratory illnesses (Alnuqaydan et al. 2021).

7.6. INTENSIVE CARE MANAGEMENT

To lower the risk of consequences like organ failure and subsequent infections, hospital inpatient care is necessary for serious patients. In infected individuals acute hypoxemic respiratory distress brought on by MERS-CoV infection, invasive-free airflow is linked to a high failure rate i.e. 92% (Al-Dorzi et al. 2016). It may be necessary to manage patients with severe symptoms in a hospital's surgical unit, where lung protecting ventilatory methods for acute respiratory distress syndrome, inotropic provision, antibiotic therapy for concurrent infections, and replacement of renal function treatment for acute kidney dysfunction can be offered (Aleebrahim-Dehkordi et al. 2021).

8. DIAGNOSIS

Rapid diagnostic tests are needed to control epidemics of virus because there isn't a particular, dependable antiviral medication or vaccine authorized for clinical use in MERS-CoV infections. A thorough

contact and travel history as well as exact laboratory tests are used to make the diagnosis of MERS. Molecular techniques, serology, and viral culture are currently used as diagnostic tools (Al Johani and Hajeer 2016).

8.1. MOLECULAR DIAGNOSTIC

The most popular diagnostic technique uses molecular detection, such as RT-PCR (reverse transcription Polymerase chain reaction), with RNA isolated from samples of the respiratory tract, such as nasopharyngeal swabs, sputum, deep tracheal aspirates, or bronchoalveolar lavage (Skariyachan et al. 2019). Nucleic acid amplification tests (NAAT) are advised by the WHO laboratory recommendations for diagnosis specimens of the lowest pulmonary system's sputum, bronchial aspirates, or lavage of the bronchoalveolar, where MERS-CoV multiplication takes place at faster and longer heights of MERS-CoV RNA, provide the highest NAAT test sensitivity (Mustafa Hellou et al. 2021).

8.2. SEROLOGICAL ASSAYS

Serology is not frequently used to diagnose acute MERS-CoV infection, but it has been a valuable technique to assess the level of infection in the vicinity of clusters and in sero-epidemiological research within people and in animals. Neutralization tests, IIFT, and ELISA are several serological techniques for detecting antibodies against MERS-CoV. As capture agents, commercial reagents or exclusive monoclonal antibodies may be used in MERS-CoV serological testing (Chan et al. 2017).

8.3. MULTIPLEX PANEL

Early MERS-CoV infection symptoms may resemble those of other respiratory infections, such as SARS, pneumonia, influenza, or pneumonia (Liya et al. 2020). A syndromic technique includes assessing infections in response to a condition like fever or acute respiratory distress; moving multiplexing arrays from individual evaluations may swiftly recognize or rule out potential solitary sample of germs. Microbead based multiplexed immune assays have been utilized for circulating reservoir analysis to find IgG antibodies for various infections (Banik et al. 2015).

9. CONCLUSION

Continually posing a threat to human life, MERS-CoV is responsible for the Middle East respiratory syndrome, which is rapidly spreading in the Middle East and around the world. MERS has become a widespread epidemic as a result of the coronavirus rapid evolution. The precise intermediate host for MERS-CoV and its geographic distribution remains unknown despite the studies that have been done to date. Despite being a zoonotic origin for the virus is utmost probable, direct or indirect contact, as well as ingestion of tainted food or food products, could also result in virus transmission. Further research is needed to determine whether or if the virus is boosting the host's involvement is transferred from bats to camels and then to humans, or whether there are other amplifying hosts implicated in the transmission of the MERS-CoV to humans. Given the nosocomial patterns of transmission within healthcare institutions, MERS-CoV continues to pose a significant risk to the public's health, and any additional international spread could have negative effects that are potentially life-threatening. Since MERS-CoV tends to be largely persistent in dromedaries across geographically extensive regions of the Middle East and Africa, zoonotic transmission and the associated danger of human disease outbreaks will very

certainly persist for many years. New MERS-CoV cases are still being reported despite significant improvements in diagnosis and public health interventions. Explosive MERS-CoV outbreaks are a severe threat to the world's public health and highlight the additional investigations are required into the epidemiology and pathophysiology of this virus. They also highlight the need for the development of efficient therapeutic and preventive MERS-CoV infection medications. To discover the viral and host variables that are crucial in the emergence of MERS in humans, it is necessary to better understand the pathophysiology of MERS-CoV that could lead to the development of potentially novel treatment and intervention options. In addition, efforts to create vaccinations against this lethal virus have been steadily expanding, which has resulted in the creation of potential therapies.

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Control Strategies of Rotavirus Infection

37

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ABSTRACT

Rotavirus is major cause of gastroenteritis particularly in young and newborn children. The main way that the virus spreads is by the fecal-oral route, however, contaminated food, drink, and surfaces can also pose a significant risk of transmission. Due to inadequate sanitation and medical facilities, low- and middle-income nations are disproportionately affected by RV infections, which cause severe morbidity and mortality on a global scale. Various animals are affected by RV infections in addition to people, resulting in a variety of types. Infection of host cells, virus replication, assembly, and release of new virus particles are all phases of the RV life cycle. Personal contact, contaminated objects, and airborne routes are the three ways the disease spreads. According to epidemiology, childhood RV infections are common, vary seasonally, and are more severe in low-income countries. RV vaccinations, such as RotaTeq and Rotarix have successfully avoided severe gastroenteritis. Passive immunization is the main focus of animal vaccines; however, RV Virus-like Particles (RV-VLPs) promise to be a more broadly serotype-covered vaccine in the future. RV continues to be a major public health concern, and developments like RV-VLPs, as well as the development and execution of efficient immunization programs, are essential for the prevention and management of disease worldwide.

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1. INTRODUCTION

Rotavirus (RV) belongs to the family Reoviridae and wheel-shaped, triple-layered virion with a diameter of about 100 nm (Nirmal and Gangar 2023). They have an 11-segment genome that codes for 5 nonstructural proteins (NSP1, NSP2, NSP3, NSP4, and NSP5) and 6 structural viral proteins (VP1, VP2, VP3, VP4, VP6 and VP7) (Azevedo et al. 2023). RV strains are categorized based on the differences between two outside proteins on the virus surface known as VP4 (P-type) and VP7 (G-type) (McDonald et al. 2009). These proteins greatly influence the specific RA strain and its antigenic characteristics. These proteins play an important role in the antigenic and strain properties of viruses. This is involved in entry into host cells, viral attachment, and the target of the host immune system. RVA, RVB, and RVC are the most prevalent infecting groups in humans and animals, with RVA strains being the most prevalent (Molinari et al. 2016). Birds like chickens and turkeys have RVD, RVG, and RVF. Some mammals like cows, horses, and pigs have RVI, RVB, RVH, RVC, and RVE (Vlasova et al. 2020). Bovine RV was the first group of RV separate in cell culture and was confirmed as a cause of diarrhea in calves in 1969 (Vlasova et al. 2017). In 1973 human RV was discovered by Bishop and his colleagues. The rotavirus mainly causes gastroenteritis, inflammation in the digestive system (Sadiq et al. 2018).

The virus has a significant risk of spreading from person to person. They can contract rotavirus through contaminated food, water, objects, or surfaces. This is primarily because it is transmitted through the fecal-oral route (Sánchez and Bosch 2016). The virus is very resilient and can persist on surfaces for extended periods. In temperate climates, RV infections occur more commonly in the winter but may occur in every season (Chao et al. 2019). The risk of infection is greater in infants and young children, and symptoms usually occur two to three days after contact. The most typical signs and symptoms include vomiting, fever, watery diarrhea, and pain in the abdomen (Fig. 1) (Reust and Williams 2016).

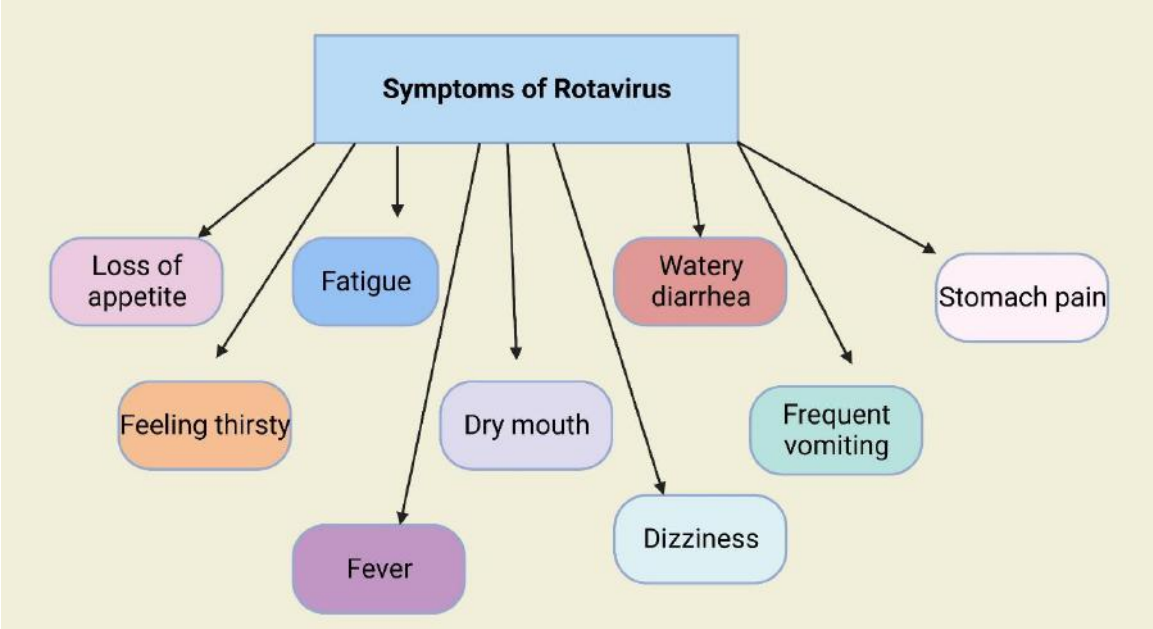

Fig. 1: Symptoms of Rotavirus (Retrieved from Biorender).

WHO estimates 200,000 deaths and millions of hospitalizations annually due to RA, primarily in areas with limited resources. Geographical differences affect the severity of rotavirus infection. Severe rotavirus sickness and death are more predominant in low and middle-income countries, mainly in Africa and Asia

(Varghese et al. 2022). The higher effect in these areas is due to limited healthcare access, clean water, and sanitation facilities (Watson et al. 2007).

2. ROTAVIRUS TRANSMISSION

RV spreads from person to person orally through feces (Yekta et al. 2021). In developing nations, RV can also spread through water that feces have polluted. RV may also transfer from child to child if caretakers' hands come into contact with contaminated objects or surfaces (Brady 2005). The rapid incubation period and frequent outbreaks suggest RV gastroenteritis is airborne. RV can be spread through the air in healthcare places (Koo et al. 2010). Children with RV infection pass 100 billion virus particles per gram of feces (Boone and Gerba 2007). These viruses can live from days to weeks on environmental surfaces, on hands for at least 4 hours, and in drinking or recreational water for weeks (Weber et al. 2010). Asymptomatic RV infections

3. EPIDEMIOLOGY OF ROTAVIRUS

RV is common and affects almost all children between the ages of three and five. Worldwide, 114 million instances of RV infection in children below 5 years old have been recorded in 2003 (Nair et al. 2010). By 2013, RV had caused more than 200,000 mortalities in children under the age of five around the world (Zhou et al. 2023). RV infections are common (about 30–50%) in hospitalized children with diarrhea worldwide. Over 90 percent of fatal RV infections happen in low-income nations (Tanaka et al. 2007). RV causes comorbid diseases like hunger, restricted access to healthcare, and a lack of availability of hydration therapy (Ren et al. 2021). Poor countries experience more cases of rotavirus caused by uncommon strains like G9P, and it affects kids at an earlier age than in rich countries. In Africa, almost 43% of all children hospitalized for RV are infants under 8 months, while in Europe, only 27% (Sadiq et al. 2018). Hospitalized patients (30-50%) and outpatient treatment patients (15-20%) are more likely to get RV-caused diarrhea than those who need home care (5-10%). Diarrhea induced by RV infection is more severe than typical (Parashar et al. 2003). RV detection rates were highest in children aged 6-23 months (41.8%) and lowest in children aged 6 months (24.7%). Of the 21,421 children enrolled during the four years of surveillance, 36.3 percent were positive for RV (Patel et al. 2013). The eastern region had the highest percentage of RV-associated diarrhea (39.8%), and the southern region had the lowest (33.8%) (Tate et al. 2016).

4. EPIDEMIOLOGY OF ROTAVIRUS IN ANIMALS

RV infections with symptoms are often more frequently found in birds and mammals. Animal RVs' molecular epidemiology is similar to that of humans in several respects (Rajendran and Kang 2014). RV diseases affect pigs, cattle, horses, and, to a lesser extent, sheep, goats, and camelids. In cattle, RV strains have been classified into 11 P types (P1, P3, P5, P6, P7, P11, P14, P17, P21, P29, and P33) and 12 G types (G1-G3, G5, G6, G8, G10, G11, G15, G17, and G24) (Matthijnssens et al. 2011). Out of 20 P and G combinations, G6P [5], G10P [11], and G6P [11] are most common in many parts of the world, making up 40% of cases (Uddin Ahmed et al. 2022). Pigs have been found at least 13 P categories (P6 or P7, P5, P8, P11, P13, P14, P19, P23, P26, P27, and P32) and 12 G (G1, G2, G3, G4, G5, G9, G6, G8, G10, G11, G12, and G26) (Papp et al. 2014: Daykin et al. 2019). However, the P and G genotypes of rotaviruses found in camelids, goats, and lambs frequently match those discovered in cattle. Canine RVs have the G3P [3] antigen combination in the majority of cases, whereas feline RVs have the G6P [9], G3P [9], and G3P [3], and genotypes (Doro et al. 2015).

5. EPIDEMIOLOGY OF ROTAVIRUS IN HUMANS

Young kids and infants between the ages of four months and three years are more prone to experience extreme clinical symptoms of RV (Khemani et al. 2017). Most kids are infected with RV by age five, although the rates vary by region (Page et al. 2016). RV infections frequently exhibit seasonal trends in temperate zone states, with the epidemic peaks more pronounced during wintertime (Shaman and Kohn 2009). In industrialized nations, one genotype dominates in a geographic location during a season. However, minority strains can still have distinct genotypes. In some years, no single dominant strain can be discovered in underdeveloped nations, and illnesses caused by many RV genotypes, that is, mixed infections, are common.17 P types (P1 to P11, P14, P15, P19, P24, and P28) and 14 G types (G1, G2, G3, G4, G5, G6, G8, G9, G10, G11, G12, G13, G14, G20 and G26), as well as almost 90 RVA antigen mixtures have been detected in youngster around the world through surveillance studies (Amimo et al. 2013). G12P [8] and G9P [8] strains have recently become widespread worldwide from 1990 to onward. G2P [8] and G1P [4] strains are frequently observed to co-circulate with G2P [4] and G1P [8] (Hungerford 2019). G2P [4] strains became more prevalent over successive seasons in regions where the national immunization strategy used the G1P [8] Rotarix vaccine (Bibera et al., 2020). The G8P [6] and G5P [8] viruses, which are found in various regions of Sub-Saharan Africa and South America, respectively, are historical instances of regionally prevalent strains (Linhares 2011). Porcine-like G4P [6] strains and G3P [9] strains are two examples that have been found in humans over the past 20 years in many countries all over the world (Wang et al. 2014).

6. LIFE CYCLE

The RV involves infecting host cells, replicating, assembling, and releasing new virus particles (Ravindran et al. 2016). In the small intestine, the RV first binds to certain receptors on the surface of host cells. A sugar molecule known as Salic acid serves as the main receptor. Following attachment, the virus enters the host cell through a process known as endocytosis, in which the cell engulfs the viral particle and produces an endosome (Abdelhakim et al. 2014). After the viral particle is engulfed by the host cell, it enters the endosome, where the outer covering is broken down, and the inner core is released. The acidic surroundings of the endosome, which lead to structural changes in the virus particle, initiate this process (Louten 2016). Eleven double-stranded RNA sections comprising the viral genetic makeup are present in the released viral core (Christiaens et al. 2020). Viral enzymes subsequently perform transcription and replication of the viral RNA inside the host cell. As a result, additional viral genome copies and messenger RNA (mRNA) is produced (Te Velthuis et al. 2010). The machinery of the host cell translates the viral mRNA into viral proteins. The structural proteins that comprise the virus particle, the non-structural proteins required for virus replication, and the enzymes involved in RNA replication belong to these proteins (Malone et al. 2022). In the host cells cytoplasm, replicated viral RNA segments and newly synthesized viral proteins generate new virus particles (Chou et al. 2013). The pre-structural of the viral genome forms a full virus particle newly constructed virus particles undergo maturate undergoing which the virus particle's exterior protein layer is changed, and it acquires infectious properties (Novoa et al. 2005). The host cell allows the virus particles to release. This can occur through several methods, such as cell lysis, in which the host cell is ruptured, or a process known as budding, in which the virus particle is encapsulated by the host cell membrane and discharged without resulting in cell death (Fig. 2) (Nanbo et al. 2018).

The released virus particles infecting additional host cells can continue the infectious cycle. Typically, the RV life cycle lasts ten to twelve hours, during which plenty of newly formed virus particles are produced. The sickness's large viral load and quick spread are attributed to this virus generation that occurs quickly.

7. DIFFERENT STRATEGIES TO CONTROL ROTAVIRUS

Strategies for controlling and preventing RV infections are being developed. Vaccination is the major method of lessening the social and financial costs of RV infections.

8. ROTAVIRUS VACCINES IN HUMAN USE

Animal virus strains induce cross-neutralizing antibodies against human strains, whereas heterologous virus strains are greatly attenuated for humans (Schwartz et al. 2007). Some were selected because they are common in neonatal units, while others were weakened through repeated cell culture passages. Live vaccines are given orally in doses to imitate RV infections and promote immunity against different variations of antigens (Azevedo et al. 2013). Non-replicating vaccines are made up of sub-unit and inactivated vaccines. The monovalent, two-dose vaccine Rotarix is made by GlaxoSmithKline (Belgium) (Braeckman et al. 2012). A single G1P [8] strain was repeatedly transmitted on cell culture to reduce it. The vaccine is widely accessible and is recommended in 70% of countries where routine RA vaccination is practiced (Danziger-Isakov et al. 2019). Table 1 shows the names of available vaccines, host and the efficacy.

RotaTeq is a pentavalent 3-dose vaccine developed by Merck (USA). Each of the 5 resistant strains in the vaccine represents a different human neutralization antigen (Matthijnssens et al. 2012). Each resistant's backbone genes are mostly provided by the parental strain, the bovine WC3, and its original neutralizing

Table 1: Vaccine names, host, strain, and efficacy against Rotavirus

Vaccine Name	Administration	Strains	Hosts	Efficacy	References
RotaTeq	Oral (liquid)	G1, G2, G3, G4, P[8]	Human-bovine	Approximately 85-98% against severe rotavirus gastroenteritis,	Cortese and Parashar 2009; Nayak et al. 2019
RotaShield	Oral (liquid)	G1, G2, G3, G4, G9, G10, P[8]	Human-bovine	Approximately 49-68% against severe rotavirus gastroenteritis	Glass et al. 2021
BRV-PV (BRVAX)	Oral (tablet)	G1P[8]	Human	Approximately 67-87% against severe rotavirus gastroenteritis	World Health Organization, 2020
Rotarix	Oral (liquid)	G1P[8]	Human	Approximately 85-98% against severe rotavirus gastroenteritis	Grimwood and Bines 2007; Ella et al. 2019
Rotavac	Oral (liquid)	G1P[8]	Human-bovine	Approximately 55-64% against severe rotavirus gastroenteritis	Burke et al. 2021
Rotavin-M1	Oral (liquid)	G1P[8]	Human	Approximately 53-67% against severe rotavirus gastroenteritis	Castellucci, 2017; Skansberg et al. 2021
Ervebo	Intramuscular	N/A	Hamster	Approximately 97.5-100% in preventing Ebola virus infection	Woolsey et al. 2022
RIX4414	Oral (liquid)	G1P[8]	Human-bovine	Approximately 85-98% against severe rotavirus gastroenteritis	Grimwood and Bines 2007
Lanzhou lamb-2 rotavirus vaccine	Oral (liquid)	G10P[15]	Lamb	Approximately 80-85% against severe rotavirus gastroenteritis	Carvalho and Gill 2018
Rotasiil	Oral (liquid)	G9P[11]	Cow	Approximately 53-67% against severe rotavirus gastroenteritis	Castellucci 2017
BRV-PV	Oral (liquid or suspension)	G1, G2, G3, G4 and G9	Human	66.7% efficacy	Folorunso and Sebolai 2020

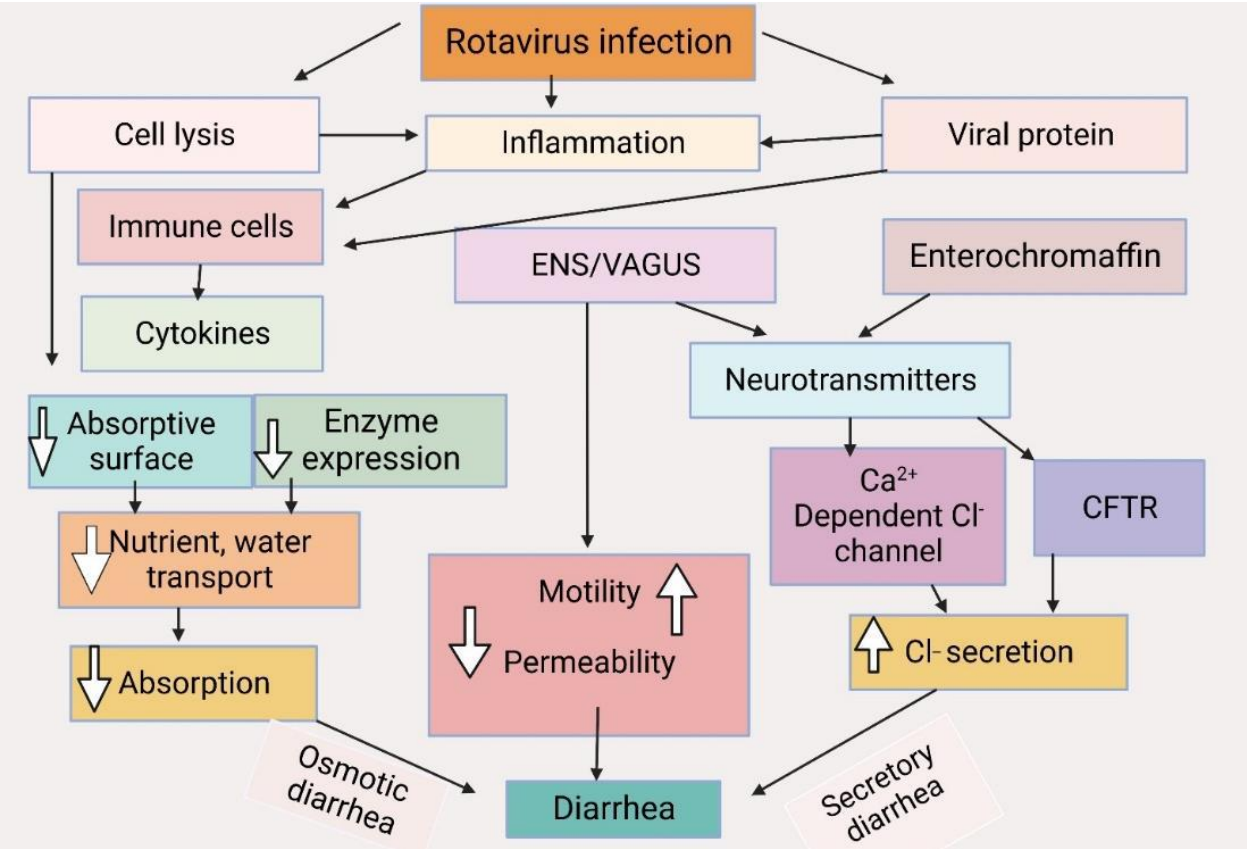

Fig. 2: Mechanism of Rotavirus Disease (Retrieved from Biorender).

antigens. The VP4 and VP7 are also detected (Doro et al. 2015). The Lanzhou Lamb RV vaccine was produced by Lanzhou Institute in China. This vaccine is monovalent and carries a G10P [15] rotavirus strain of an ovine origin (Li et al. 2018). Rotavac is a monovalent 3-dose vaccine and produced by Bharat Biotech in India. The vaccine contains a single human G9P [11] strain, which was discovered in an Indian youngster who was asymptomatic (Skansberg et al. 2021). After a Phase 3 trial showed a positive safety and efficacy profile, the vaccines were commercialized in 2014. A monovalent vaccine called Rotavin-M1 was developed at the center for research and production of vaccines and granted a license for Vietnam in 2007 (Kirkwood et al. 2019).

9. ROTAVIRUS VACCINES IN ANIMAL USE

Animal immunization strategies differ from those used to prevent rotavirus infections in infants and young children (Dhama et al. 2009). In humans, the main goal is to prolong the active immunity induced by vaccination during the first few years of a child's life, when the risk of extreme infections is at its highest after the parental antibody level has decreased by the age of four to six months (Kinyanjui et al. 2015). RV primarily affects the offspring of animals and passive vaccination is the major treatment for animals. This principle of passive vaccination is based on parental antibodies that can cross the placenta or be released in colostrum and give kids temporary protective immunity against clinically evident RV infection (Vojtek et al. 2018). Both inactivated and live attenuated vaccinations can raise the antibody concentration in pregnant animals. These vaccinations are given late in pregnancy, and RA antigens are frequently included

in polyvalent vaccines containing antigens from other significant intestinal infections (Obaro et al. 2014). The USA has access to a live modified vaccine used to vaccinate young piglets (Tizard 2020) actively.

10. RV VIRUS-LIKE PARTICLES

Production of rotavirus virus-like particles (RV-VLPs) was 1st reported in 1980. The formation of VLPs that can be easily isolated was subsequently achieved by co-expressing the VP6 and VP2 proteins in insect and mammalian cells (Kushnir et al. 2012). The expression of VP2 itself has been demonstrated to produce pseudo-core-like particles. RV- VLPs can significantly increase immune responses regardless of the method of vaccination used (intraperitoneal, intramuscular, intranasal, parenteral, intrarectal, and oral) (Marashi et al. 2014). The following factors make rotavirus VLPs a promising candidate and an alternative to conventional vaccines, they are effective immunogens and cannot transform into infectious forms because they lack genetic material, handling is risk-free, the viral proteins remain in their natural approval, they can be combined with an adjuvant to increase immunogenicity and large-scale recombinant vaccines for new serotype can be produced (Jere et al. 2014). Furthermore, a lower antigen can elicit the same immune response compared to subunit vaccinations since VLPs are similar to the parent virus (Noad and Roy 2003).

11. RECENT DEVELOPMENTS IN RV VIRUS-LIKE PARTICLES TECHNOLOGY

Several groups are currently focusing on developing combinatorial vaccines to improve their immunogenicity against different infections following the success of RV-VLP manufacturing systems (Changotra and Vij 2017). A potential combination vaccination against acute adolescent gastroenteritis that combines recombinant polymeric RV VP6 protein and norovirus VLPs generated in baculovirus-insect cell production systems (Blazevic et al. 2016). Additionally, it has been demonstrated that the RV VP6 protein affects the activation and maturation of antigen-presenting cells in vitro and has an adjuvant impact on norovirus-specific antibody reactions in vivo (Malm et al. 2017). None of the RV-VLPs have been tried on humans. However, gnotobiotic pigs, mice, and rabbits have been used to assess the RV-VLPs' immunogenicity, effectiveness, and safety (Yuan et al. 2000). Two VLP-based RV subunit vaccines, however, are made up of truncated VP8 in norovirus P particles and VP 2/6/7 and VP 2/4/6/7 in VP-based vaccines that are now in the preclinical stage of development (Heinimäki et al. 2020).

12. OTHER STRATEGIES

The challenges of removing rotaviruses from hands or infected surfaces must be addressed by rotavirus control techniques (Greenberg and Estes 2009). Rotaviruses are not easily destroyed by the chemical antiseptics and disinfectants frequently employed in hospitals and other institutions (Todd et al. 2010). Effective disinfectants should be used to clean environmental surfaces. Quaternary ammonium compounds and chlorhexidine gluconate, the active component of Hibiclens, should be used in formulations with a high alcohol content to become active against rotavirus (Dennehy, 2000). Rotavirus becomes inactive by quarternary ammonium compounds that contain >40% isopropyl alcohol by volume or formulations of chlorhexidine gluconate 0.5% w/v in 70% ethanol by volume (Hibitane in ethanol) (Rotter 2004). When applied to inanimate surfaces that had been experimentally contaminated with an infectious form of the RV, Lysol Brand Disinfectant Spray (79% ethyl alcohol, 0.1% o-phenyl phenol) effectively prevented the spread of rotavirus infection to humans (Boussettine et al. 2020). RV cannot be removed from hands using regular soap, and handwashing increases the risk of the virus spreading to more skin surfaces. Use a waterless hand cleaner with alcohol when washing your hands before and after coming into touch with sick kids (Bloomfield et al. 2007).

13. CONCLUSION

It is concluded that reducing the significant negative effects of rotavirus infection on public health, particularly in infants and young children, depends on controlling the infection. Vaccination remains the basis of prevention with multiple efficient vaccinations, including RotaTeq and Rotarix. The production of RV-VLPs shows promise as a candidate for a future vaccine. RV-VLPs greater serotype coverage and viral mimicry stimulate humoral and cellular immune responses. To further control and lessen the effects of RV infection globally, a multifaceted strategy involving vaccination, better hygiene habits, and continued research into new vaccine technologies like RV-VLPs is crucial.

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Dog-borne Zoonotic Diseases

38

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ABSTRACT

The increasing significance of the human-animal bond in contemporary society, especially in the context of pets serving various roles such as entertainment, companionship, and support, underscores the need to address potential health threats. This chapter explores the intricate relationship between dogs and their owners, emphasizing the heightened risk of zoonotic diseases transmission. Zoonoses, particularly those transmitted by dogs, pose a global threat to public health, with both developed and developing nations grappling with diseases like Leishmaniasis and Chagas disease. The epidemiology of these zoonotic diseases is multifaceted, involving environmental, socioeconomic, religious, and cultural factors, incurring substantial costs. Dogs serve as reservoirs for diverse pathogens, including bacteria, protozoa, and arthropods. Bacterial infections, such as canine brucellosis and leptospirosis, highlight the potential severity of zoonotic diseases. Protozoal infections like babesiosis, leishmaniasis, trypanosomiasis, and giardiasis demonstrate the broad spectrum of diseases associated with dogs. Moreover, mycoses, particularly dermatophytosis, showcase the prevalence of fungal infections. Arthropods, such as fleas, ticks, scabies mites, and demodex, play a pivotal role in disease transmission. This chapter outlines the infections caused by these pathogens and discusses preventive strategies, emphasizing the importance of maintaining the health of both dogs and their owners. Additionally, the impact of dog-borne zoonotic diseases on global health is addressed, emphasizing the need for coordinated efforts between government authorities and society to curb the spread of these diseases. Strategies for prevention, encompassing vaccination, hygiene practices, and veterinary care, are crucial in mitigating the risks associated with zoonotic diseases.

Keywords: Zoonotic diseases, Dogs, Bacterial infections, Protozoal infections, Arthropods

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1. INTRODUCTION

In today's society, the human-animal relationship is becoming essential, particularly in pets participating in entertainment, companionship, farming, military purposes, for people with disabilities, and emotional support for their owners. However, such a bond between dogs and owners potentially increases the possibility of acquiring zoonotic diseases (Alho et al. 2018).

The threat to public health due to zoonotic diseases transmitted by pets is reported in both developed and developing countries i.e., diseases such as Leishmaniasis and Chagas disease become a serious problem in tropical and subtropical regions (Dantas-Torres and Otranto 2016). The epidemiology of zoonotic diseases involves several components, i.e., environmental, socioeconomic, religious, and cultural factors, causing significant costs (Kardjadj and Ben-Mahdi 2019).

Dogs could serve as reservoirs of several pathogens, including viruses, bacteria, helminths, protozoa, and vector-borne diseases such as fleas, ticks, mosquitoes, sand flies, and several other flies (Irwin 2014). This chapter highlights the infections caused by bacteria, protozoa and finally, arthropods from dogs (Fig. 1). In addition, it discusses strategies to prevent transmission from those pathogens and maintain the dog owners protected. Ultimately, different effects of dog-borne zoonotic diseases are addressed in human health and its cots from government programs.

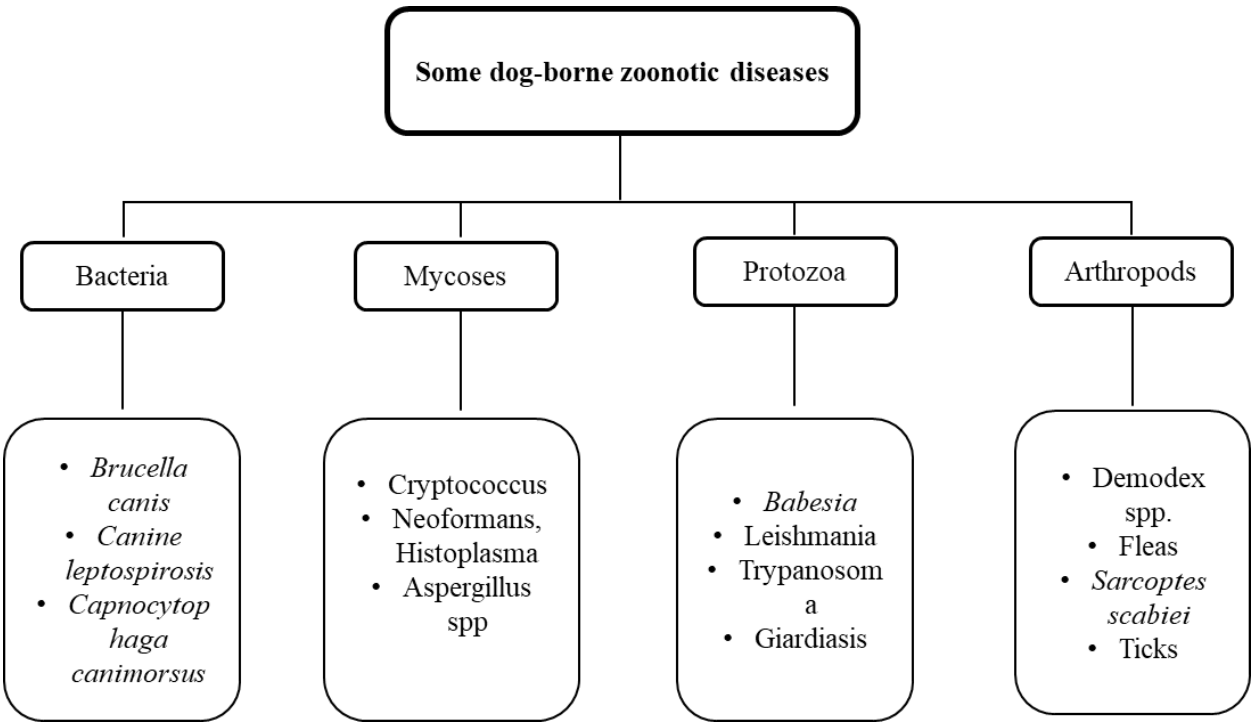

Fig. 1: Schematic outline of dog-borne zoonotic diseases.

2. BACTERIAL INFECTIONS

2.1. *BRUCELLA CANIS*

Canine brucellosis is a zoonotic disease that can cause reproductive problems, infertility, and abortion (Wanke 2004). More cases have been reported in humans when in contact with secretions of animals

infected with *Brucella (B.) canis*. On the other hand, the genus Brucella has more than eight species reported with zoonotic potential (Sánchez-Jiménez et al. 2013). *B. canis* is a large negative coccobacillus, an immotile bacterium lacking a capsule, spore and flagella. It was first isolated in 1966 by Carmichael (Nárez et al. 1999).

However, the serological tests necessary for diagnosis still need to be improved, and molecular tools are currently being sought for diagnosis. The disease can be asymptomatic or can show symptoms. *B. canis* infection penetrates the dog, starts as a bacterial infection, and then spreads in the organism. Initially, it can lodge in the lymph nodes, spleen, liver, uterus, prostate glands, vesicles, and bone marrow (Carmichael and Kenney 1970). In addition, it is important to mention that significant seropositivity frequencies have been reported, between 8.5 and 17% in various breeds (Bulldog, Poodle, Pug, Beagle, Schnauzer, Shih Tzu, Labrador retriever and Maltese) (Giraldo Echeverri et al. 2009).

In the case of human infection, it may or may not show symptoms, and many years can pass without showing signs (Corbel 1997). Nevertheless, documented cases in humans present symptoms such as fever, sore throat, chills, asthenia, muscle pain, joint pain, arthritis, weakness, anorexia, diarrhoea, weight loss, pneumonia and endocarditis (Paixão et al. 2009; Manias et al. 2013). Sanchéz-Jiménez et al. (2013) proposed a model of infection by the oral route, the bacterium passes until it reaches the stomach and activates the "ure" operon, then comes the adherence and cell invasion, ending with the establishment of the infection.

2.2. CANINE LEPTOSPIROSIS

It is a disease associated with a pathogenic bacterium, which can be transmitted by ingestion, or exposure of mucous membranes to canine urine residues or infected people. This bacterium can also live in contaminated water. The worldwide incidence of human Leptospirosis was estimated at one million people and almost 59,000 deaths yearly (World Health Organization 2011). In addition, the Event Management System considers Leptospirosis among the top ten public health risks or threats.

Canines can acquire the disease from infected wild animals such as rats, raccoons, and rodents. An infected dog may not show symptoms or present severe liver and kidney infections, sometimes even risking the canine's life. Antibiotic treatments are commonly used for humans and animals, including ampicillin, amoxicillin, doxycycline, penicillin, ceftriaxone, cefotaxime or, in more severe cases, blood transfusions (Harrison 2006). There are some vaccines to prevent Leptospirosis in dogs. A total of 26 biological products produced by 15 different commercial laboratories have been reported to protect against Leptospirosis (Luna et al. 2008).

When a human is infected, leptospires are distributed throughout the bloodstream to the organs and initiate with the symptoms i.e., headache, fever (39°C), malaise, muscle and joint pain, renal failure and abdominal or thoracic pain, cutaneous or mucosal haemorrhages, jaundice, haemoptysis and ultimately liver failure. The disease is diagnosed by various serological tests (World Health Organization 2008).

2.3. *CAPNOCYTOPHAGA CANIMORSUS*

This is one of the main bacteria associated with dog bites. These bacteria are the part of the flora of dogs and require 5 to 10% CO2 for their growth (Chanqueo et al. 2019). *Capnocytophaga (C.) canimorsus* is a gram-negative bacterium. For the diagnosis of this bacterium, biochemical tests, the catalase test, oxidase, and 16S rRNA sequence are used. These tests are used because sometimes it

is complicated to grow the bacterium due to its nutritional requirements and the speed of its growth (Fernández-Vecilla et al. 2022).
The transmission of *C. canimorsus* bacteria was sometimes observed after the canine bite. Most of the cases reported after five days without treatment and 28% could have a fatal evolution. They were showing a great variety of symptoms, mild or lethal. In patients with a history of splenectomy or with functional hyposplenism (chronic alcoholics or cirrhotic), fulminant sepsis with shock, disseminated intravascular coagulation, renal failure and pulmonary infiltrates or meningitis may occur (Le Moal et al. 2003). On the other hand, the bite area may also present gangrene (Henry 2018).
For its treatment, amoxicillin-clavulanic acid or 3rd generation cephalosporins are recommended. Other antibiotics, such as imipenem, clindamycin, and doxycycline, have also shown clinical efficacy (Dorronsoro 2001).

3. PROTOZOAL INFECTIONS

3.1. BABESIOSIS

Babesiosis has a considerable economic and public health impact and is one of the most common tick-borne diseases transmitted to dogs around the world and can infect various vertebrates, including humans (Petra et al. 2018). It is also known as piroplasmosis, which is a multisystem disease caused by the protozoa belonging to the genus *Babesia* (Hildebrandt et al. 2021).
The main route of infection is through the tick bite. However, vertical transmission, transmission by blood transfusion or organ transplantation, in addition to possessing reservoirs in wildlife, has been reported (Tołkacz et al. 2017). Symptoms in humans can vary from mild to fatal disease with multisystem failure (Bajer et al. 2022), in addition to synergising with other tick-borne diseases, which can change it to a more severe form of the disease (Kumar et al. 2021). Infections occur throughout the year but more frequently in temperate zones in early summer to late autumn (Vannier and Krause 2012).
Control in endemic areas is carried out to prevent vector infestation. A vaccine against *Boophilus microplus*, the primary transmitter of Babesia to cattle, is now available and reducing transmission. Self-immunisation is used in newly admitted animals in endemic areas with blood from healthy carriers infected with *Babesia*, resulting in a mild infection that can be treated with palliatives (Petra et al. 2018).

3.2. LEISHMANIASIS

This genus constitutes one of the most widespread parasitic species and produces a disease called leishmaniasis. In humans, it has three forms i.e., cutaneous, mucosal and visceral. One of the main species transmitted by dogs to humans is *Leishmania (L.) infantum*, which occurs as a multisystem disease that affects dogs which constitute as its main reservoir (Alvar et al. 2004). Its life cycle includes a mammalian host and the sand fly (Phlebotomidae), which acts as a vector and needs vertebrate blood to mature its eggs (Morales-Yuste et al. 2022). It is challenging to cure leishmaniasis in dogs, however, it seeks to control the sinology and reduce the disease to asymptomatic levels. Therapy depends on the level of the disease and is classified into four stages: Stage I: no signs or are very mild and may not be treated or treated with allopurinol only; Stage II and III: have moderate (II) to severe signs and may be associated with chronic kidney disease (III), these animals are treated with mixtures of allopurinol and antimonials/miltefosine; stage IV: animals with very severe disease having nephrotic syndrome and treated with allopurinol to prevent damage to the kidneys, in addition to including management for chronic kidney disease (Solano-Gallego et al. 2011).

3.3. TRYPANOSOMIASIS

This parasite has a high prevalence in dogs and cats, which are the main reservoir of this disease for humans. The Triatomidae family are the main vectors of this disease, which are infected by feeding on the blood of infected mammals, from where they obtain the trypomastigotes which reproduce in the insect and, finally, after 15 to 30 days, they appear as metacyclic trypanosomes in the faeces of these insects (Acha and Szyfres 2001).

Dogs chronically infected with trypanosomiasis show atrial and ventricular arrhythmias, as well as the dilation of the cardiac chambers and in the acute phase, presents fever, eyelid oedema, hepatomegaly and alterations of the nervous system. The acute phase of the disease lasts for 10 to 30 days after which the disease enters an indeterminate chronic stage (Freitas et al. 2022).

Because the drugs used for the treatment of the acute phase of Chagas disease are toxic, it is decided not to treat the animals and measures are established to prevent the transmission of the disease. In areas where the vector is present, measures are taken to eliminate cracks and crevices where the vectors breed, as well as the use of residual insecticides such as pyrethroids in places with high infestations. Blood transmission is prevented by using donor blood tests, treating donors with gentian violet at 250 mg/mL 24 hours before donation, and using ascorbic acid and exposing the blood to light (Timm et al. 2023).

3.4. GIARDIASIS

This disease is considered endemic worldwide and can be prevalent in developing countries, with more than 15% of infections in children. Although most infections are asymptomatic, if there is any damage to the immune system in puppies, diarrhoea, stomach inflammation, and abdominal pain, sometimes accompanied by vomiting, occur. In humans, the disease can be prolonged, and episodes of diarrhoea, flatulence, urticaria and intolerance to certain foods occur that are discontinued after treatment (Acha and Szyfres 2001). The main reservoir of Giardia towards animals is man, and the source of contamination is faeces contaminated with oocysts that reach water sources from where dogs consume them. Animals with chronic diseases ensure the agent's persistence (Scorza and Lappin 2021).

The control of this disease consists of protecting water sources from faecal contamination. Measures such as boiling water, filtering it or sedimentation flocculation and filtration methods are also helpful for disease control (Acha and Szyfres 2003). The drugs of choice for the treatment of Giardia are fenbendazole and metronidazole, which can be used alone or in combination for a period of three days (ESCCAP 2013). A recent study reports 100% effectiveness of the drug secnidazole, which was supported by a homoeopathic remedy to reduce diarrhoea in puppies (Glombowskv et al. 2020).

4. MYCOSES

Mycosis is the proliferation of fungi on the skin of animals. Depending on the location of this infection, it is divided into 1) superficial and 2) deep. The superficial one is characterized by an infection that develops in the stratum corneum, and the deep one in the animals' fermis and internal organs (Bourdeau 2018).

The pathogens that fungi produce is grouped into three large groups: 1) primary, 2) opportunistic and 3) pathogens. Table 1 and Fig. 2 shows the brief classification of fungi based on their pathogenicity.

Table 1: The classification of fungi.

Group	Examples	Reference
Primaries	Blastomyces, Coccidioidomycoses, *Cryptococcus neoformans*, Histoplasma	(Brömel and Sykes 2005; Lin et al. 2011)
Opportunist	Moulds and yeasts (*Aspergillus* spp.)	(Bennett et al. 2018; Elad 2019)
Pathogens	Dermatophytes (Dermatophytosis), Microsporum y Trichophyton	(Segundo et al. 2004)

4.1. DERMATOPHYTOSIS

Dermatophytosis is a disease that affects dogs and is one of the most frequent infections as it represents 50-60%. The species of fungi that cause this disease are *Trichophyton mentagrophytes, Microsporum gypseum* and *Microsporum persicolor*. The clinical signs are hard hair, fistulas and nodules, and it is contagious which vary according to different characteristics such as race and season of the year (temperature and relative humidity). This disease is controlled through chemical products i.e., griseofulvin, ketoconazole and itraconazole that have been reported as effective to control this mycosis (Segundo 2004; Gupta et al. 2005).

5. ARTHROPODS

5.1. DEMODEX SPP

Demodex is a parasite found on the skin of dogs and cats as part of their physiological fauna and is generally not associated with any disease. However, sometimes alopecia or mild to moderate dermatitis is usually found when the number of mites increases excessively (Foley et al. 2021).
Demodex (D.) canis is the most common mite in dogs, although *D. injai* or other species are usually found (Xhaxhiu et al. 2009). The most reported species in humans are *D. folliculorum* and *D. brevis* (Czepita et al. 2007). Demodicosis is not transmissible by contact between animals or other species. Demodex mites adapt to a definitive host, and there is no evidence of cross-infectivity. There is one report of *D. folliculorum* infection of a child and his dog, the only case reported so far of the same species of Demodex (Morsy et al. 1995). Due to the characteristics of Demodex mites, it should not be considered as a zoonotic risk (Gazi et al. 2019).

5.2. FLEAS

Fleas are 2 to 4 cm long and have no wings. Approximately 2200 species and subspecies of fleas exist; however, very few infect dogs (Blagburn and Dryden 2009). Dogs are usually infected by *Ctenocephalides felis* (cat flea) (Rinaldi et al. 2007). *Pulex irritans* (human flea) and *Echidnophaga gallinacea* (sticky poultry flea) can occasionally infect dogs. The most common species in humans is *Pulex irritans*. However, it is not exclusive to the humans as it is found in other species, including cats, dogs, wild canids and pigs (Weese and Peregrine 2011).
Fleas use visual and thermal signals to locate their host. The flea's life cycle lasts in about 3 to 8 weeks (Blagburn and Dryden 2009). Once fed, the female flea will produce eggs within 20 to 24 hours of feeding (Young et al. 2020).
Infestation rates of 6.8 to 17% have been found in dogs and 2.5 to 23% in cats (Farkas et al. 2009). The means of infestation is the environment. Transmission is usually direct between pets in the same household or by transient contact with other pets in parks, kennels or veterinary clinics. It can also occur by contact with wildlife (Blagburn and Dryden 2009). Humans are usually infected by meeting animals that have fleas (Weese and Peregrine 2011).

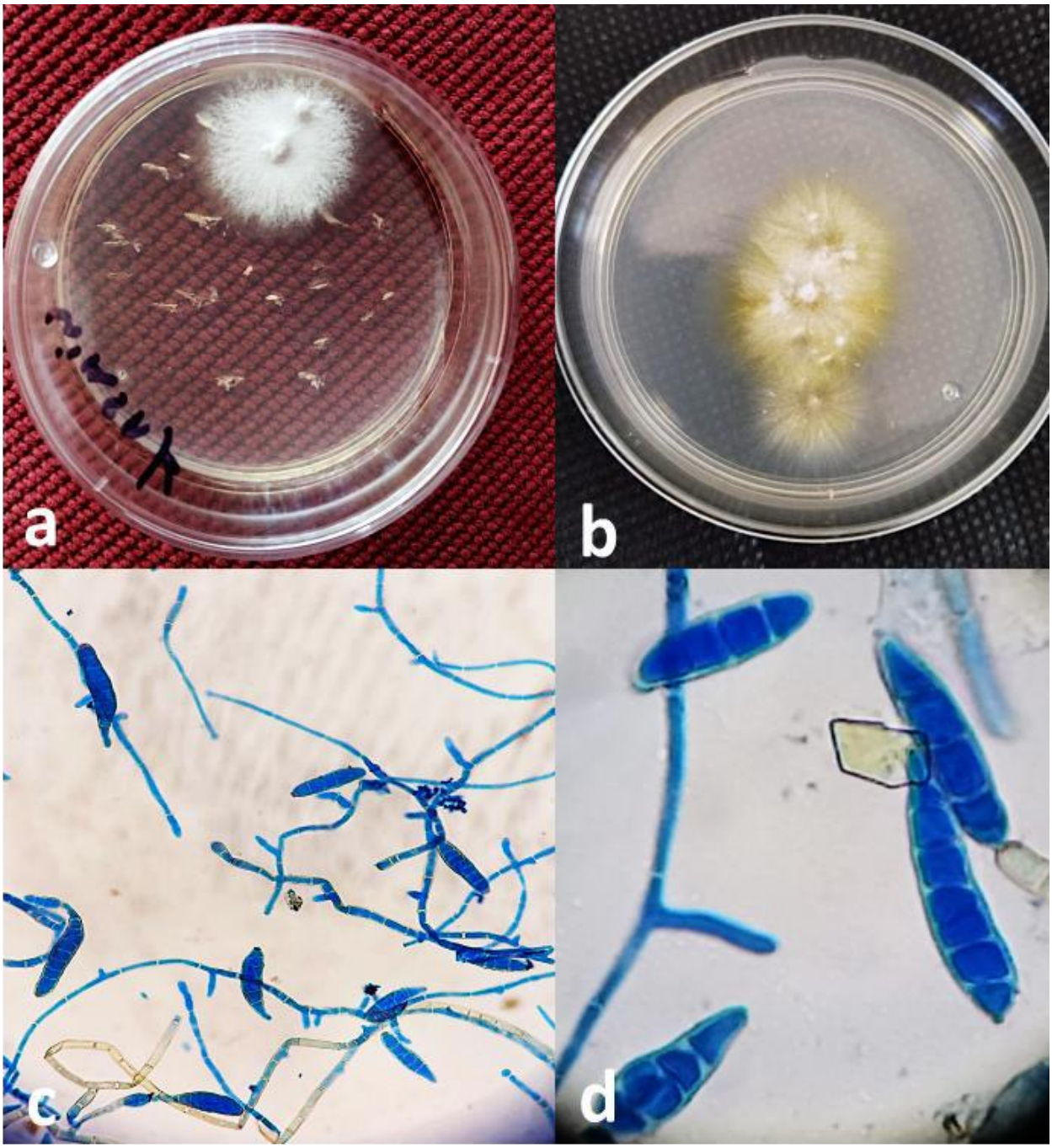

Fig. 2: a) Culture of *Nannizzia gypsea* in Petri dishes. b) Macroconidia of *Nannizzia gypsea*. c) *Microsporidium canis* in Petri dishes. d) *Microsporidium canis* in optical microscopy (Photograph by Dr Isabel Garcia-Abundis)

Exposure to fleas in humans usually causes transient or recurrent itching, a universal response caused as an antigenic response to flea saliva, which occurs mainly in allergic individuals (Scott and Horn Jr 1987). Another severe problem that fleas can cause is the transmission of pathogens. The most common pathogens are Bartonella spp., *Rickettsia felis*, *Rickettsia typhi*, *Yersinia pestis* and *Dipylidium caninum* (Beugnet and Marié 2009).

Lesions from flea bites can be observed in groups of three and are known as breakfast, lunch and dinner of fleas (Scott and Horn Jr 1987). Children are the mainly affected by fleas. The distal extremities, mainly the legs, are the most affected regions in children where urticaria papules can be observed (Naimer et al. 2002).

Human diagnosis of a flea infestation is rarely diagnosed by the presence of flea infestation or faeces. Clinical signs and a history of flea infestation in pets or other flea-infested animals or environments are indications to suspect the disease (Weese and Peregrine 2011).

5.3. *SARCOPTES SCABIEI*

Sarcoptes (S.) scabiei is a mite that digs into the skin and causes intense itching, culminates in skin problems, and mainly occurs in dogs, coyotes, foxes and humans. The varieties that *S. scabiei* cause infestations in humans and canines are different, but cross-infestation can occur (Mofiz et al. 2016).

There are only one species of *S. scabiei* that is called *S. scabiei* var. *canis* in dogs (Arther 2009), and *S. scabiei* var. *hominis* in humans. There is evidence of genetic variation among *S. scabiei* var. *canis* and *S. scabiei* var. *hominis* (Walton et al. 1999).

S. scabiei mites enter the epidermis, causing intense itching and a type I and IV hypersensitivity reaction to the host. The life cycle of this mite is completed in 30 days, and this begins when the strands lay eggs on the walls of the excavations. The larvae hatch and moult to become nymphs one and moult again to nymphs 2 that later become adults (Arther 2009). Adult males die after mating, and females migrate to dig their burrows (Sunderkötter et al. 2016).

Prevalence from 7 to 19% *has* been found in stray dogs. According to a study, dogs that interact with stray dogs are at higher risk of infection (Rodríguez-Vivas et al. 2003). Mild to moderate infestations usually occur when mites adapted to one species are transmitted to another species (Arther 2009).

S. scabiei var *hominis* can affect all socioeconomic levels; however, poor hygiene, poverty, malnutrition, and sexual promiscuity increases the risk of infection (Diaz 2005a). Close contact with infected persons can cause infestation, mainly in endemic areas (Rodríguez-Vivas et al. 2003). When a human infestation occurs by an infected animal, it is considered a zoonotic transmission of great relevance since they are scarce (Meijer and van Voorst Vader 1990). The scabies mite usually lives in humans for about six days, and usually, at 24 to 96 hours of the infestation, rashes arise on the skin (Moriello 2003).

S. scabiei cause intense itching with papular rash in adults and children. The most affected areas are the interdigital folds, elbows, armpits, navel and genitals. In younger children, vesicular lesions usually appear on the scalp, face and palms of the hands (American Academy of Pediatrics 2003). In immunocompromised patients, particularly with HIV/AIDS, generalised or localised or crusty hyperkeratotic plaques are often present (Zafar et al. 2002). Although zoonotic mange is difficult to differentiate from human mange, we can observe some differences, such as *S. scabiei* var. *canis* tends to cause milder, self-limiting disease, and burrows should not be present (Diaz 2005a).

5.4. TICKS

Ticks are the insects belonging to the class Arachnida. They are characterised by sucking the blood of their host. There are two types of ticks: Ixodidae (hard ticks) and Argasidae (soft ticks). The Ixodidae include three more genera: Ixodes, Rhipicephalus and Amblyomma, which are related to zoonotic diseases and involve pets and humans (Dantas-Torres 2010).

For most tick-borne diseases infection occurs during feeding (Greene 2006). This point is essential as timely identification and proper disposal reduce the risk of pathogen transmission. Finding ticks in pets is

important to human health, as it indicates that they are present in the area and there is human exposure to the agent. The tick could leave the animal and attach itself to the human. Human-to-human transmission is unknown (Weese and Peregrine 2011).

When there is a risk of being in an area potentially infested with ticks, animals and humans should be carefully inspected for ticks. Close examination is required, particularly for the poppy-sized nymph (Diaz 2005b). Humans should pay attention to the scalp, pubis, and armpits (Wagner and Stallmeister 2000).

In one locality in Italy, 240 individuals infected between 1995 and 1996 were found with an average of 1.3 ticks per individual. 89% individuals were infected with *Ixodes ricinus* at all stages. *R. sanguineous* was the second most prevalent species found with 10%, and Dermacentor was third with 1%. Cases occurred in 11% children, 26% students, 22% workers and 24% retirees (Manfredi et al. 1999).

A study conducted at a medical school in Georgia, U.S.A. and recorded 521 infestations in two and a half year with an average of 1.3 ticks per person (Felz and Durden 1999). Another study in Chile showed 2.2% tick bites in 1384 patients referred for spider bites (Acha and Szyfres 2001). Table 2 highlights the zoonotic pathogens found in ticks of companion animals.

6. STRATEGIES FOR PREVENTION AND CONTROL OF DOG-BORNE ZOONOTIC DISEASES

Different control strategies should be considered to prevent any bacterial agents, mycosis, protozoa, helminths, and arthropods. In constant contact with canines, it is necessary to have control of the pet and its history to maintain the health of dog and the human. Some diseases can be prevented by vaccination and thus prevent exposure to these diseases (Grassmann et al. 2017).

It is also vital to maintain hygiene and a constant check-up of canine with the veterinarian. In addition, it is better not to leave a person's wounds exposed, as it can generate complications due to poor care or exposure to other agents. Furthermore, take care of the canine's feeding and storing the canine's food in a different place than the food consumed by people (Li-Wui Y and Orozco-Cardenas A 2014).

Care should also be taken for the excretions and secretions of the canine and its correct handling for the surrounding people. Do not manipulate faeces or urine directly with unprotected hands and after this manipulation, washing hands with soap and water is necessary. In the case of dog bites, it is necessary to go immediately to the doctor for medical attention and not to let the event pass, which could later generate more complications. There are some zoonotic diseases eligible for vaccines which is a strategy adopted by some countries but not used worldwide. (Koizumi and Watanabe 2005; Grassmann et al. 2017). Prevention of zoonotic diseases needs the coordination of government authorities, society and awareness campaigns (Shiferaw et al. 2017).

7. GLOBAL IMPACTS OF DOG-BORNE ZOONOTIC DISEASES

About 14 to 62% of pet owners allow their pets into their rooms, which could increase the occurrence of zoonoses (Chomel and Sun 2011). Companion animals and pets have increased in recent decades but are also an integral source of disease-producing agents. The growing popularity of pets and companion animals has put human health at risk due to the possible spread of infections (Fig. 3). In many homes today, pets of exotic species are kept along with ordinary pets. Therefore, significant individuals are at risk of acquiring new zoonotic diseases from pets, companion animals, and exotic birds and animals (Chomel 2014).

Various infectious diseases (viral, bacterial, parasitic, and fungal) are associated with pets and companion animals (Halsby et al. 2014). Zoonotic diseases frequently associated with pets and companion animals include brucellosis, campylobacteriosis, chlamydiosis, cat scratch fever (*Bartonella henselae*), ehrlichiosis, giardiasis, hantavirus, hookworm, influenza, rabies, Lyme disease, Rocky Mountain spotted fever, plague,

Table 2: Zoonotic pathogens found in ticks of companion animals (Weese and Peregrine 2011).

Tick	Pathogen(s)
Rhipicephalus sanguineus	*Coxiella burnetii*
	Rickettsia rickettsii
	Rickettsia conorii
	Bartonella vinsonii subsp.--
	Berkhoffi
Ixodes scapularis	*Anaplasma phagocytophilum*
	Ehrlichia chaffeensis
	Ehrlichia ewingii
	Bartonella henselae (possibly)
	Borrelia burgdorferi
	R. rickettsii
	R. conorii
Ixodes pacifi cus	*B. burgdorferi*
Ixodes ricinus	*A. phagocytophilum*
	C. burnetii
	Borrelia spp.
Amblyomma americanum	*E. chaffeensis*
	E. ewingii
	B. burgdorferi
	Francisella tularensis
Dermacentor variabilis	*R. rickettsii*
	F. tularensis
Dermacentor andersoni	*R. rickettsii*
	F. tularensis

Leptospirosis, monkeypox, Pasteurella, Q fever, roundworms, salmonellosis, methicillin-resistant *Staphylococcus aureus* (MRSA), streptococcus and toxoplasmosis (Jacob and Lorber 2015; Day 2016). Many zoonoses, such as salmonellosis, diseases caused by staphylococcus, and rabies, are also found in many pets and companion animals (Halsby et al. 2014).

The transmission of pathogens from these animals occurs by direct or indirect contact. Transmission can occur at home, outside, pet stores, hospitals, or elsewhere. In many cases, transmission occurs when these animals and birds are taken to shows and competitions (Belchior et al. 2011). Typically, animal bites or scratches are routes through which humans contract infections, such as pasteurellosis and cat scratch disease (Chomel 2014).

It has been shown that 50% of European households allow dogs to lick their owners' faces or share ice cream (Overgaauw et al. 2009). However, more indications have been found that licking a dog can cause infections or severe health consequences (Van Knapen and Overgaauw 2015). A study conducted in the Netherlands showed that pet owners allow dogs to sleep in the bedroom (33-56%) or even sleep in the owner's bed (18-50%), undoubtedly contributing to the transmission of zoonoses, including parasites. Intensive contact with the skin and nose can lead to contamination with MRSA. It should be noted that the most common zoonotic disease associated with dogs is rabies, caused by the *Lyssavirus* (family: Rhabdoviridae), which kills tens of thousands of people every year. Similarly, pet-associated MRSA is a serious health problem for humans worldwide (Faires et al. 2009; Burgos-Cáceres 2011).

Zoonoses have countless impacts on human and animal health. However, the impact of zoonoses is challenging to quantify because many of these diseases are undiagnosed, not nationally notifiable and can be transmitted from sources other than companion animals. It can be assessed by disease prevalence, incidence, morbidity, mortality, and economic losses (Meslin 2006). Given these limitations, a review of

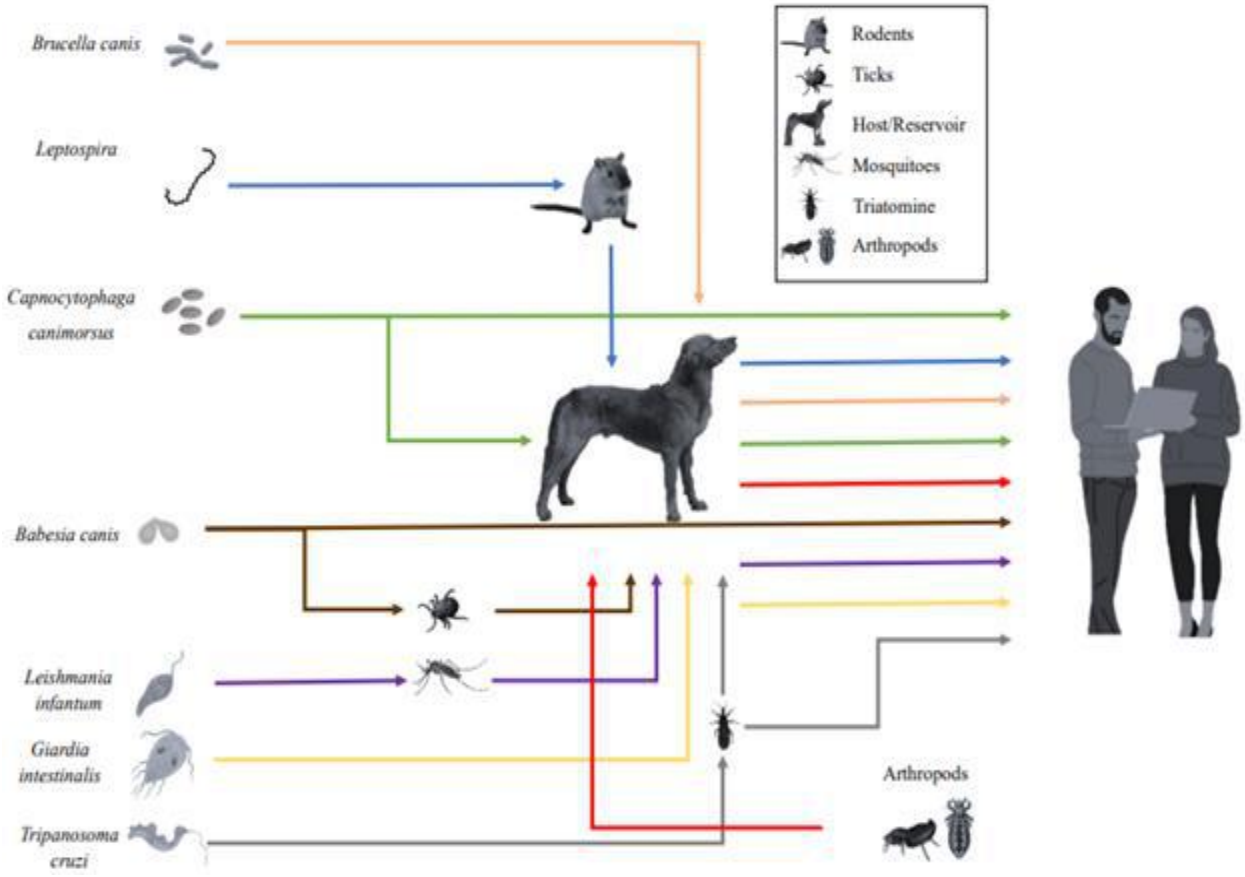

Fig. 3: Agents, hosts, reservoirs, and possible route of transmission of dog-borne zoonotic diseases.

national disease surveillance data and published literature suggests that more than four million people in the United States are infected annually with pet-borne zoonoses at a cost of more than $300 million. These costs include those of direct medical care during an acute illness (e.g., salmonellosis), chronic supportive care (e.g., congenital toxoplasmosis) and disease prevention (e.g., rabies), but not the loss of life - or quality of life - resulting from these diseases. Efforts should be made to prevent the transmission of zoonoses from pet animals to humans through appropriate pet health care to eliminate infectious agents and by educating the public, in particular pet owners, about the zoonotic potential of these diseases so that they can take precautions to minimise the risks of disease transmission (Pfukenyi et al. 2010).

8. CONCLUSION

Human-dog bonds nowadays could increase the risk of acquiring zoonotic diseases. However, it is undeniable that the role of dogs in the current lifestyle of their owners is due to different purposes, such as emotional support, work, and companionship. The epidemiological actions to protect pets and, most importantly, humans against dog-borne zoonotic diseases have been discussed briefly. To reach this point, we must develop social campaigns informing people about how to prevent diseases caused by bacteria, mycoses, ticks, and arthropods. The latter pathogens cause several signs and symptoms in animals and owners, respectively.

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Replicative Cycle of Ebola Virus

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ABSTRACT

Ebola virus responsible for hemorrhagic fever, belongs to filoviridae and fall in biosafety level-4 pathogen. The genome is linear, single stranded RNA, non-segmented and 19kb long. The genome encodes seven important structural proteins and all have essential role in virus replication. These structural proteins are nucleoprotein (NP), Large Protein (L Protein), Viral Protein 35 (VP35), Viral protein 40 (VP40), Glycoprotein (GP), Viral Protein 30 (VP30), and Viral Protein 24 (VP24). The replicative cycle of Ebola virus is crucial at the point of attachment and entry, while VP30 is involved in transcription. Once the virus enter into the cells, VP30 regulate the transcription and replication of viral genome. The phosphorylated VP30 block viral transcription because of the weakened interaction of promoter cofactor VP35. Several studies on recombinant EBOV and wild type EBOV have shown that VP30 containing serine 29 residue has major role in initiation of primary and secondary transcription. This difference is explained by alterations in the balance between the transcription and replication processes and appear to be associated with the state of VP30 phosphorylation. When replication have completed, newly synthesize genome and proteins are carried at site of budding where all these building blocks of virus come together to form virions and then release from the cell to infect other cells.

Keywords: Ebola virus, Structural Proteins, Micropinocytosis, Transcription, Niemann-Pick C1, Acylation, Nucleo-capsid, Nucleoprotein (NP), Large protein (L protein), Viral protein 35 (VP 35), Viral protein (VP 40), Viral protein 30 (VP 30), Viral protein 24 (VP 24), Glycoprotein (GP).

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1. INTRODUCTION

Ebola virus, the causative agent of Ebola hemorrhagic fever, is a well-known member of filoviridae family. Because the form of the virion similar to a twisted thread when examined through an electron microscope, the family name Filoviridae is derived from the Latin word "filum," meaning thread (Ascenzi et al. 2008; Feldman et al. 2013). The Filoviridae family, which belongs to the order Mononegavirales, comprises three genera. 1) Ebola virus 2) Marburg virus 3) Cueva virus (Jun et al. 2015; Burk et al. 2016). All of these have ssRNA, enveloped and a distinctive heterogeneous filamentous (filo; Thread) form (Slenczka 1999). The genome is uniformly 80 nm in diameter and ranges in length from 970nm to 1200 nm. A single molecule of linear, non-segmented, ssRNA, measuring about 19 kilobases (kb), is present in the virion core (Geisbert et al. 1995). Genus Ebola virus (EBOV) has five different distinct species: 1) Virus of Zaire (Zaire Ebola Virus); 2) Sudan's virus (Sudan Ebola Virus); 3) Bundibugyo virus (Bundibugyo Ebola virus); 4) Forest virus (Taï Forest Ebola Virus); 5) virus of Ruston (Reston Ebola virus) (Schieffelin et al. 2014). The first Ebola Virus Epidemic (EVD) reported in Zaire in 1976, which rebaptized to Democratic Republic of Congo, near the Ebola River (Nicastri et al. 2019). In 1976, epidemics of viral hemorrhagic fever (HF) were found to be caused by EBOV in the Congo and Sudan (Emond et al. 1977). EBOV caused disease known as EVD or Ebola Virus Disease, which is rare but deadly (with a mortality rate more than 90%) for mammals and non-human primates (Weingartl et al. 2013; Feldmann and Feldmann 2014).

The Ebola virus is categorized as a category A list pathogen and a biosafety level 4 pathogen. After an incubation period of 4 to 10 days, illness symptoms start to manifest. There are currently no authorized alternatives available for either postexposure prophylaxis or therapy. Virions are sensitive to lipid solvents, Photo induced alkylating probe 1,5 iodonaphthylazide, phenolic disinfectants, irradiations and formalin treatment (Mitchell et al. 1984; Warfield et al. 2007).

The major routes of transmission during an outbreak are nauseating humans or interaction with human bodies, although the natural reservoir of the virus is most likely fruit bats that are asymptomatic and infected with filoviruses, which have extremely high genetic diversity (Towner et al. 2009; Carroll et al. 2013). Other possible transmission methods of virus (present in saliva, stool, semen, body fluids) including direct touch, fomite, vaporizer and droplets (Bausch et al. 2007).

The EBOV structure plays vital act in peculiar infection. RNA based genome of Ebola virus encodes seven structural proteins from leader 3' to the trailer 5': 1) Nucleoprotein (NP); 2) Virion protein 35 (VP35); 3) VP40; 4) Glycoprotein (GP); 5) VP30; 6) VP24; 7) RNA- dependent RNA polymerase (L) (Hoenen et al. 2006; Martin et al. 2016). All the proteins have crucial role in virus replication and transcription as mention in Table 1.

Table 1: Role of structural genes in virus replication and pathogenesis

Proteins	Main Function
NP	Necessary for the development of nucleocapsid-like structures that encapsulates the viral genome, plays central role in virus replication and protects mRNA from destruction (Noda et al. 2005; Kirchdoerfer et al. 2015).
L	Participating in transcription, regulation of viral genome and mRNA editing (Volchov et al. 1999; Ayub et al. 2016).
VP35	Function as an innate immune antagonist; impairs dendritic cell maturation and inhibits antiviral effects by blocking protein kinase R (Basler et al. 2002).
VP40	Necessary for viral assembly at plasma membrane interlinked with viral and cellular component and budding from the host cell (Adu-Gyamfi et al. 2013).
GP $_{1,2}$	Virus attachment and entry; GP_1 make a link of cell surface receptors with viral particles; GP_2 consist of a fusion loop critical for membrane fusion (Volchkov et al. 1998).
VP30	Initiates transcription; involved in packaging of ssRNA and nucleocapsid assembly (Muhlberger et al. 1999).
VP24	Inhibit IFN- α/β and IFN-γ signaling through interaction with importins which is necessary for functional nucleocapsid (Han et al. 2003; Noda et al. 2007)

2. REPLICATIVE CYCLE

Similar to most negative stranded RNA viruses, the replication cycle of Ebola virus follows a basic similar pattern. A generalized sequence of the replicative stages is as follows:

3. ATTACHMENT AND ENTRY

The broad range of mammalian primary cells and cell lines that filoviruses can infect makes it challenging to pinpoint the specific cellular proteins that play a crucial role in viral attachment. After gaining entry parentally through the skin and mucous membrane, Ebola virus attaches to host surface though specific interaction among viral proteins and receptors present on the host's cell surface. The surface of Ebola virus is covered with glycoproteins (Chan et al. 2001) Earlier research has established that the interaction between the viral envelope GP1 protein and specific cell surface factors facilitates the attachment of the virus to its target cells (Chan et al. 2001). GP1 consists of three characteristic domains: 1. Receptor binding domain; 2. Glycan cap; 3. Heavily O-linked glycosylated mucin-like domain. In mature GP_1, receptor binding domain exists along with additional regions that engage with one or multiple receptors located on the surface cells (Kuhn et al. 2006). Although the EBOV mucin domain is not essential for virus entry (Yang et al. 2000; Jeffers et al. 2002), several roles have been proposed for this domain. The X-ray crystallography analysis revealed that the receptor-binding domain is encircled by the glycosylated glycan cap and MLD (membrane-proximal external region), forming a protective layer consisting of complex oligosaccharides (Beniac and Booth 2017). These include human folate receptors, β1 integrins, CLECs (C-type lectins) that specifically bind to glycans on the viral glycoprotein, and phosphatidylserine (PtdSer) receptors that cooperate with the viral envelope. These molecules play crucial roles in facilitating the entry and infection process of EBOV into host cells (Moller-Tank et al. 2013). The C-type lectin family consists of several important members, including DC-SIGN (dendritic cell specific intercellular adhesion molecule 3 grabbing non-integrin) and L-SIGN (liver/lymph node-specific ICAM-3 grabbing non-integrin), along with human macrophage galactose lectin. These lectins play crucial roles in various biological processes, such as cell adhesion and immune response regulation (Alvarez et al. 2002). Recently, a significant role has been attributed to cellular receptors that interact with PtdSer found in viral envelope. These receptors include TIM-1 and TIM-4, which relate to the T-cell immunoglobulin and mucin domain (TIM) family, as well as protein complexes comprising Gas6 or Protein S along with the TAM receptor family of tyrosine kinases (Tyro3, Axl, and Mer). It is well established that PtdSer is present in these interactions (Kondratowicz et al. 2011).

β1 integrins are proteins responsible for attaching cells to the extracellular matrix. The Tyro3 protein kinase (TAM) family consists of Axl, Dtk, and Mer receptors, which are present on the cell's outer membrane in various cell types. When these receptors are activated, they promote cell migration, division, and viability, leading to enhanced cellular functions (Linger et al. 2008). Additionally, it has been shown that folate receptor serves as a coreceptor for Ebola virus and Marburg virus lycol protein making it easier for the viruses to connect to the cells that are expressing their glycoproteins and enter cells more quickly (Simmons et al. 2003; Sinn et al. 2003).

Upon binding to receptor, Ebola Virus move in the host cells through three mechanisms: (a) Macropinocytosis (Quinn et al. 2009), (b) Clathrin-mediated endocytosis (Bhattacharyya et al. 2011; Bhattacharyya et al. 2010) and (c) caveolin-mediated endocytosis. At present, micropinocytosis is supposed to be the chief endorsement process (Saeed et al. 2010; Nanbo et al. 2010; Mulherkar et al. 2011).

Macropinocytosis, observed in certain immune cells like dendritic cells and macrophages, is distinguished by actin-driven membrane ruffling (Jones 2007; Kerr and Teasdale 2009; Mercer and Helenius 2009). Macropinocytosis is linked to the activation of Rho GTPases, such as Rac1 and Cdc42, which trigger the development of membrane ruffles through actin polymerization. For instance, in Vero cells, the entry is mediated by T-cell immune globulin and mucin domain 1 (TIM 1) and involves the activation of the Phosphoinositide 3-kinase signaling pathway. On the other hand, SNB19 cells require TAM tyrosine kinase and phospholipase signaling for viral entry (Liu et al. 2020).

4. FUSION AND UNCOATING

After endocytosis, the subsequent stages involve viral membrane fusion and uncoating where the viral membrane merges with membrane bound vesicles to release viral genetic material in cytoplasm of host cell (Martin et al. 2016). Virion envelopes of enveloped viruses join with the cell's outer membrane during a process of attachment known as fusion (Levinson 2008). EBOV produced three discrete proteins from glycoprotein gene that are, glycoprotein, soluble glycoprotein, and small soluble glycoprotein. whose appearance is influenced, in part, by transcription excision at a specific site containing seven remains of uridine (Volchkov et al. 1995; Sanchez et al. 1996; Mehedi et al. 2011). Crucially, membrane fusion and receptor binding are accomplished by the same transmembrane GP. Within trans-Golgi network (TGN), host cell proteases, including furine, cleave EBOV GP to produce the two components glycoproteins that are GP1 and GP2 (Volchkov et al. 1998; Jeffers et al. 2002). A glycoprotein core, a receptor-binding domain, glycosyl capped, and a mucin-like domain are all components of the GP1 subunit. The GP2 subunit has a cytoplasmic tail, a transmembrane region, heptad repeats 1 and 2, and an internal fusion loop (Sanchez et al. 1996). GP1 plays a crucial role in attaching through receptor-binding site in the host cell (Kuhn et al. 2006). On the other hand, GP2 is responsible for facilitating host cell membrane and virus membrane fusion (Malashkevich et al. 1999). Additionally, the internal fusion loop of GP2 and glycan cap of GP1 may interact to limiting accessibility of fusion peptide and preventing from early fusion events (Weissenhorn et al. 1998). Low pH conditions are required for conformational alternation in the fusion loop that encourage fusion (Gregory et al. 2011).

After the virion has been internalized by micropinocytosis and has moved along the endocytic pathways, the receptor binding site is revealed by the host endosomal cysteine, and cathepsins proteases (low PH-dependent) such as L and B Proteases cleaves the GP1 and GP2 mucin-like domains and glycan capped (Gong et al. 2016). For the virus to connect with the Niemann-Pick C1 obligatory host receptor and transporter cholesterol, this type of proteolysis of EBOV GP1 is necessary (Carette et al. 2011). NPC1 is a thirteen-pass transmembrane protein that is found in delayed endosomes and is thought to be involved in the transport of lysosomal cholesterol. NPC1 is a crucial viral receptor and a host factor for the entry, infection, and pathogenesis of filoviruses (Miller et al. 2012). It has six small cytoplasmic loops, a cytoplasmic tail, 4 small and 3 large luminal loops, and 13 transmembrane domains. The sterol-sensing domain is housed within NPC1 transmembrane regions (Davies and Ioannou 2000). With the aid of a soluble NPC2 protein, it helps cholesterol exit late endosomes so that it can be redistributed to cellular membranes including the endoplasmic reticulum and plasma membrane (Sleat et al. 2004). The late endosome/early lysosome's NPC1 receptor and GP1,2 receptor binding site interact to cause conformational modification in GP1 and GP2, which guide the merging of the virion and endosomal membranes and releases viral genome in cytoplasm (Gong et al. 2016).

5. TRANSCRIPTION AND REPLICATION

The transcription of Ebola virus starts with the synthesis of viral mRNA genome from single stranded and negative sense RNA genome by formation of complementary sequence to existing negative sense sequence. Though the genome contains many nucleotides roughly estimated between 18,000 to 19,000 that encodes for many crucial proteins. Majorly Ebola virus has seven genes that code for many crucial proteins that play significant role in viral life cycle. Due to the diverse and complicated life cycle of Ebola virus, many factors including viral and host, help virus to evade immune system and to manipulate the immune response. The seven genes code for the proteins include nucleoproteins, viral protein 35, viral protein 40, viral protein 30, viral protein 24, glycoprotein and RNA dependent RNA polymerase(L) (Hoenen et al. 2006; Martin et al. 2016.). NP encloses a viral genome which proceed as a model for viral RNA transcription and replication (Ruigrok et al. 2011). Once the virus get entry into the cell, the replicative cycle begins within the host cell cytoplasm (Fig. 1). There also formed secondary sites, termed as inclusion bodies which are formed by the accumulation of NP and other vial proteins, serve as other site of transcription and replication of viral genome (Hoenen et al. 2012; Nanbo et al. 2013; Lier et al. 2017). NP and all its associated proteins play significant role in primary and secondary transcription of viral genome. Transcription starts at the promoter site of viral genome that leads to the transcription of gene from start (Weik et al. 2005). When ample number of proteins have been synthesized from newly made RNA transcript, it leads to the replication of filoviral genome and antigenome. The formation of more and more viral genome act as a template for the formation of more viral protein (referred as secondary transcription). The pre translational editing of EBOV GP gene result into three transcript, pre-sGP, pre-GP, and pre-ssGP, these transcripts respectively translated into pre-sGP pre-GP and pre-ssGP. sGP is encoded by the GP gene of all five species of Ebolavirus. It is initially synthesized as pre-sGP, a golgi-Specific precursor, which undergoes post-translational proteolytic cleavage at its C-terminus by cellular proteases, such as furin, to yield he mature form of the protein. The post translational editing involves cleavage of pre-sGP by furin into sGP and Δ-peptide (Delta peptides of filovirus are actually non-structural peptides and are termed as viroporins, major role in viral pathology) and cleaving Pre-GP forms GP post-translationally into GP1 and GP2 subunits (Sanchez et al. 1998; Volchkov et al. 1998; Jeffers et al. 2002). The mechanism of transcription and replication go side by side, but still the actual phenomenon of regulation of transcription and replication is unclear.

The protein named VP30 has major impact on transcription and replication of EBOV genome (Modrof et al. 2002; Martinez et al. 2008). Phosphorylation of VP30 results in the blockage of transcription and it is due to the weakened interaction of polymerase cofactor VP35. Non phosphorylated VP30 in association with the polymerase cofactor 35 and NP regulate the transcription. The VP30 phosphorylation occurs at six N- proximal serine residue (S29-S31, S42, S44, and S46) and at threonine 143 and 146 (Modrof et al. 2002.; Ilinykh et al. 2014). By checking the mutation at these residual points by alanine which shows up active transcription and aspartate with strong phosphorylated character shows up defective transcription (Elliott et al. 1985; Modrof et al. 2002; Martinez et al. 2008), it shows the actual behavior of phosphorylation towards viral protein transcription. The non-phosphorylated and weak phosphorylation of VP30 show up viral transcription along with replication. Current researches have shown that association in phosphorylated VP30 and polymerase complex ceases the transcription complex and favors the easy access of replicase complex to NP -RNA template (Martinez et al. 2011; Biedenkopf et al. 2013). Only dephosphorylated VP30 mediate viral transcription (referred as transcription activator). Several studies on recombinant EBOV and wild type EBOV have shown that VP30 containing serine 29 residue has major role in initiation of primary and secondary transcription (Elliott et al. 1985; Modrof et al. 2002; Modrof et al. 2003; Martinez et al. 2008; Biedenkopf et al. 2016).

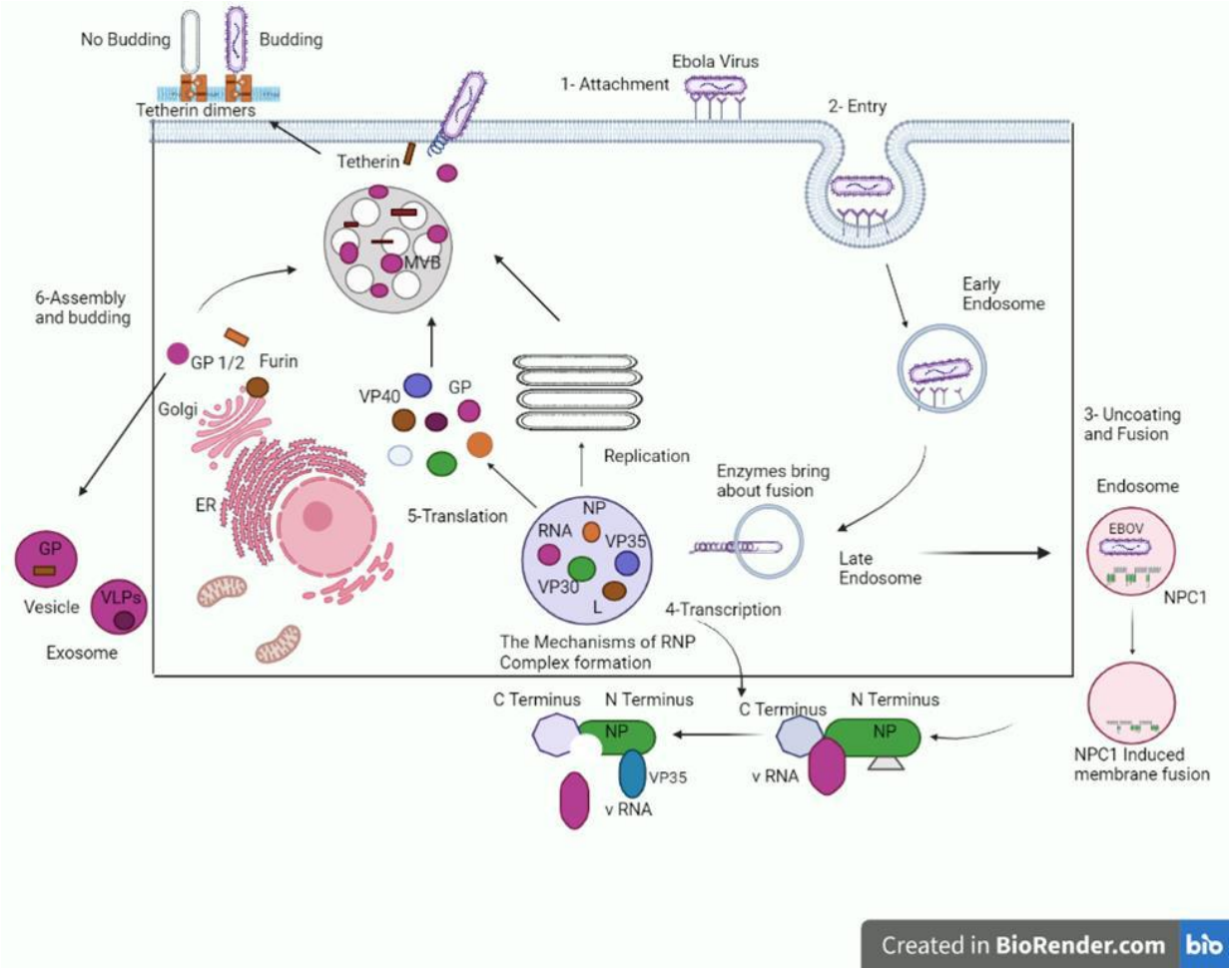

Fig. 1: Replicative cycle of Ebola Virus. Arrows represents the steps involved in Ebola virus replication. Virus attachment to cell surface receptors; Gains entry, Uncoat and fuse with membrane. Replication of genome and viral protein and after assembly and budding release a competent virus from cell.

Some previous work has found two cellular phosphatases i.e., PP1 and PP2A. PP1 and PP2A belong to the phosphoprotein phosphatase (PPP) superfamily. These phosphatases are important for dephosphorylation of VP30 which is mediated by NP (Modrof et al. 2002; Ilinykh et al. 2014; Lier et al. 2017). NP recruits the cellular phosphatase PP2A and VP30 in the viral inclusion bodies via some viral motifs. The degree of proximity between the VP30 and PP2A determines the efficient dephosphorylation of VP30 (Kirchdoerfer et al. 2016; Kruse et al. 2018).

6. ASSEMBLY AND BUDDING

When replication have completed, freshly created proteins and RNA of genome are carried at site of budding, where all these building blocks of virus come together to form virions (Harty et al. 2000; Martin-Serrano et al. 2001; Bavari et al. 2002; Timmins et al. 2003). Despite the few available reading frames for the Ebola virus, little is understood about viral assembly and the regulation of virus replication. According to some research, new formed bits of virus are gathered and budded at cell membrane, whereas viral duplication occurs in the cytoplasm (Feldmann et al. 1996, 1999).

The production of virus capsid with enclosed NA (cylinder shaped duct made up of associated NPNTDs with lumps), which amass in the area around the nucleus and transferred to the burgeoning sites at the cell membrane, is the first step in assembly of viral particles (Beniac et al. 2012; Bharat et al. 2012; Wan et al. 2017). Different functions in viral assembly and budding are played by Virus protein 40, Glycoprotein and NA complexes, and the slight grid protein (VP24) of the Ebola virus (Harty et al. 2000; Bavari et al. 2002; Han et al. 2003).

6.1. ROLE OF THE GLYCOPROTEIN

Glycoprotein produced by endoplasmic reticulum is translated at ER-bound ribosomes (Geisbert et al. 1995; Kolesnikova et al. 2000; Mittler et al. 2013), whereas all other virus-related proteins are decoded at open ribosomes in the cytosol. Acylation, oglycosylation, and ripening of N- linked glycans are all steps in processing of precursor GP before furin's proteolytic cleavage (IIto et al. 2001; Ji et al. 2005; Johnson et al. 2006). Another posttranslational alteration of viral GP, known as acylation, is essential for particle production, including virus assembly and budding. Following those procedures, VP40 and GP come across in the late endosome for assembly and budding (Neil et al. 2008). The Ebola virus is better able to emerge from these specialized microdomains when GP is localized to lipid raft domains (Bavari et al. 2002).

6.2. THE FUNCTION OF SLIGHT GRID VP24 PROTEIN

The function of VP24 has been hypothesized to involve assembly, budding, and, most recently, effective capsids with enclosed NA (nucleic acid) aggregation (Huang et al. 2002; Han et al. 2003). The number of released virions decreased when VP24 RNA was silenced, but viral transcription and duplication were unaffected (Huang et al. 2002).

6.3. ROLE OF THE NP PROTEIN

Nucleoproteins interactions with eachother and with RNA are carried by the hydrophobic amino group, end of the NP protein, whereas the hydrophilic Carboxyl end undergoes a change during the NP-VP40 collaboration (Mateo et al. 2010; Garcia-Dorival et al. 2016).

6.4. NP AND VP40 INTERACTION DURING THE FORMATION OF VP40-INDUCED VLPS

The sandwich structure of the Ebola virus protein VP40 consists of two structurally related realms (Dessen et al. 2000). The inhibition of viral transcription and replication through interactions between the matrix protein VP40 and NP may be accomplished by partial capsids with enclosed NA abridgment, while these interactions also promote NC envelopment at cell membrane and budding (Dolnik et al. 2010; Hoenen et al. 2010; Bharat et al. 2012; Kolesnikova et al. 2012; Wu et al. 2020). Before NP oligomerizes and the viral RNA is encapsidated concurrently with replication, a free amino group peptide of VP35 keeps nucleoprotein in a monomeric form (Kirchdoerfer et al.2015; Leung et al. 2015; Liu et al. 2017).

6.5. MICROTUBULES ARE REQUIRED FOR VLP BUDDING

EBV uses processes based on microtubules to mediate within cell conveyance of NCs to cell membrane and their integration into virions (Greber and Way 2006). VP40 facilitates the association of the Ebola

virus with microtubules. NP comes together to create helical tubes and then joins forces with VP35 and VP24 to form a nucleocapsid-like structure, after forming NC like structure, they are transferred at cell membrane by means of tubulin polymers and interrelates with VP40 to be integrated into virions (Noda et al. 2006; Baker et al. 2016).

6.6. VIRAL PROTEIN 40 IS ESSENTIAL FOR VIRION AMALGAMATION AND THE CONVEYANCE OF NC-LIKE STRUCTURES

The Ebola virus's most prevalent virion protein, VP40, is found underneath the envelop and is important for competent virus release (Harty et al. 2000; Jasenosky et al. 2001; Timmins et al. 2001). The free amino group and carboxyl group realms of VP40 have a distinct folding pattern (Bornholdt et al. 2013), while the Carboxyl side realm of VP 40 is required for membrane contact, the amino group region is sufficient for oligomerization (Ruigrok et al. 2000). The presence of late realm sequences at the amino group side of VP40 including Tsg101 and Vps4 have been found to interact with the components of cells and supports the involvement of VP40 in budding (Harty et al. 2000; Martin-Serrano et al. 2001; Licata et al.2003; Timmins et al. 2003; Yasuda et al. 2003). For a complete virus to be released, cell collaboration between VP40 and inner leaflet also happens as VP40 electrostatic and hydrophobic components are linked to plasma membrane PS which controls the location and oligomerization of VP40 on inner leaflet of plasma membrane (Moller-Tank et al. 2013; Moller-Tank et al. 2014) (Fig. 1).

Another important mechanism in Fledgling is the interaction between GP2 and small glycosylated membrane protein, which can cause an entire virus particle preservation on the cell membrane and is triggered by IFN-α (Neil et al. 2008; Lopez et al. 2010; NH Vande Burgt et al. 2015). A hydrophobic membrane spanning realm and glycosyl cap found in GP2 are thought to contribute significantly to tetherin antagonism (Han et al. 2003; Gnirss et al. 2014).

Since interactions with host cell components are necessary to facilitate the long filovirus NC's movement, it cannot get to the budding site by diffusion alone. An actin cytoskeleton drives the trafficking of filovirus NCs (Licata et al. 2004; Schudt et al. 2013, 2015; Takamatsu et al. 2018). Actin comet tails on one side of moving NCs and NCLS indicate a transport mechanism based on the polymerization of branching actin filaments (Welch et al. 2013; Mueller et al. 2014). Inside IBs, transport-capable NCs made up of all the NC proteins are produced. Actin appendages are created at 1 side of the NC in the cytosol, that propels their movement outside the IBs. Maturing of viruses occurs mostly in long, slender cellular protrusions after reaching the cell membrane, where myosin 10 may facilitate the movement of capsids with enclosed NA along parallel microfilaments. The favored budding sites for filoviruses are enriched filopodia (Kolesnikova et al. 2007; Schudt et al. 2013. 2015; Dolnik et al. 2014). Strongly enhancing NCLS recruitment into filopodia is EBOV VP40 (Takamatsu et al. 2018). Long, thin cellular protrusions known as filopodia are distinctive parallel microfilaments which are cross-linked by fascin (Bornholdt et al. 2013).

In addition to the cell membrane, the internal membranes of MVBs and late endosomes have also been found to host filoviral maturing (Silvestri et al. 2007). Any of two alternative ways of viral budding can occur in virus-infected cells that had numerous virions on their surface. Although numerous virions can emerge horizontally through the cell membrane, filamentous virions are discharged vertically from the cell surface (Roberts and Compans 1998; Brown et al. 2002; Simpson-Holley et al. 2002).

7. CONCLUSION

In conclusion, tremendous advancements have been achieved in the process of Ebola Virus replicative cycles, but still numerous areas that need more clarification.

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Commencing Mad Cow to Public Health; BSE socio-economic Impact and Zoonotic Perspective

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ABSTRACT

Bovine Spongiform Encephalopathy (BSE), also referred to as Mad Cow Disease, has become a significant public health issue with significant consequences for both society and the economy. This study examines the social and economic consequences of BSE (bovine spongiform encephalopathy) and studies its potential to be transmitted to humans. It addresses the complex network of relationships between human health, agriculture, and the environment. The socio-economic research examines the impact of BSE outbreaks on the agricultural sector, including the substantial financial losses experienced by farmers, the meat industry, and associated businesses. Moreover, this study investigates the widespread impact on international trade, consumer choices, and public trust in food safety, highlighting the importance of efficient risk communication and crisis management measures. This research examines the possible transmission of BSE from animals to people, with a specific focus on the zoonotic perspective. Gaining knowledge on the processes of zoonotic transmission is essential in order to effectively prevent the occurrence of novel human prion disorders. This study examines the scientific information on how BSE can be transmitted and evaluates the dangers and uncertainties connected with BSE as a zoonotic concern.

In conclusion, this comprehensive analysis provides insights into the complex interplay between BSE, public health, and socio-economic factors. The findings contribute to a better understanding of the challenges posed by BSE and offer valuable information for policymakers, health professionals, and stakeholders involved in managing the impact of zoonotic diseases on both human health and the broader societal landscape.

Keywords: Bovine Spongiform Encephalopathy, Mad Cow Disease, One Health, Public Health, Zoonosis

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1. INTRODUCTION

Zoonotic diseases are those which have the ability to transmit from animals to humans and are caused by different pathogenic organisms that can be bacteria, viruses, parasites, and prions. This pose a serious concern to public health since it is estimated that zoonotic diseases account for 60% of recognized infectious diseases and 75% of new infectious illnesses (Kulkarni et al.2015). According to research, these diseases cause around 2.5 billion morbidities and 2.7 million mortalities each year, resulting in significant economic losses (Spence et al. 2022). In our current culture, governments prioritize zoonotic disease prevention and control via public health measures and the implementation of a multidisciplinary strategy known as "One Health." In treating these severe illnesses, this strategy recognizes the connection of human, animal, and environmental health (Ghai et al. 2022).

BSE, sometimes known as "mad cow disease," is deadly neurological illnesses that have an impact on the livestock. There is certain class of diseases known as transmissible spongiform encephalopathy (TSEs) that also includes Mad Cow disease and BSE, which may affect humans and other animals and result in the development of BSE in cattle. A prion protein that is aberrant causes misfolding and aggregation of other normal proteins, resulting in brain damage (Prusiner 1998; Belay and Schonberger 2002). (. BSE was thought to be the sole strain of prion disease in cattle until now. In humans the occurrence of BSE C is associated with the emergence of a prion disease called the variant Creutzfeldt Jakob disease (Kong et al. 2008).

BSE, also known as mad cow disease was first discovered in the mid-1980s, in the United Kingdom and rapidly spread across Europe and other countries around the globe. BSE is mainly transmitted by contaminated feed. The worries about BSE crossing species barriers and posing a threat to humans became a reality when the first case of Creutzfeldt Jakob disease (vCJD) was diagnosed in 1996. These concerns arose from the belief that BSE could potentially lead to illness in humans. It was later discovered that consuming beef products contaminated with the BSE prion was indeed responsible for vCJD cases (Collins et al. 2002).

BSE has been categorized as a zoonotic disease by the World Health Organization (WHO). Although the number of vCJD cases has dropped considerably during the 1990s, but still exists as public health issue. BSE outbreaks have had substantial economic consequences, such as lowered beef consumption, prominent culling of infected animals and trade restrictions on beef products from affected countries (Jin et al. 2004).

It is thought that the disease spreads mostly when cattle ingest feed infected with meals especially, meat meal and bone meal which is regarded as the principal mode of transmission, thus controlling the food chain in terms of BSE is a serious issue. For example, in 2008, South Korea prohibited the importation of beef from the United States owing to worries about the possible spread of BSE disease in South Korea (Park and Sohn 2013).

Initially, the public's perception of BSE was manifested by neglect and denial on the part of government authorities and the livestock sector. Unfortunately, as the situation became evident, this method merely exacerbated it. This event emphasized the importance of public health transparency, communication, and risk mitigation methods (Dowler et al. 2006). Moreover, careless actions resulted in recurring outbreaks, the first occurring in the United Kingdom in 1985 and then spreading to European and non-European nations, affecting nearly 1,90,000 cattle (Karanikolaou 2022).

2. SOCIO-ECONOMIC IMPACT OF BSE

2.1. THE ECONOMIC IMPACT OF BSE ON THE LIVESTOCK INDUSTRY AND RELATED SECTORS

BSE has the potential to have a significant economic effect on the cattle and other industries. It caused significant economic losses which are due to the deaths, slaughtering, and culling of vulnerable

animals (Belay and Schonberger 2002). Countries that reported BSE cases suffered a drop in worldwide beef exports during the early stages of the outbreak (Kimberlin 1992). Furthermore, BSE had a significant impact on other livestock-related industries, such as the meat processing and rendering industries. Concerns about the spread of BSE through meat and bone meal reduced demand for these food products, resulting in decreased revenue for cattle and other related industries (Henson and Mazzocchi 2002).

Before the slaughtering policy, farmers bore all the losses, however farmers were financially compensated when the slaughtering policy was implemented. In the Czech Republic, for example, between February 2001 and the end of 2014, total 18,79,749 cows were tested, and 4,243 cows were culled. During this time, the Czech Republic gave farmers EUR 7,7,52,000 in compensation. As a result, governments suffered significant economic losses in the form of testing expenses, costs of culling animals, and compensation costs paid to the farmers (Pospíšil 2015).

Additionally, the implementation of BSE prevention and control measures, including feed restrictions and monitoring programs, caused substantial costs for the cattle industry and related sectors. For example, when a case of BSE was discovered in the Canadian province of Alberta in May 2003, the borders were restricted and international trade of beef and live animals was constrained. Since 47% of Canadian-produced beef was previously exported, this halt had a significant effect on the Canadian economy (Mathews et al. 2006). Agriculture and industries linked with the trading, transportation, and storage of beef and live animals are among the sectors of Canadian economy that are impacted by BSE (Petigara et al. 2011). The demand for beef in the US might decrease up to 15% during the BSE outbreak. In 2003, $4 billion in exports constituted 10% of US beef output, and the beef restrictions caused a reduction in exports by 82% (Yeboah et al. 2007). This resuls int low income and loss of jobs of farmers and families working in the livestock and agriculture industry severely affected their health by increasing the ongoing uncertainty and stress among them (Mitra et al. 2009).

3. BSE'S SOCIOCULTURAL IMPACT ON CONSUMER CONFIDENCE AND FOOD SAFETY REGULATIONS

The global impact of Bovine Spongiform Encephalopathy (BSE) on consumer confidence and the requirements for food safety has been significant. Following the 1980s discovery of BSE, the general public and legislators were concerned about the safety of beef products (Yeung and Morris 2001). However, Pritchett and coworkers have investigated the social consequences of BSE on consumer trust and food safety standards such as those in United Kingdom, where it is discovered that the BSE outbreak had a considerable harmful impact on consumer trust in beef products (Pritchett et al. 2005). Similarly, Canadian research found that the BSE epidemic reduced beef consumption while increasing the number of alternative protein sources (Umberger 2003). Another study carried out in the European Union discovered that the BSE outbreak resulted in a large fall in beef output and consumption, which adversely affected the economy (Knowles et al. 2007). Many countries implemented strict food safety regulations in response to the BSE crisis. These steps included increasing BSE testing and bans on certain cattle products. As a result, these measures have substantially impacted the livestock industry and related sectors. Overall, the impact of BSE on consumer confidence and food safety standards had a substantial effect on society (Henson and Jaffee 2008).

4. BSE'S PUBLIC HEALTH SIGNIFICANCE; VARIANT CREUTZFELDT-JAKOB DISEASE (VCJD) LEADING TO MASTERING PRIONS' BIOLOGY

Prions are the infectious organisms that cause BSE, and their unique features make them difficult to study and explain. Prions are deformed variants of the normal protein PrP, which is found throughout

the body, especially among neurons in the central nervous system. The normal protein is changed into the misfolded prion in an infected human or animal, and this prion then builds up in plaques that cover the sick brain as seen in Fig. 1. When PrP misfolds into prion form, it becomes extremely resistant to standard disinfection treatments and may start a chain reaction that results in folding errors across other PrP molecules (Morales et al.2007).

The misfolding and deposition of prions in the brain causes the neurodegenerative symptoms of BSE and associated disorders like vCJD. While the exact process of prion transmission is still unknown, it is obvious that it may spread via infected animal products including meat, bone meal, and other byproducts (Collinge 2005).

5. TRANSMISSION OF BSE

BSE is not a contagious disease and therefore, it cannot be transmitted by simple contact between cattle and other animals. But it can be transferred to other species including domestic or farm ruminants and cats through consumption of contaminated feed which is the primary route of transmission (Doherr 2003). Feed contamination occurs as a consequence of incorporation of contaminated additives such as meat and bone meal (MBM) and specified risk materials (SRM) that contain prion protein derived from infected cattle directly by the rendering plant or indirectly from the slaughterhouse (Nathanson et al.1997; Umberger 2003). The infectious agent, prion is not entirely inactivated by standard rendering methods

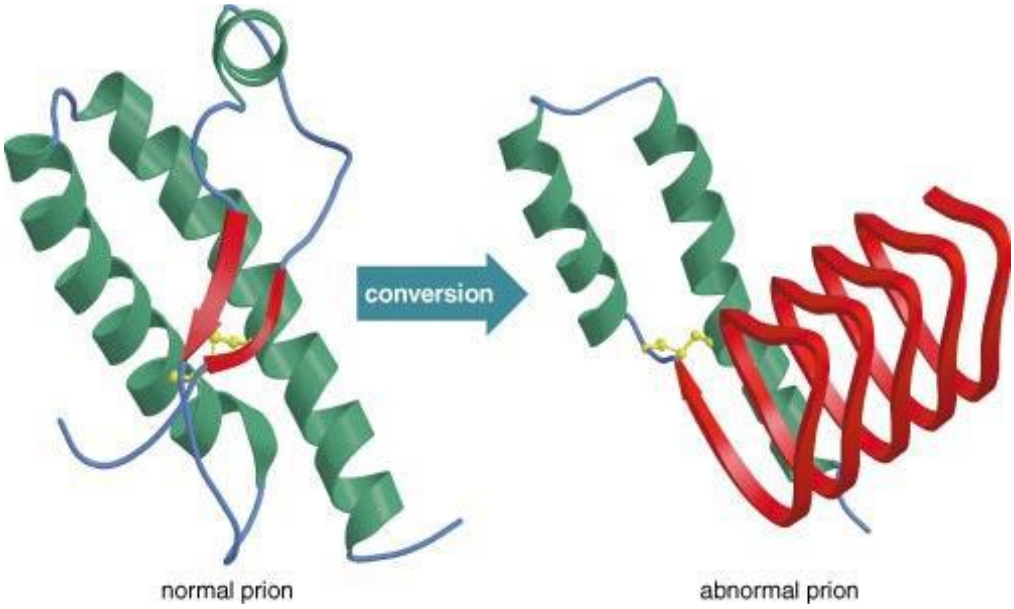

Fig. 1: In a healthy individual, the normal prion molecule (left) typically resides on the surfaces of cells, including neurons in the brain. Whereas the misfolded protein molecule (right) is critically involved in transmissible spongiform encephalopathy (Image courtesy of Paul Brown)

because they are resistant to inactivation, and can endure high temperatures and harsh chemicals. As a result, rendered protein generated from diseased animals, such as meat-and-bone meals, may carry the infectious agent. Animals that ingest feed that has been made from contaminated meat products get diseased (Taylor 1999). However, there is no empirical proof of horizontal transmission of BSE, but it may be spread vertically in a herd, making the cattle a dead-end host for the agent and there is also no confirmation of BSE transmission via physical contact of humans with live-infected cattle (Somerville et al. 2019). However, ingesting infected meat and meat products and utilizing specified bovine offals (SBO) such as brains, spinal cords, and other tissues or meat products manufactured from them are feasible routes for BSE to spread to humans (Cassano-Piche et al. 2009).

These contaminated meat-containing infectious agents can cause a food-borne zoonotic disease named variant Creutzfeldt-Jakob disease (vCJD) **(**Prater 2003**).** The most prevalent TSE in humans is CJD which can be transferred horizontally by lymphoid and neural tissues and blood whereas vCJD can be transferred by blood transfusions, organ transplants, and infected surgical tools (Sutton et al. 2006). Both classic CJD and new variant CJD can be cross-transferred by intracerebral inoculation as shown in Fig. 2 (Douet et al. 2014).

6. CLINICAL SIGNS

The clinical signs and side effects of variant Creutzfeldt-Jakob sickness (vCJD) are numerous and frequently vague, which makes conclusion troublesome. The clinical sickness starts with neurological side effects like social anomalies, sadness, nervousness or mental trips, appendage or joint agony, excruciating paraesthesia or dysaesthesia, and advances to additional particular neurologic side effects like mental degradation, ataxia, or wild developments. In later stages, myoclonus or choreatic movements, including akinetic mutism, usually emerge (Zerr and Poser 2002; Conti and Arnone 2016).

7. DIAGNOSIS

The primary challenge is making an early and accurate diagnosis of diseases caused by neurodegenerative protein misfolding. Human prion diseases like CJD are important because prions are fatal, contagious, and resistant to decontamination (Orrú et al. 2015). In vCJD, prion protein is found in the lymph nodes, tonsil, spleen, and appendix and similar organ damage is caused by other TSEs (Llewelyn et al. 2004). Furthermore, some genetic factors can increase a person's vulnerability to vCJD infection (Saba and Booth 2013).

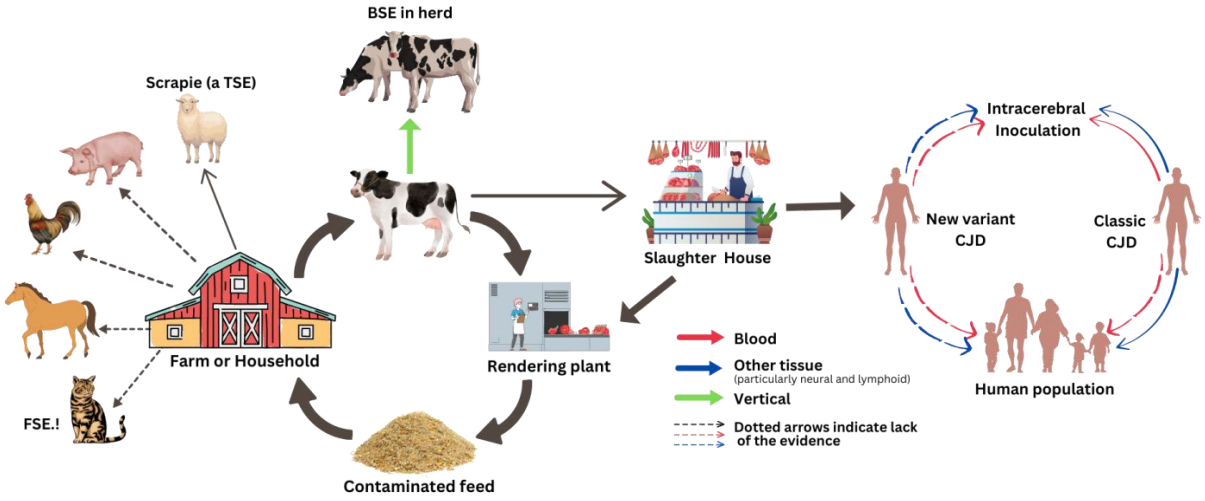

Fig. 2: The demonstration cycle of BSE infection and exposure of other species to products of a cow origin. Solid arrows (--) indicate direct exposure to cattle-derived products (cattle-derived food, cattle feed), Solid green arrows show vertical transmission, and dotted arrows (.....) indicate exposure to feed produced for pigs or poultry, and cats. Colored broken arrows (-.-.) and solid arrows indicate transmission within humans.

However, there are several diagnostic methods such as biomarkers and imaging technologies that can assist with diagnosis but, there is no authoritative test for diagnosing vCJD during life, and analysis are

made through clinical assessment along with technology like MRI, EEG, and conventional cerebrospinal fluid (CSF) biomarker analyses. But, these tests do have certain limitations, and only post-mortem analysis of brain tissue can provide a confirmatory diagnosis (Zerr et al. 2009).

A few efficient methods include protein misfolding cyclic amplification (PMCA) technology which is fit for generating prions from blood tests, and the improvement of a blood test in light of the location of prion protein antibodies (Saá et al. 2006) and Real-time quaking-induced conversion (RT-QuIC) that can identify prion-seeding activity in brain homogenates from sporadic CJD patients of any subtype. RT-QuIC had 96% sensitivity and 100% specificity for CSF PrPCJD detection (Zanusso et al. 2016).

Whereas, in cattle, the early identification of BSE cases is crucial in stopping the disease from spreading and minimizing the transmission risk to humans. For early diagnosis, rapid symptomatic tests, such as ELISA and Western smear, are used to confirm the presence of BSE prions in cerebrum tissues. These tests have successfully increased the ability to detect cases at an early stage, which is essential for preventing the spread of this fatal disease (Hayashi et al. 2004).

8. INVESTIGATING THE IMPLICATIONS OF VCJD FOR GENERAL HEALTH AND ITS IMPACT ON HUMAN WELL-BEING

Variant Creutzfeldt-Jakob Disease (vCJD) is a fatal and uncommon neurological disease that affects individuals. It is thought that ingesting BSE-tainted beef products causes the illness. The first case of vCJD was discovered in the Assembled Realm in 1996. Since then, more than 231 instances have been documented around the world (Ward et al. 2018).

The public health implications of vCJD are serious as Classic CJD effects mostly individuals at the of of 60 or 70 years (Boesenberg et al. 2005) whereas, vCJD has a majority of cases reported under the age of 30 and an extended duration of disease suggesting that, it can affect a larger population over a longer period of time (Ghani et al. 2003).

Furthermore, it is important to note that vCJD lacks a cure and has limited treatment options available (Blajchman et al. 2004). There are worries regarding the spread of vCJD through blood transfusions and other medical procedures. Consequently, strict measures have been established to screen blood donors to minimize the spread of vCJD (McManus et al. 2022). Aside, from the impact of disease itself, vCJD had reaching consequences on public health. The emergence of BSE and vCJD in the UK caused a loss of trust regarding the safety of beef and other animal products. As a result, regulations were implemented to prevent the disease from spreading (Oosterveer 2002). Additionally, BSE outbreaks had implications for agricultural and food industries, as well as public health systems, and vCJD has health implications and is a major concern for health authorities worldwide (Burnett 2008).

9. MANAGEMENT OF BSE

When it comes to controlling and managing BSE, conducting tests on animals before their death is crucial for assessing and managing the risks associated with it. Indeed, a BSE eradication programme may be justified by the use of a serum-based test that would enable the evaluation of the dairy cattle population (Lasch et al. 2003). Following are a few examples of BSE regulations, restrictions, and risk mitigation measures.

9.1. FEED BANS

The feed boycott is the most effective technique for preventing BSE. This should be achieved by following standards that limit the feeding of animal protein to ruminants, lowering the risk of BSE transmission through contaminated feed (Bradley and Wilesmith 1993).

9.2. RESTRICTION ON THE USE OF CERTAIN PROBABILITY MATERIAL IN ANIMAL FEED

Specific risk materials (SRM) and specified bovine offals (SBO) which are parts of the animal that are more likely to contain BSE prions include the brain, spinal cord, and certain other tissues. There should be a ban on the use of these materials to make feed safe for feeding the animal which is one of the main animal health control measures (Ducrot et al. 2013).

9.3. SPECIFIED IMPORT REGULATIONS

There should be specified regulations on the imports of meat and meat products from a country which have a significant number of BSE cases as it can enter the food chain of another country and eventually the burst of BSE cases in that area (Coffey et al. 2005).

9.4. ANIMAL IDENTIFICATION AND TRACEABILITY

During a BSE outbreak, animal identification and traceability systems can be useful in locating and identifying infected animals. Animal identification and traceability systems, such the National Animal Identification System, have previously been implemented in the United States which proved an effective way of controlling the spread of BSE (Greene 2010).

9.5. A LIMITED BLOOD DONOR PROHIBITION STRATEGY

A limited blood donor exclusion policy is an effective way to reduce the spread of vCJD through blood transfusion. This policy restricts the donation of blood from one who has been exposed to BSE prions (Tyshenko and Krewski 2010).

9.6. RISK ASSESSMENT AND MANAGEMENT

It is essential to use early risk assessment and managment to identify, recognize, and limit the possibility of BSE contamination in order to reduce the risk of its transmission. (Todd 2020). Within the European Association, there is a working body called BIOHAZ that provides risk assessments and guidance on BSE-related matters (EFSA 2007).

10. CONTROL MEASURES

There are a number of measures that can be implemented to control the risk of BSE transmission including to avoid to serve the remaining feed of one ruminant to the others and a banning on the use of specified risk materials (SRM) and meat and bone meals (MBM), animal identification and traceability, specified import regulations and surveillance of high-risk animals (Lewis et al. 2010; Yamanouchi and Yoshikawa 2007). For high-protein feed supplement, farms use meat-and-bone meal (MBM) which may cause disease. BSE is more likely to affect dairy cattle than beef cattle. During the outbreak, the later are regularly suckled and rarely fed concentrate feeds. Dairy cow calves are taken from their mothers at birth and nurtured on milk replacements before being weaned on to hay and concentrates, which frequently include MBM (Smith and Bradley 2003). Infected bovine residues having bone marrow, if consumed by humans can spread disease with clinical signs to them. This risk can be mitigated by using a consistent delivery cycle of crude bone material (Sogal et al. 1999).

Prions can survive in the harsh environment for an extended period of time, making disinfection difficult. Indeed, even the PrPSc is very impervious to sanitizers, bright radiation, heat, ionizing radiation, and

formalin, especially if present in tissues, dried natural material, or at an extremely high titer (Dudhatra et al. 2011). That's why cooking does not completely inactivate the infectious agent in the meat as it can endure high temperatures, so it is possible to get BSE from eating improperly cooked beef (Coghlan 2001). A single permeable burden autoclave cycle at 134-138°C for 18 minutes has also been recommended for inactivation; however, the prion protein may not be completely destroyed at these temperatures (Antloga et al. 2000).

Effective chemical disinfectants such as sodium hydroxide and sodium hypochlorite should be applied to surfaces for more than 1 hour at 20°C for equipment's and rendering should be done at a temperature of 1330 ^{0}C under a pressure of three bars for a minimum of 20 minutes. If there is a high risk of contracting highly infectious CJD tissue, many medical professionals advise to use disposable instruments in neurosurgery. These suggested decontamination strategies will lower titers, but they might not be 100% effective when handling the highly infectious material, such as those tissues which are preserved in aldehyde fixative or dried organic matter (Whitehead et al. 2011).

11. OBSERVATION PROGRAMS FOR EARLY RECOGNITION OF BSE CASES

Surveillance programs play a vital role to monitor BSE prevalence and in the early detection of BSE cases. In these programs, the health of animals is carefully observed, their movements are closely tracked, and they are thoroughly tested to confirm if BSE is present in the population (Dennis 2007). Many countries around the world have initiated the strict surveillance programs to effectively monitor and track BSE in cattle herds and mandate testing for all cattle before slaughter for human consumption (Stärk et al. 2006). For example, in the European Association, obligatory testing is performed on all dairy cattle over a specific age at the timeof slaughtering to check if there is something wrong with the meat before it goes dispatched for public consumption The National Animal Health Monitoring System (NAHMS) conducts dairy cattle reviews in the US to screen and analyze the predominance of BSE (Salman 2003). Moreover, the USDA has put in place a program, for monitoring BSE that involves testing cattle at risk and selectively sampling cattle (Fox et al. 2005).

In addition, surveillance programs also include the monitoring and examination of the animal feed supply chain to ensure that no contaminated substances are given to cattle. This surveillance involves conducting tests on feed samples to identify any BSE prions and enforcing restrictions on using high-risk materials in the feed (Sapkota et al. 2007).

12. FUTURE DIRECTIONS FOR BSE RESEARCH AND MANAGEMENT

Several research studies have explored the factors that could influence the spread of BSE. When researching prion diseases, it is critical to consider factors such as the age of the animals, their sensitivity to disease, and their exposure to substances that might contain prions (McCutcheon et al. 2011). They have also investigated how diseases can spread beyond regions by affecting tissues and muscles (Gough and Maddison 2010). They have been dedicating their efforts to discovering ways to prevent and treat BSE. These endeavors include implementing regulations regarding the use of animal feed and enhancing monitoring systems to identify and control outbreaks (Kumagai et al. 2019).

Furthermore, remarkable progress has been made in the progress of developments aimed at killing prions in food (Laible et al. 2015). The understanding of BSE and prion diseases has gotten more advanced, which has opened up opportunities for the development of treatment approaches. For example, current studies are exploring the advantages of RNA interference (RNAi) and immunotherapy in the management of prion diseases (Colini Baldeschi et al. 2020). The goal of the research has been

to develop prescriptions that can prevent the transition of common prion proteins into infection-causing structures (Zaib et al. 2023).

13. CONCLUSION

In conclusion, the journey from mad cow to public health has been long and complex. In the 1990s, there were substantial concerns about public health due to the discovery of Bovine Spongiform Encephalopathy (BSE) in cattle and its possible transmission to people by ingesting beef products that were contaminated. BSE was first linked to variant Creutzfeldt-Jakob disease (vCJD) in humans in the United Kingdom, and strong efforts have been made to restrict its spread among cattle and reduce the risk of human infection. Despite the fact that there haven't been many vCJD cases, there is still a lot of concern about the long-term health effects of BSE and vCJD. Prions diseases usually have long incubation period and it may take years to fully understand their nature and effect. But, ongoing research is helping us to better understand the transmission dynamics, and allowing us to create more accurate diagnostic tools while additionally chasing potential treatments and vaccines. Rigorous measures should be carried out to prevent the spread of BSE. Nonetheless, we must remain vigilant at all times in order to fully understand and address the disease's public health implications. This journey in a one health perspective demonstrates the significance of maintaining vigilance, control measures, conducting research, and collaborating globally to protect public health.

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Leishmania and Animal Reservoirs: A Major Challenge for Disease Control

41

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ABSTRACT

Leishmaniasis, caused by parasitic protozoans of the genus Leishmania, is a neglected tropical disease with significant global health consequences, particularly in regions lacking adequate healthcare infrastructure. The disease, transmitted by infected sandfly vectors, manifests in various clinical forms, ranging from self-healing skin ulcers to potentially fatal visceral infections. Animal reservoirs, including domestic and wild species, play a pivotal role in the perpetuation of Leishmania life cycles, acting as carriers without displaying any symptoms. The intricate interplay between Leishmania parasites, sandfly vectors, humans, and animal reservoirs poses a substantial challenge for effective disease control. The interaction between Leishmania and animal reservoirs exists, which emphasizes the challenges presented by the reservoirs for disease control. The geographical distribution of Leishmaniasis is linked to the presence and activity of animal reservoirs, influenced by environmental, biological, and ecological factors. Challenges in controlling Leishmaniasis via animal reservoirs include identification and monitoring, zoonotic transmission dynamics, resistance to conventional methods, limited therapeutics, heterogeneity among reservoirs, wildlife interactions, and resource constraints. The One Health approach, recognizing the interconnectedness of human, animal, and environmental health, emerges as a comprehensive strategy for addressing the complex challenges of Leishmaniasis. Surveillance and diagnostics for animal reservoirs are crucial components of control strategies, incorporating parasitological, immunological, molecular, and xenodiagnosis techniques. In conclusion, there is urgent need for a multidisciplinary, collaborative strategy to effectively address the challenges posed by animal reservoirs in Leishmaniasis control. From the complexities of surveillance to the risks of zoonotic transmission and the resistance to conventional control measures, it's clear that these reservoirs are not to be underestimated.

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1. INTRODUCTION

Leishmaniasis is a neglected disease of tropical and subtropical regions caused by intracellular parasitic protozoans of the genus *Leishmania* (Torres-Guerrero et al. 2017). Leishmaniasis, a poor man's disease, affects millions of people every year due to its vast geographic spread and varied clinical presentations, especially in areas with poor healthcare infrastructure and resources (Sasidharan and Saudagar 2021). Leishmaniasis is one of the seven most significant tropical diseases, and it poses a severe threat to global health due to its wide range of potentially lethal clinical symptoms. It is a vector-borne disease transmitted to human beings by the bite of an infected female sandfly, mainly *Phlebotomus* spp. (Torres-Guerrero et al. 2017). The parasite replicates after injection into the host's bloodstream, leading to a range of clinical outcomes, from self-healing skin ulcers to potentially fatal visceral infections (Mann et al. 2021).

Animal reservoirs are crucial for many *Leishmania* species to continue their life cycles. Various domestic and wild animals, from dogs and rodents to larger mammals, can serve as reservoirs for *Leishmania* parasites. These animals harbor the parasites without displaying obvious symptoms, contributing to the perpetuation of the disease in the environment (Alemayehu and Alemayehu 2017). The complexity of this leishmaniasis is amplified by the role of animal reservoirs in its transmission cycle, presenting a major challenge for effective disease control strategies. Understanding the interplay between *Leishmania* parasites, sandfly vectors, humans, and animal reservoirs is crucial for designing effective control strategies that target all components of the transmission cycle (Cecílio et al. 2022).

This chapter's aim is to explore the complex interaction between *Leishmania* parasites and animal reservoirs while highlighting the challenges these reservoirs present for disease prevention efforts. It also explores the biology of *Leishmania* parasites, the role of animal reservoirs in the transmission cycle, and the epidemiological impact of reservoir populations. The challenges of controlling animal reservoirs for the management of leishmaniasis will also be covered in this chapter, along with the shortcomings of present therapies and the possibilities for a One Health strategy. Through this exploration, this chapter will shed light on the complexity of Leishmaniasis transmission and inspire collaborative efforts to address this public health challenge from a multidisciplinary perspective.

2. THE BIOLOGY OF *LEISHMANIA*

Leishmania is a vector-borne parasitic disease. Phlebotomine sand flies and 98 species of the genera are responsible for transmitting *Leishmania* parasites through bites. The two proven or potential human leishmaniasis vectors include *Phlebotomus* and *Lutzomyia* (Steverding 2017). This parasite exhibits a digenetic life cycle that alternates between insect vectors and mammalian hosts. The *Leishmania* life cycle is restricted to the sand fly's digestive system outside of the vertebrate host (Dostálová and Volf 2012). When a mammalian host is fed on by an infected female sandfly, promastigote forms of the *Leishmania* parasite are introduced into the host's circulation. The immune cell-type macrophages engulf the promastigotes after they have entered the host. The parasite's intracellular form, amastigotes, develops from promastigotes inside the macrophages. As the amastigotes develop inside the host cells, the cells eventually burst, releasing additional parasites into the circulation. The cycle can

be continued by the freshly released amastigotes infecting more macrophages. When an uninfected sandfly bites an infected animal and consumes the amastigote-rich macrophages, the cycle is completed. The amastigotes change back into promastigotes inside the sandfly's gut. When the sandfly feeds again, these promastigotes travel to the proboscis, where they are prepared to infect another mammalian host (Serafim et al. 2021).

Leishmania parasites are remarkably diverse, with over 20 species known to cause various forms of Leishmaniasis. Leishmaniasis exists in three general forms i.e. cutaneous, visceral, and mucosal (Goncalves et al. 2020). Cutaneous leishmaniasis can be caused by *Leishmania major, L. mexicana, L. amazonensis,* or *L. braziliensis* in the arid regions, whereas *L. donovani* causes visceral Leishmaniasis in parts of Africa and Asia (Kbaich et al. 2017, Özbilgin et al. 2017).

Sandflies, as the vectors of *Leishmania* parasites, are influenced by climatic conditions, habitat types, and breeding sites. Changes in these factors can alter the distribution and behavior of sandfly populations, subsequently impacting parasite transmission (Shymanovich et al. 2019). Similarly, there are different animal species that vary in their susceptibility to *Leishmania* infection (Pérez-Cabezas et al. 2019). Some species, such as domestic dogs, may be highly susceptible and serve as effective reservoirs, while others may exhibit resistance to infection (Campino and Maia 2018). There are several other factors that influence the transmission of *Leishmania* parasites among animals and humans which include socioeconomics, climatic, and environmental variables (Valero and Uriate 2020).

3. ANIMAL RESERVOIRS OF LEISHMANIASIS

Leishmaniasis has a strong zoonotic potential, meaning that the disease can be transmitted from animals to humans, as shown in Fig. 1. Zoonotic transmission can result in diverse clinical manifestations in humans, ranging from cutaneous to visceral forms. This zoonotic transmission is influenced by factors such as the species of *Leishmania*, the vector species, and the genetic compatibility between parasites from animal and human hosts (Montaner-Angoiti and Llobat 2023). The implications of zoonotic potential for human health are considerable. Outbreaks among humans can be triggered by increases in reservoir populations or changes in environmental conditions that favor vector proliferation (Baker et al. 2022). Animal reservoirs significantly contribute to the complex epidemiology of Leishmaniasis. Identifying these reservoirs, understanding their roles, and assessing their zoonotic potential are crucial steps in devising effective control strategies (Pal et al. 2022).

Reservoirs are defined as living host that harbor the parasite without exhibiting apparent symptoms of the disease (Roque and Jansen 2014). Understanding the role of the reservoir species in disease transmission is made easier by longitudinal study when paired with ecological and genetic studies (Blanchong et al. 2016). Dogs are among the domesticated animals that serve as the disease's main reservoir hosts. Infected dogs serve as a reservoir for sandflies that bite them, subsequently transmitting the parasite to humans (Campino and Maia 2018). Cats and livestock can also contribute to the reservoir, though their role may be less significant compared to dogs (Maia and Campino 2011). This close proximity between humans and domestic animals increases the risk of zoonotic transmission (Keesing and Ostfeld 2021). Aside from domestic animals, wild animals like wolves, foxes, and jackals have also been connected to diverse areas' reservoirs of pathogens. These species frequently occupy a variety of ecological niches, which helps the disease's global spread (Campino and Maia 2018). These interactions between wild and domestic reservoirs can lead to complex transmission dynamics (Alexander et al. 2012).

4. EPIDEMIOLOGY OF LEISHMANIASIS: FOCUS ON RESERVOIRS

The geographical distribution of Leishmaniasis is intimately tied to the presence and activity of animal reservoirs, which are hosts that harbor the parasite and serve as a source of infection for humans and sandflies (Dvorak et al. 2018; Roque and Jansen 2014). Leishmaniasis is endemic in 98 countries around the world, including parts of Latin America, Africa, Asia, and the Mediterranean (Pal et al. 2022). The presence of reservoir species frequently coincides with the presence of the disease. For instance, canine Leishmaniasis seems to be more common in South America, where dogs are important reservoirs (Alemayehu and Alemayehu 2017). Different *Leishmania* species are linked to particular geographic regions and reservoir hosts. This leads to regional variations in disease prevalence and clinical manifestations (Jagadesh et al. 2021). *Leishmania* infection and transmission rates differ across various animal reservoirs. The capacity of reservoir animals to spread the parasite to sandflies might vary. Some animals may have higher parasitemia, making them more infectious to sandfly vectors. Certain reservoir species may have a stronger attraction for sandfly vectors, leading to higher transmission rates (Bourdeau et al. 2020).

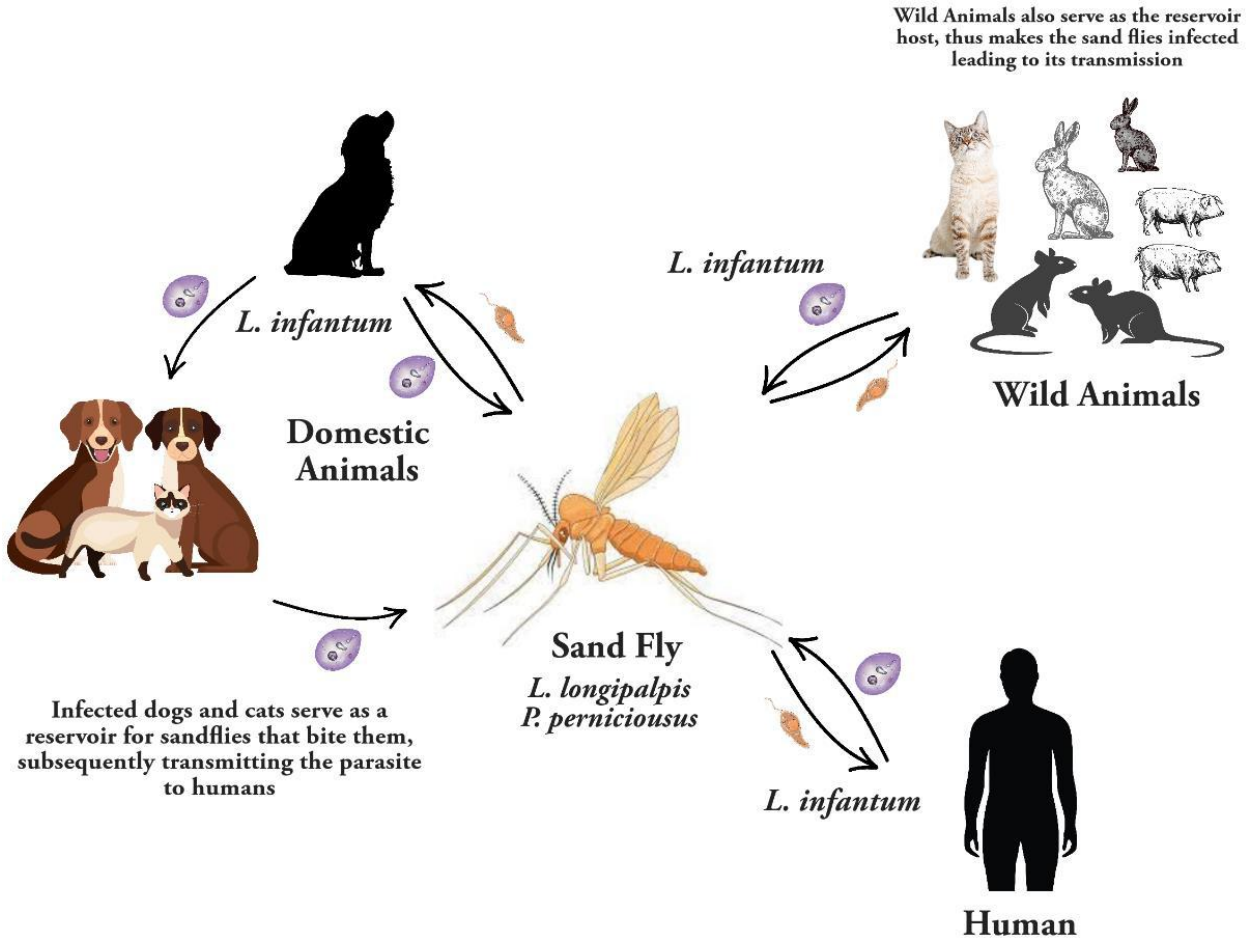

Fig. 1*:* Zoonotic Transmission of Leishmaniasis.

The presence and abundance of animal reservoirs are influenced by environmental, biological, and ecological factors. According to Ghatee et al. (2018), these variables are crucial in determining the

composition of animal reservoir populations for leishmaniasis. These variables affect the distribution, abundance, and behavior of the reservoir species and the disease-carrying vectors, which has an effect on the dynamics of the disease's transmission (Eder et al. 2018). The distribution and density of both sandfly vectors and reservoir animals are directly influenced by the local climatic variables, including temperature, humidity, and the amount of vegetation (Ghatee et al. 2018). Changes in climate can alter the range of Leishmaniasis, shifting disease transmission zones (Semenza and Suk 2018). Seasonal changes in temperature and rainfall can also influence both sandfly and reservoir populations, leading to fluctuations in disease transmission rates, often peaking during specific seasons (Karmaoui 2020). Additionally, the seasonal or migratory behavior of some reservoir species can impact the spatial distribution of Leishmaniasis and introduce the disease to new areas (Charrahy et al. 2022). Human activities such as deforestation and urbanization can fragment natural habitats, disrupting the habitats of reservoir species and affecting their population distribution and dynamics. Anthropogenic activities, such as irrigation projects, can create new breeding sites for sandflies, increasing the likelihood of disease transmission, while land use practices that reduce vegetation cover can disrupt sandfly habitats (White and Razgour 2020). The spread of *Leishmania* parasites can be impacted by the degree of biodiversity in a certain habitat. By lowering the frequency of interaction between vulnerable hosts and infected sandflies, high biodiversity can reduce the incidence of leishmaniasis in reservoir populations, while low biodiversity regions may see more concentrated transmission (Kocher et al. 2023). The number of reservoir hosts is intimately related to the ecology of sandfly vectors, particularly their nesting locations and accessibility to blood meals (Dvorak et al. 2018). The range and density of reservoir populations are impacted by changes in sandfly ecology, which can affect disease transmission (Oryan and Akbari 2016).

5. CHALLENGES IN CONTROLLING LEISHMANIASIS VIA ANIMAL RESERVOIRS

Globally, leishmaniasis control has significant challenges. Leishmaniasis is one of the hardest diseases to manage or eradicate since each of its characteristics presents particular challenges (Kamhawi 2017). Some of the challenges posed are;

5.1. IDENTIFICATION AND MONITORING

The identification and monitoring of reservoir populations is one of the major obstacles. Animals do not often exhibit overt symptoms in the same way that humans do, making it difficult to identify infected animals. Reliable surveillance techniques can lessen fatalities and further transmission by identifying, monitoring, and treating reservoirs (Prakash Singh et al. 2016).

5.2. ZOONOTIC TRANSMISSION DYNAMICS

Zoonotic transmission dynamics are the consequence of the intricate interactions between humans and animal reservoirs, which frequently occur in the same habitat (Borlase et al. 2021). This complexity can complicate control efforts, as the disease can cycle between animals and humans, making it challenging to break transmission chains (Cable et al. 2017).

5.3. RESISTANCE TO CONVENTIONAL METHODS

Leishmania parasites are susceptible to developing resistance to traditional controls, including pesticides used to kill sandfly vectors. Moreover, the treatment of infected animals is often less effective than in humans, further complicating control strategies (Alvar and Arana 2018).

5.4. LIMITED THERAPEUTICS OPTIONS

Unlike human Leishmaniasis, there are limited vaccines and treatment options available for animals. Developing effective vaccines and treatments for animals is an ongoing challenge, as it requires consideration of diverse reservoir species (Volpedo et al. 2021).

5.5. HETEROGENEITY OF RESERVOIR

Leishmaniasis-carrying animals come in a vast variety of species, each with its own distinct traits. While certain reservoirs may have high parasite burdens, others could show signs of infection resistance. Tailoring control measures to address this heterogeneity is a challenge (Alemayehu and Alemayehu 2017).

5.6. WILDLIFE INTERACTION

Wildlife can be the source of newly emerging transmissible diseases that impact both humans and cattle. Several wild animals, including foxes, can act as reservoir hosts. In regions where wildlife serves as reservoirs, interactions between domestic animals and wildlife can complicate disease management. A thorough understanding of the ecology and behaviour of animals is necessary to control leishmaniasis in such environments (Hailu et al. 2016).

5.7. RESOURCE CONSTRAINTS

Leishmaniasis is especially prevalent in developing countries. Effective control measures might be hindered by a lack of resources, both financial and logistical, especially in resource-scarce endemic locations. Significant expenditures are needed to coordinate multifaceted treatments including humans, animals, and vectors (Wijerathna et al. 2017).

5.8. ENVIRONMENTAL FACTORS

Environmental changes, such as urbanization and deforestation, might affect disease transmission by changing the habitat distribution of reservoirs and sandfly vectors. Predicting and adapting to these changes is a persistent challenge (White and Razgour 2020).

6. ONE HEALTH APPROACH FOR LEISHMANIASIS

In recognition of the interdependence of human, animal, and environmental health, the One Health method is a comprehensive and team-based strategy (Mackenzie and Jeggo 2019). Examples of effective one-health initiatives include those used to combat the rabies, Ebola, and Zika virus outbreaks (Ryu et al. 2017, Acharya et al. 2020). Potential pandemics have been successfully averted because of this strategy (Kelly et al. 2020). Similarly, the One Health strategy offers a strong foundation for tackling the complex problems brought on by leishmaniasis and its animal reservoirs. By integrating human, animal, and environmental health efforts, this complex disease can better be understood, detected, and controlled, ultimately working towards its elimination and improved public health outcomes (Webster et al. 2016). Leishmaniasis transmission involves a triad of hosts (humans, animals and sandflies) and their shared environment. Early diagnosis of Leishmaniasis outbreaks is made possible by cooperation among human health specialists, veterinary professionals, entomologists, and ecologists. Combining resources and

expertise from multiple disciplines optimizes the allocation of limited resources, thereby enhancing the efficiency of control measures (Turkson 2020). Due of the growing impact of humans on the environment, Leishmaniasis is re-emerging in endemic regions and emerging in non-endemic regions. The One Health strategy must be used in order to effectively control the disease, taking into consideration the complexity of the condition (Hong et al. 2020).

7. SURVEILLANCE AND DIAGNOSTICS FOR ANIMAL RESERVOIRS

Surveillance and diagnostics for animal reservoirs are critical components of Leishmaniasis control strategies. Effectively identifying and monitoring reservoir populations are essential for managing the disease's transmission dynamics (Prakash Singh et al. 2016). In spite of recent improvements in diagnostic methods, detecting leishmaniases still poses significant difficulties in the rural regions of endemic nations worldwide. Additionally, identifying the relevant *Leishmania* species is essential for disease management and treatments due to the disease's intricate transmission cycle, which involves several biological entities (Hong et al. 2020). Numerous diagnostic techniques have been developed, with significant differences in their accuracy of diagnosis, including molecular diagnostics, serological approach, and parasitological examination (histopathology, microscopy, and parasite culture) (Thakur et al. 2020).

7.1. PARASITOLOGICAL DIAGNOSES

For diagnosing leishmaniasis, parasitological techniques continue to be the gold standard (de Vries et al. 2015). In order to make a parasitological diagnosis, a suspected case of visceral leishmaniasis is subjected to tissue aspirations from the spleen, bone marrow, lymph nodes, peripheral blood, or skin biopsies/smears from ulcers/lesions. If parasites are present in samples, they can either be immediately observed using optical microscopy or cultivated in the proper culture medium and then viewed under a microscope later (in vitro culture) (WHO 2010). It is also possible to inoculate parasites into laboratory animals such mice, guinea pigs, hamsters, or rats (Ready 2014), although this approach is not regarded as a first method of diagnosis because it takes them several weeks to show signs of being infected with parasite (Thakur et al. 2020). By injecting the parasites into animals that are susceptible and then performing an in vivo culture, it is possible to determine viability of parasite (Hong et al. 2020). It is the most preferred and initial line of diagnostics for identifying the disease. However, the limited sensitivity of parasitological techniques, the need for technical skill to perform the operation, and additional hazards related to the examinations are drawbacks of the strategy (Reithinger 2008).

7.2. IMMUNOLOGICAL DIAGNOSIS

Immunological diagnostic techniques were developed to address the shortcomings of parasitological techniques (Singh and Sundar 2015). These techniques are based on the existence of certain humoral reactions (Elmahallawy et al. 2014). The Leishmanin Skin Test (LST), also known as the Montenegro Skin Test (MST), the Complement Fixation Reaction (CFR), the Direct Agglutination Test (DAT), the Indirect Immunofluorescence Antibody Test (IFAT), various ELISAs, Western blotting, the Immunochromatographic Test (ICT), and the rK39 antigen-based immunochromatographic test are among the available techniques. These immunological tests' sensitivity mostly rely on the assay and its technique, although their specificity is more influenced by the antigen than by the particular serological format (Elmahallawy et al. 2014). Immunological diagnoses provide rather high diagnostic precision, particularly during the acute stage of

Visceral Leishmaniasis. Contrarily, they are not frequently utilized for Cutaneous Leishmaniasis because of their poor sensitivity and erratic specificity, as cutaneous lesions frequently exhibit lower amounts of antibodies (Hong et al. 2020).

7.3. MOLECULAR DIAGNOSTICS

Leishmaniasis may be diagnosed by traditional parasitological and serological methods, but these approaches have certain limitations (de Paiva-Cavalcanti et al. 2015). As a result, molecular approaches have been developed (Tlamcani 2016). Molecular methods are used as a complement to traditional diagnostic procedures as well as a substitute. The practicality, safety, and dependability of molecular instruments is the primary justification for the acceptance of molecular methods in normal laboratories across the world. Although other molecular diagnostic techniques, including pulse-field gel electrophoresis and multilocus enzyme electrophoresis, have been developed, tests based on polymerase chain reactions currently serve as the primary molecular diagnostic tool for practitioners and researchers. (Thakur et al. 2020). In epidemiological studies, pairing PCR with other methods including Restriction Fragment Length Polymorphism (RFLP) analysis and gene sequencing has aided in the confirmation of several species (Wang et al. 2011).

7.4. XENODIAGNOSES

This technique of diagnosis involves exposing the infected lesion or tissues to the phlebotomine vector, then afterwards examining the gut of the vector to check for the presence of *Leishmania* flagellates (Sadlova et al. 2015). In a study by Sadlova et al. (2015), *L. donovani* was administered intradermally to the ear pinna of BALB/c mice. This work shown that even a small number of mouse parasites can result in a huge infection in the vector *Phlebotomus orientalis*, making it an ideal laboratory animal for xenodiagnoses. Although Xenodiagnosis is considerably easier to use than other procedures and has great sensitivity, it is unable to distinguish between various *Leishmania* species. Additionally, it takes a lot of time and is impossible without the insect or animal (Akhoundi et al. 2017).

8. CONCLUSION

In conclusion, it's essential to reflect on the challenges that animal reservoirs pose in efforts to control Leishmaniasis. This chapter's investigation has shown the complex web of elements that contribute to the disease's persistence, emphasizing the crucial part that animal reservoirs play in the dynamics of the disease's transmission. From the complexities of surveillance to the risks of zoonotic transmission and the resistance to conventional control measures, it's clear that these reservoirs are not to be underestimated. In order to properly manage leishmaniasis, they demand consideration, comprehension, and creative techniques. The way forward is a call to action—an urgent call for a multidisciplinary, collaborative strategy. The issue of leishmaniasis cannot be resolved on its own. It requires experts from a range of disciplines, including human health, veterinary medicine, entomology, ecology, and more, to combine their knowledge, resources, and experience. Only by working together will we be able to address the complexities of leishmaniasis. With a deep understanding of the intricate transmission dynamics between animals and humans, precise and context-specific interventions can be crafted. These measures are not only successful in lowering the disease burden, but they also successfully stop the spread of leishmaniasis from animals to people, which is a crucial step on the path to ultimate disease eradication.

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Management and Control of Dengue Fever through One Health Approach

42

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ABSTRACT

Dengue fever, a virus transmitted by mosquitoes, continues to pose a significant health challenge on a global scale, especially in tropical areas. The One Health approach, which considers the interconnected areas of human, animal, and environmental health, is becoming a comprehensive strategy for managing and controlling this intricate infectious disease. A key aspect involves improved diagnostic abilities and smooth information exchange between healthcare facilities, which are crucial for surveillance and early detection. Effective dengue management relies on cooperation between public health and environmental agencies to carry out specific interventions such as insecticides, biological controls, and environmental modifications to prevent mosquito breeding. This collaboration is vital for controlling dengue. At the same time, a comprehensive approach to environmental management includes coordinated land use planning and recognizes the influence of climate change on mosquito carriers. Public awareness initiatives are essential in highlighting the importance of community involvement and individual accountability in reducing the breeding grounds for mosquitoes. It is crucial to conduct interdisciplinary research in order to progress our comprehension of dengue patterns and to encourage the development of inventive control methods, such as the genetic alteration of mosquitoes. In terms of policy, it is crucial to encourage collaboration between different agencies and countries, to support the creation and execution of policies that align with a unified One Health approach. By combining forces from various fields such as health, agriculture, environment, and education, the One Health strategy provides an effective way to reduce the spread of dengue fever, recognizing the complex interconnections between humans, animals, and the environment. This comprehensive method not only strengthens our ability to protect against dengue, but also lays a strong groundwork for tackling other new infectious risks that affect multiple areas of health.

Keyword: Dengue Fever; One Health Approach; Vector Control; Interdisciplinary Collaboration; Public Awareness.

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1. INTRODUCTION

Dengue fever is a major global health concern affecting millions of people globally. Dengue fever is widespread in more than 100 nations, as reported by the World Health Organization (WHO), causing an average of 390 million infections every year. Aedes mosquitos spread the disease, and its signs and symptoms vary from low-grade fever to severe hemorrhagic fever, which may prove fatal if neglected (WHO 2023). Because of the seriousness of the illness and expanding prevalence, successful dengue fever prevention and control have become a critical public health priority (Chowdhury and Chakraborty 2017).

One Health is a cooperative, multidisciplinary strategy that recognizes the interdependence of individual, animal, and environmental wellness. The One Health concept has gained importance in the past few years as a potential option for managing and preventing dengue fever. The One Health strategy seeks to limit the spread of virus and enhance the well-being of human and animal communities by targeting the disease's environmental, natural, and social factors (Cataldo et al. 2023).

Dengue fever has a large economic impact, with an anticipated 100 million symptomatic infections along with 10,000 deaths every year (Semenza et al. 2022). It has the greatest incidence in Asia, as well as Latin America, where most child having less than the age of 15 bear the majority of the disease's incidence. The growing frequency of dengue fever and the difficulties associated with its management and control render the One Health strategy an intriguing strategy for lowering the incidence of disease and enhancing public health benefits (Yang et al. 2021).

This chapter aims to offer a brief insight into dengue fever alongside the One Health approach, which further explains ways for preventing and treating dengue fever by adopting the One Health method.

2. BACKGROUND OF DENGUE FEVER

Dengue fever is an infection transmitted through the dengue virus (DENV) which is spread by the bite of infected *Aedes* mosquitos. It is most common in tropical and subtropical regions of the world, such as Asia, South America and Africa (Xiang et al., 2022). According to WHO, dengue fever is responsible for an estimated 50 million illnesses across the world each year.

The dengue virus is a member of family Flaviviridae, including the viruses responsible for Zika and yellow fever. Infections with one serotype do not resist the other strains (DENV-1, DENV-2, DENV-3, and DENV-4). On the other hand, additional infection with a distinct serotype might cause more severe forms of dengue hemorrhagic fever (DHF) or dengue shock disorder (DSS) (Zerfu et al. 2023).

Dengue fever has long been reported in Southeast Asia and other tropical places. Disease outbreaks were first documented in Asia, Africa, and the United States during the 1770s (Chong et al. 2023). Dengue fever has expanded to other nations and continents throughout the years, growing endemic in numerous regions of the world. Changes in the climate, urbanization, and population expansion are only a few variables that have led to dengue fever's growing impact (Petzold et al. 2022).

The primary underlying cause of the illness is infections caused by the dengue virus, which is transferred to humans via bite of infected *Aedes* mosquitos. *Aedes aegypti* is the principal carrier of the dengue virus in many regions of the world; however, *Aedes albopictus* may also propagate the disease. These mosquitos breed in stagnant water, such as flower pots, old tyres, and reservoirs for water (Manuahe et al. 2020).

Disease symptoms include a high temperature, severe headache, discomfort in the eyes, muscles and joints, rash, and slight bleeding from the nostrils or gums. In some situations, dengue fever might proceed to DHF or dengue shock syndrome (DSS); both can be lethal (Hashmi et al. 2023).

3. DIAGNOSIS OF DENGUE FEVER

Dengue fever laboratory diagnosis is critical for confirming the infection, identifying the viral serotype, monitoring disease development, and guiding treatment. Depending on the stage of infection, the availability of resources, and the goal of testing, multiple methods and assays can be employed for laboratory diagnosis of dengue fever(Kelly et al. 2023). Following are the tests used for diagnosis of infections:

3.1. NAATS (NUCLEIC ACID AMPLIFICATION TESTS)

These assays use reverse transcription polymerase chain reaction (RT-PCR) or loop-mediated isothermal amplification (LAMP) to detect viral genomic sequences. Because they are very sensitive, specific, and fast, they are the primary approach for laboratory diagnosis of dengue fever. They can also distinguish between virus serotypes and genotypes. NAATs should be done on serum samples collected within 7 days of the beginning of symptoms (Jiang et al. 2023).

3.2. ANTIGEN DETECTION TESTS

These immunoassay tests detect the viral nonstructural protein 1 (NS1) antigen. They are also sensitive, specific, and fast, and can be used on serum, plasma, or whole blood samples. The NS1 antigen is capable of detected from the very first day of infection until 9 days later2. In addition, NS1 antigen detection and IgM antibody detection can be coupled in a single test (Fisher et al. 2023).

3.3. ANTIBODY DETECTION TESTS

These examinations use enzyme-linked immunosorbent assays (ELISA) or rapid diagnostic tests (RDT) to detect the IgM and IgG antibodies that are produced by the host's immune system during response to dengue infection. They can help in diagnosis later in the disease (>4 days after fever onset), when NAATs and antigen detection examinations may be negative. They do, however, have certain limitations, including cross-reactivity with various other flaviviruses, difficulties identifying primary from secondary infections, and a delay in antibody generation (Fisher et al. 2023).

3.4. PRNT (PLAQUE REDUCTION NEUTRALISATION TEST)

This test determines whether or not neutralising antibodies can limit virus infectivity in cell culture. It is regarded as the gold standard for dengue serological diagnosis since it can confirm illness, identify viral serotypes, and distinguish between primary and subsequent infections. However, it is technically difficult, time-consuming, and necessitates the use of a biosafety laboratory of level 3 (Merakou et al. 2023).

Dengue fever laboratory diagnosis is critical but difficult, requiring a mix of several procedures and assays to produce an accurate and timely result. More research and development are required to improve the performance, availability, and affordability of dengue fever diagnostic assays. Dengue fever

laboratory diagnosis is critical but difficult, requiring a mix of several procedures and assays to produce an accurate and timely result. More research and development are required to improve the performance, availability, and affordability of dengue fever diagnostic assays (Kulkarni et al. 2023).

4. ONE HEALTH APPROACH

The One Health concept is an interactive, multidisciplinary strategy that acknowledges the interdependence of individual, animal, and environmental health. It recognizes that human, animal, and environmental health are all interconnected and that transmission of diseases can occur at the intersection of each of these areas. This approach emphasizes the importance of collaborative and integrated efforts throughout fields to address complicated health concerns (Cabrera et al. 2022).

5. IMPORTANCE OF THE ONE HEALTH APPROACH IN MANAGING AND CONTROLLING DENGUE FEVER

The One Health concept is becoming widely recognized as a valuable tool for preventing and treating dengue fever. The One Health strategy strives to limit virus transmission and enhance the well-being of human and animal habitats by tackling the disease's natural, environmental, and social causes (Socha et al. 2022).

The transmission of dengue fever is shown in Fig. 1.

The One Health strategy, for instance, acknowledges that variables which include shifting land use, urbanization, changes in the climate, and human behavior affects the dengue fever spread. Resolving these fundamental issues requires coordination among environmental health experts, public health officials, and other stakeholders to foster environment friendly land use, limit urbanization, and encourage behavior change, such as good waste management practices (Mulakoli et al. 2022).

6. ROLE OF DIFFERENT STAKEHOLDERS IN THE ONE HEALTH APPROACH

Collaboration and communication amongst many stakeholders, such as public health authorities, veterinary professionals, and health care professionals, are essential components of the One Health strategy. Public health personnel are in charge of illness monitoring and oversight, epidemiological studies, and knowledge dissemination to public. Veterinarians are crucial in discovering zoonotic infections and undertaking animal community monitoring. They can help with zoonotic disease prevention by emphasizing disease reservoirs and pushing for a global perspective, as well as concentrating on individual patient well-being. Both government and private veterinarians play critical front-line roles in national zoonoses surveillance (Steele et al. 2021).

The American Veterinary Medical Association (AVMA) considers that veterinarians play a crucial part in One Health since animals can influence and influenced by people and the environment. Veterinarians are critical to develop One Health strategies and maintaining the health and safety of its three pillars: animals, people, and the environment, whether as clinical practitioners, epidemiologists, or ecological experts (Ghanbari et al. 2020). Environmental health professionals can shed light on the effects of shifts in land use as well as additional external variables on the transmission of diseases (Iftikhar et al. 2023).

A recent study of Brazil discovered that the One Health approach, which involved collaboration among public health professionals, veterinary professionals, and environmentalists, was beneficial in reducing the prevalence of dengue fever and increasing public health outcomes (Owusu-Asenso 2023).

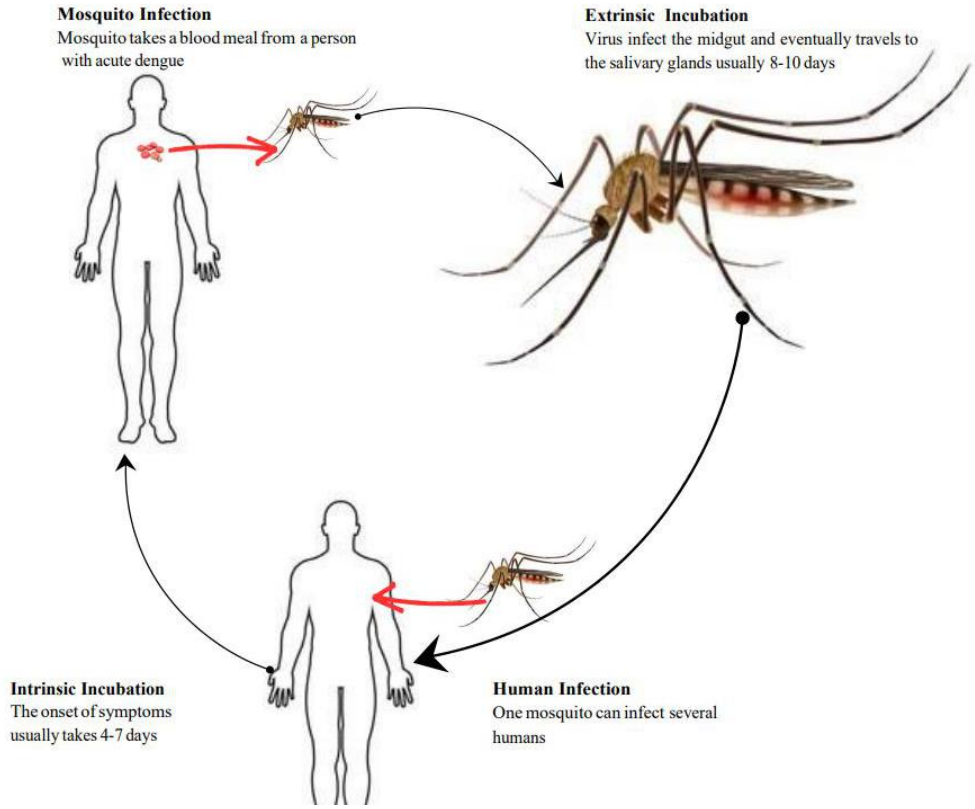

Fig. 1: Transmission of Dengue Fever

7. MANAGEMENT AND CONTROL STRATEGIES

7.1. VACCINATION PROGRAMS

Another key technique for managing and reducing dengue fever is vaccination programs. Several vaccinations have been produced and are already in use in various countries. Dengvaxia, the initial dengue vaccine, received clearance for use in numerous countries in 2015. TAK-003 as well as TV003/TV005 vaccines, are now being researched and evaluated in clinical trials (Wilder-Smith 2022).
Studies have demonstrated vaccination programs to be beneficial for decreasing the prevalence of dengue fever (Capeding et al. 2014; Hadinegoro et al. 2015). Dengvaxia was found to be beneficial in avoiding severe dengue fever among kids aged 9 to 16 years old in an investigation in Latin America (Villar et al. 2015). However, The efficiency of vaccination programs varies depending on the mosquito serotypes common in the location, the ages of people in the area, and vaccine effectiveness (Hussain et al. 2023).

8. DENGUE SURVEILLANCE

Dengue surveillance is a way of monitoring dengue cases and vector populations on a regular basis. Dengue fever cases are reported to national health officials. The World Health Organization (WHO) recommends that every dengue-endemic country require official reporting of dengue cases. Electronic reporting solutions should be developed and widely deployed to accelerate data delivery to stakeholders. Dengue surveillance data should at the very least include rates of dengue fever, dengue hemorrhagic fever, dengue shock syndrome and dengue mortality (WHO 2023).

Hospitalization and mortality rates by age group should be provided. Additional studies (e.g., capture/recapture) should be undertaken on a regular basis to check under-detection, under-reporting, and surveillance quality. Standardization of laboratory methodologies and protocols is required. National governments should encourage laboratories to form networks in order to share expertise and data. The suggested procedures for confirming an acute dengue infection include RT-PCR and virus isolation (and perhaps identification of the NS1 protein), but only for the first four days after fever onset—after that, the IgM-capture enzyme-linked immunosorbent assay (ELISA) is advised (Beatty et al. 2010).

9. VECTOR CONTROL MEASURES

Vector control measures aim to reduce dengue virus transmission by targeting the *Aedes* mosquito. Standard vector control measures include using insecticides, sanitation measures, and implementing breeding site reduction programs. Insecticides, such as pyrethroids and organophosphates, are commonly used to control adult mosquitoes, while larvicides target mosquito larvae in breeding sites (Mahmud et al. 2022).

In addition to these precautions, WHO recommends that people take actions to control mosquitoes inside as well as outside their houses. This includes using screens on windows and doors, wearing long-sleeved shirts and long pants, treating boots, pants, socks and tents with 0.5% permethrin, or purchasing permethrin-treated clothes and gear. Effective vector control approaches are crucial for attaining and maintaining dengue morbidity reductions. The goal of preventive and vector control actions is to limit dengue transmission, lowering the incidence of illness and averting disease outbreaks (Rather et al. 2017).

10. CLINICAL MANAGEMENT

Dengue fever clinical care comprises symptomatic treatment, fluid management for severe dengue fever, close monitoring of vital signs and test markers, and early diagnosis and management of warning signals. Early warning indications of severe dengue include prolonged vomiting, severe stomach pain, fluid accumulation, mucosal bleeding, trouble breathing, lethargy/restlessness, postural hypotension, liver enlargement, and gradual increase in hematocrit. Other danger signals include clinical fluid accumulation and lethargy/restlessness. One of the laboratory signs to look for is an increase in hematocrit followed by a rapid decrease in platelet count (WHO 2023).

11. PUBLIC HEALTH EDUCATION CAMPAIGNS

Public health education efforts aim to increase awareness of dengue fever and encourage behavior change to reduce the possibility of transmission. Community involvement, social media marketing, and health education offered through universities and other community-serving organizations are standard methods. These programs may urge consumers to eliminate breeding places, use mosquito repellent, and seek medical attention if they show signs of dengue fever (Hasan et al. 2022).

Public health education has been shown to be effective in reducing the incidence of dengue fever. A neighborhood-based educational program in Brazil effectively decreased mosquito breeding sites and lowered the incidence of dengue sickness (Andrioli et al. 2020). However, the effectiveness of such initiatives may be influenced by the factors such as the population's economic standing, level of learning, and cultural attitudes toward sickness prevention (Hasan et al. 2022).

12. MANAGEMENT AND SUPPORTIVE TREATMENT FOR DENGUE FEVER

Dengue fever is caused by a viral infection carried by mosquitos. Dengue fever has no particular antiviral agent. Supportive care is recommended: Because of their anticoagulant qualities, patients should be encouraged to stay hydrated and avoid aspirin (acetylsalicylic acid), aspirin-containing medicines, and other nonsteroidal anti-inflammatory drugs (such as ibuprofen) (Kaagaard et al., 2023). Acetaminophen and tepid sponge baths should be used to treat fever. Fluids that might increase volume include 5% albumin, normal saline, plasma or plasma substitutes, ringer lactate, and 5% glucose diluted in normal saline in a 1:2 or 1:1 ratio. Fluids may be used with analgesics. The potential of carbazochrome sodium sulfonate to inhibit capillary permeability in dengue hemorrhagic fever/dengue shock syndrome has been evaluated however the results have been inconsistent (Majeed et al. 2023).

13. MEDICINAL PLANTS AGAINST DENGUE FEVER

Crude drugs derived from plants have emerged as essential constituents in the fight against dengue fever, highlighting their significance in treatment. Plant-based medicines contain bioactive compounds that possess antiviral, anti-inflammatory, and immunomodulatory properties, making them an advantageous addition to managing dengue fever. Many plants, including *Arrabidaea pulchra, Andrographis paniculata, Mimosa catechu, Carica papaya, Azadirachta indica, Allium sativum, Ficus septica,* and *Quercus lusitanica,* have shown potential activity against dengue fever treatment (Huang et al. 2017; Ali-Seyed and Vijayaraghavan 2020; Ester et al. 2020; Lim et al. 2021; Dwivedi et al. 2021; Altamish et al. 2022; Babbar et al. 2023). These plants contain diverse bioactive compounds, such as alkaloids, Phenolics and flavonoids, contributing to their therapeutic properties. Integrating crude drugs from these medicinal plants into dengue fever management strategies holds promise for developing effective treatments and reducing the disease burden as shown in Table 3.

14. CASE STUDIES

14.1. SINGAPORE

Singapore is a Southeast Asian Island city-state that has effectively adopted the One Health method to manage and control dengue fever. The nation has seen multiple dengue outbreaks, with 22,170 cases documented in 2013. Singapore implemented the One Health strategy to control dengue transmission, which entails coordination amongst several sectors and fields of study, particularly the health care, veterinary, and ecological sectors (Sim et al. 2020).

Singapore's primary techniques for controlling dengue fever include the One Health method and Wolbachia-infected *Aedes* mosquito. Wolbachia-infected *Aedes* mosquitos to limit the number of dengue-carrying *Aedes* mosquitos. *Wolbachia* is a commonly existing bacterium that can diminish *Aedes* mosquitos' ability to spread the dengue virus. In 2016, pilot research in Singapore found that releasing Wolbachia-infected mosquitos decreased the prevalence of dengue fever (Ong et al. 2022).

Singapore also employed active monitoring and reaction to the dengue epidemics as a control method. Singapore has established a statewide dengue monitoring program that tracks the total number of cases, their distribution, and the number of mosquitoes present. Whenever an outbreak is discovered, officials respond by implementing targeted vector control actions and health education efforts (Soh et al. 2021). A research investigation conducted in 2020 discovered that the arrival of Wolbachia-infected mosquitoes was linked with a 78% decrease in the prevalence of dengue illness in the pilot study region (Chng et al. 2022).

Table 1: Control and Management Strategies of Dengue Fever according to International Guidelines (WHO 2023)

Sr#	Strategy	International Guidelines
1.	Vaccination Programs	• Dengvaxia is recommended for use in children 9-16 years old.
2.	Surveillance	• Regular monitoring of dengue cases and vector populations • Reporting of cases to national health authorities
3.	Vector Control	• Integrated vector management (IVM) approach • Source Reduction (elimination of breeding sites). • Larviciding (use of larvicides to target mosquito larvae). • Insecticides-treated bed nets and screens
4.	Clinical Management	• Symptomatic treatment for dengue fever cases • Fluid management for severe dengue fever • Close monitoring of vital signs and laboratory parameters • Early recognition and management of warning signs
5.	Health Education	• Public awareness campaigns on dengue prevention • Education on personal protective measures • Community involvement in vector control efforts • Emphasis on cleanliness and proper waste management • Promotion of household-level preventive measures

Table 2: Management and Supportive Treatment for Dengue Fever (Majeed et al. 2023)

Sr. no.	Treatments
1.	Fluids that could increase the volume are 5% albumin, normal saline, plasma or plasma substitutes, ringer lactate and 5% glucose diluted in a ratio of 1:2 or 1:1 in normal saline. Analgesics may be used along with fluids.
2.	Acetaminophen can be used for the treatment of fever.
3.	Give carbazochrome sodium sulfonate to reduce the high permeability of blood vessels.
4.	The use of drugs like corticosteroids, aspirin, ibuprofen and NSAIDs should be contraindicated.

14.2. AUSTRALIA

Australia is another region that has effectively applied the One Health strategy to manage and control dengue fever. Dengue fever is uncommon in Australia; however, cases have been observed in the country's north. Australia has created a robust surveillance system that combines coordination between the public wellness, veterinary, and ecological sectors to avoid the arrival and transmission of dengue (Madzokere et al. 2022).

Australia's primary goal is the adoption of border management measures that will avoid the spread of the dengue virus entering the country. It involves screening travelers from dengue-endemic nations, using pesticide sprays, and fumigating all the aircraft and ships coming from these countries where dengue is common (Akter et al. 2019).

Active monitoring and reaction to foreign dengue cases are other tactics that Australia employs. The authorities launched focused vector control initiatives and public health awareness programs in response to discovering an immigrant dengue patient to avert local spread (Trewin et al. 2022).

Above mentioned studies have demonstrated that the One Health strategy, which incorporates measures to control borders and continuous monitoring and reaction, has successfully halted the arrival and expansion of dengue in Australia. Australia has efficient border control procedures and a monitoring system; therefore the danger of dengue transmission is low (Nguyen et al. 2022).

14.3. PUNJAB, PAKISTAN

Among the areas with the worst dengue fever outbreaks is Punjab which is Pakistan's largest state. A record high of 22,000 cases was recorded in 2011 during one of the province's previous dengue fever

Table 3: Medicinal plants having natural cures against Dengue fever

Botanical name	Phytopharmaceuticals	Part used	Formulation	Mechanism	Reference
Arrabidaea pulchra	Caffeoylcalleryanin	leaves	Ethanol extract	Showed anti-DENV-2 activity	(Lim et al. 2021)
Andrographis paniculata	Flavonoids, flavonoid glycosides, diterpenes glycosides, lactones and diterpenes(andrographolide).	Whole plant	Methanol extracts	Inhibited the viral activity of DENV-1.	(Ali-Seyed and Vijayaraghavan 2020)
Mimosa catechu	catechin, quercetin, catechol, and catechol amines	Several plant portions	Crude extract	Reduced peptides found in the DENV outer coating in various DENV types	(Babbar et al. 2023)
• *Carica* papaya	Quercetin	Leaves	Methanolic crude and methanolic silver synthesized nanoparticles	Effective against dengue virus type 2 by Increasing platelet counts	(Babbar et al. 2023)
• *Azadirachta indica*	Bioflavonoids (kaempferol,, rutin hyperoside and epicatechin	Leaf	Aqueous crude extract	Inhibited DENV-2 replication in both in vitro and in vivo, Increased the platelet counts	(Dwivedi et al. 2021)
• Allium sativum	Allicin, Diallyl disulfide	Bulb	Solutions with different concentration	Killing Aedes sp. at larval stage.	(Ester et al. 2020)
• *Ficus septica*	Alkaloids, i.e. phenanthroindolizidine, aminocarophenone and pyrrolidine.	Fruit, heartwood, leaves and stem	methanol extract	Inhibited DENV infection in human lung epithelial carcinoma cells and human hepatocellular carcinoma cells. Disrupt DENV-1 and DENV-2 enveloped viral layer	(Huang et al. 2017)
Quercus lusitanica,	Methyl gallate	Gall	crude methanol extracts/	Inhibited NS3 protease activity, effective against DENV-2 serotype.	(Altamish et al. 2022)

epidemics. The One Health strategy was adopted by the Punjab government to prevent the global spread of dengue (Akram et al. 2022).

Punjab utilized an integrated vector management (IVM) program as one of its main strategies to combat dengue fever as shown in Table 1. This program included public health campaigns to raise awareness and targeted vector control methods such as applying insecticides and eliminating breeding grounds (Azhar and Khan 2020).

Punjab implemented a proactive surveillance and reaction system as an additional tactic. The authorities established a dengue surveillance system to keep track of the prevalence and dispersion of dengue cases. The government's response to the outbreak was to launch focused vector control operations and public health awareness campaigns (Khatri et al. 2022).

According to research, the One Health strategy, which includes enacting an IVM program and active surveillance and reaction, has successfully lowered dengue fever prevalence in Punjab. According to a 2019 study, the region's prevalence of dengue fever and mosquito population significantly decreased when the IVM program was implemented (Khatri et al. 2022).

15. CONCLUSION

One Health strategy is essential for controlling and handling dengue fever. This strategy aims to find and treat the disease's underlying causes through interdisciplinary interaction between the human, animal, and ecological health sectors. The epidemiological studies, dynamics of transfer, and variation in genes of the virus that causes dengue need to be better understood in Pakistan, where it is an endemic disease. Recent research has highlighted the importance of community involvement, vector surveillance, and effective mosquito control techniques in preventing and managing dengue epidemics. Therefore, future studies in Pakistan should focus on implementing these strategies and assessing their effectiveness in reducing the incidence of dengue fever.

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Etiology, Treatment and Complications of Dengue Fever: A Systematic Analysis

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ABSTRACT

Dengue fever, a viral illness transmitted by mosquitoes, presents a major health concern worldwide, especially in warm and humid areas. This comprehensive examination delves into the important aspects of Dengue Fever, such as its causes, methods of treatment, and potential negative effects. The Dengue virus, which has four different serotypes, is primarily transmitted through the bite of Aedes mosquitoes that are infected. Comprehensive knowledge of the numerous underlying causes is essential for creating successful measures to prevent and manage the issue. The primary approach to treating Dengue Fever is providing support by relieving symptoms and preventing further complications. Managing pain and fever can be achieved with analgesics such as acetaminophen, and it is crucial to carefully monitor fluid intake to avoid dehydration. In serious instances, hospitalization, blood transfusions, and careful monitoring may be required to reduce the likelihood of developing complications like Dengue Hemorrhagic Fever and Dengue Shock Syndrome. These serious symptoms include bleeding, fluid escaping from blood vessels, and, occasionally, damage to organs, underscoring the necessity of identifying and addressing the problem early. Preventive measures include controlling the mosquito population by getting rid of their breeding sites, using insecticides, and encouraging individuals to use personal protective measures. Furthermore, vaccination initiatives have become a hopeful solution in regions with high disease prevalence. This thorough analysis offers a complete picture of Dengue Fever, highlighting the importance of comprehensive approaches that cover understanding the cause, treatment plans, and strong prevention methods to reduce the impact of this widespread and potentially serious viral illness.

Keyword: Dengue Fever; Etiology; Treatment; Complications; Mosquito-borne

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1. INTRODUCTION

A famous quote from Jill Lepore, a Historian states that "Epidemiologists study patterns to combat infections, but it's important to remember that stories about outbreaks also follow patterns. While stories may not be physically deadly, they possess a different kind of power. They can spread rapidly, weaken resistance, and wreak havoc on our perception of reality".(Uwishema et al. 2021).

Dengue Fever (DF) is a widespread viral infection that affects millions of people worldwide each year. Itis a mosquito-borne viral infection caused by the dengue virus, which is transmitted primarily by the *Aedes* mosquito. Usually, dengue symptoms appear 5 to 7 days after a healthy person is bitten by a mosquito carrying the virus. Due to the existence of the distinct virus kinds, an individual may suffer numerous infections. During the DF stage, the patient develops symptoms including headaches, muscular soreness, and itching as well as an increase in body temperature each day. The patient may also have slight bleeding from the nose, gums, or skin during the dengue hemorrhagic fever (DHF) stage, as well as a drop in body temperature. The body temperature fluctuates as the patient approaches the stage of dengue shock syndrome (DSS), and vomiting may occur along with the presence of trace amounts of blood (Murhekar et al. 2019; Rastogi et al. 2019; Dourjoy et al. 2021).

Due to the disease's high rates of morbidity and mortality, which are endemic in many tropical and subtropical countries, it presents a serious public health concern. According to World Health Organisation (WHO) the DENV affects about 50 million individuals each year, killing over 15,000 people. In Pakistan, the months of September to November are very crucial for DF, having a big influence on population. In Pakistan, an alarming 34.75% of patients who suffer from an acute febrile illness are reported to have DF. In addition, a thorough retrospective investigation of Dengue infection during pregnancy in the Pakistani population found a significant maternal death incidence of 7%. These data demonstrate the seriousness of the situation and the pressing need for its solutions (Ahmed and Aman 2022).

2. ETIOLOGY OF DF

The DENV is a member of the Flaviviridae family and categorized into four different serotypes called DENV-1, DENV-2, DENV-3 and DENV-4 (Gulati et al. 2020). These serotypes are further separated into several genotypes with minute genetic variances. Infected female *Aedes* mosquitoes, especially *Aedes aegypti* and, to a lesser extent, *Aedes albopictus*, bite victims to spread the virus. These mosquitoes are generally found in cities and semi-urban settings, where they thrive in stagnant water sources including flowerpots, waste tires, and water storage containers (Saha et al. 2019; Adnan et al. 2021).

People who are infected with the DENV may suddenly develop a high fever, a strong headache, retro-orbital discomfort, muscle and joint pain (myalgia and arthralgia), rash, and minor bleeding symptoms such as petechial haemorrhage and gum bleeding after an incubation period of 4 to 10 days(Gulati et al. 2020). The DENV targets the skin's immune cells, such as dendritic cells and monocytes, after infecting a person through a mosquito bite. After that, it multiplies within these cells before spreading throughout the circulation and lymph nodes. A major component in the severity of DF is the virus capacity to sabotage and regulate the host's immune response (Brar et al. 2021; Uwishema et al. 2021).

3. PATHOGENESIS AND CLINICAL MANIFESTATIONS

The full understanding of dengue's illness, which is characterized by a complicated interplay between virus and host factors, is still inadequate. DF can present in a spectrum of clinical manifestations, ranging from mild DF to severe DHF and DSS (Mulik et al. 2021).The major contributor to fatalities caused by this

infectious disease in severe cases are plasma leakage and thrombocytopenia, a condition characterized by low platelet count. By modifying the bone marrow environment, the DENV affects the platelet count of the host directly or indirectly, altering several components involved in platelet synthesis, shattering, and reproducing inside platelets, and finally causing a reduction in the number of circulating platelets (Bandara and Herath 2020).

The infection of DENV is initiated when the virus binds to host cell receptors. The virus then gets inside the cell via clathrin-mediated endocytosis and the acidic environment within the endosome triggers the fusion of the viral membrane. The viral genome is translated into a polyprotein after membrane fusion and removal of the protective protein coat, and this polyprotein is then cleaved into seven non-structural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) and three structural proteins(S)(Capsid, Membrane, and E). The NS proteins aid RNA replication, resulting in the formation of positive (blue) and negative (green) sense single-stranded RNA copies. The (S) envelope (E) and pre-membrane (prM) are transported to the endoplasmic reticulum (ER). The genomic RNA (blue) is packaged by capsid proteins, and the resulting nucleocapsid buds into the ER lumen, forming an immature virion. The prM protein is subsequently broken down to create the M protein as the immature virions are then transported along the secretory route. Exocytosis is ultimately responsible for the discharge of mature virus particles from the cell(Troost and Smit 2020).

When the immune system is activated by dengue infection, chemokines and cytokines are released, endothelium cells undergo autophagy and apoptosis in T cells. These elements work together to cause endothelial cell dysfunction, which in turn causes fluid loss in the third space, intravascular volume contraction, and plasma leakage. A cascade of hypoxic damage occurs across numerous organ systems as a result of poor organ perfusion and shock-like symptoms brought on by intravascular volume reduction. When the virus triggers the immune response, it causes increased permeability in the blood vessels and leads to plasma leaking into tissues, resulting in shock and organ failure. A common outcome of this chain of events is shock and multi-organ dysfunction, which accounts for a significant cause of fatalities in dengue cases(Islam et al. 2020; Schaefer et al. 2022).

4. MANAGEMENT OF DF

The patient's understanding of their participation in dengue management, especially the identification of warning signals demand rapid hospitalisation, has been recognised as a weak area. This delay in treatment has been a substantial contributor to higher death. Since there is no specific antiviral medication for DF, supportive care and the early identification of severe cases are the main management of DF. In order to properly manage dengue and lower its death rate, early diagnosis is essential. The prompt identification of warning signs is crucial to prevent progression to severe disease and reduce mortality rates. Medical professionals can only alleviate the symptoms associated with the disease. Several suggestions should be followed to control dengue such as bed rest, controlling temperature by using antipyretics or sponging methods, relieving discomfort with light sedatives, and ensuring adequate hydration with fluid or electrolyte treatment(Ksularatnam et al. 2019;Jayawickreme et al. 2021).

In situations of severe dengue, it is necessary to carefully evaluate and cope with organ involvement. It's crucial to recognise secondary hemophagocytic lymphohistiocytosis, a dengue complication that might be fatal. By identifying this ailment, healthcare professionals may put into practise certain treatment plans such as giving intravenous immunoglobulin or steroids, which may improve patient outcomes. However, there is no evidence to support any of these claims. There have been talks about the function of corticosteroids in DSS and the potential to stop the development to severe disease if taken early in

the course (Singh et al. 2019; Dhooria et al. 2021).Reduced blood flow, hemolysis, rhabdomyolysis, the direct effects of the dengue virus, and immune-mediated damage can all contribute to renal impairment in dengue. Careful fluid administration is required for a urine output of greater than 0.5 ml/kg/h, and when necessary, early initiation of renal replacement treatment is required. The preferable method is continuous veno-venous hemofiltration (CVVH) (Tayal et al. 2023).

Myocarditis and cardiogenic shock in dengue patients necessitate highly careful fluid resuscitation and prompt use of inotropic drugs. These people have an increased likelihood of getting pulmonary edema and congestive heart failure (Gupta et al. 2021; Teysseyre et al. 2021; Wijaya and Krisnawati 2022).

Both direct invasion and antibody-dependent enhancement by the dengue virus can result in neural damage. Supportive care includes required protection of airways, keeping track of consciousness levels, hydration, and giving anti-seizure drugs as necessary, and when clinically necessary taking steps to lower excessive intracranial pressure. Post-dengue Guillain-Barré syndrome (acute or severe polyradiculoneuropathy a rare case in DF) can be managed by the use of intravenous immunoglobulin (IVIg) (Kulkarni et al. 2021).

A serious health risk is the co-infections of dengue virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The prospect of a more serious course of sickness in such circumstances has given rise to speculation. Patients who have co-infection of both viruses frequently have a more severe illness, a greater risk of ICU admission, and a higher fatality rate. This is caused by the two viruses' same pathophysiology, which results in capillary leakage, cytokine storms, coagulopathy, and thrombocytopenia. The two viruses in a co-infection can harm a number of organs either jointly or separately (Omame et al. 2022; Dutta et al. 2023; Prapty et al. 2023).

Identification of particular symptoms such as plasma leakage, erratic hemostasis, and increased vascular permeability is necessary to differentiate between DHF and DF. According to World Health Organisation (WHO) standards, patients with severe syndromes should be given isotonic crystalloid solutions, such as 0.9% normal saline, Ringer's lactate, or Hartmann's solution. Patients can recover quickly once they have passed the crucial stage of their sickness. The restoration of appetite and the reabsorption of extravascular fluids are indicators of improvement and the general health of the patient(Wang et al. 2020).

To stop the spread of dengue, vector control measures are essential. Populations of *Aedes* mosquitoes have been successfully reduced using integrated methods that combine environmental management, source reduction, and the application of pesticides. The importance of community involvement and educsation programmes in spreading knowledge about dengue preventative measures and control strategies are vital to raise awareness (Selvarajoo et al., 2020; Radhika et al. 2019; Yoshikawa et al. 2019; Chng et al. 2022).

5. ADVANCEMENTS IN RESEARCH

The development of new antiviral medications and vaccines, along with the improvements to diagnostic techniques and understanding of virus interaction with its host, have all been the major areas of attention in dengue research. Understanding the pathophysiology of DF has advanced significantly in recent years, offering important new information on potential therapeutic targets (Halstead 2019).

The development of host-directed medicines, which focus on the host immune system rather than the virus itself, is one promising field of research. Several host factors including the type I interferon response and the inflammasome pathway are two host variables that have been recognized as crucial players in the immune response to DENV infection. Host-directed therapies have shown promising results in preclinical studies, suggesting their potential for treating DF(Shrivastava et al. 2020; Duncan et al. 2021).

The use of monoclonal antibodies as a treatment for DF is another area of study that has attracted a lot of interest. Highly specialized monoclonal antibodies can attack either the S or NS proteins of the virus. In *in-vitro* and animal models, a number of monoclonal antibodies that target the DENV envelope protein, have demonstrated strong antiviral activity, suggesting their potential therapy for DF (Pecetta et al. 2020;Dussupt et al. 2021; Kotaki et al. 2021).

In addition to therapeutic treatments, research has also concentrated on creating more accurate and focussed DF diagnostic techniques. The sensitivity and specificity of current diagnostic techniques, such as enzyme-linked immunosorbent assays (ELISA) and polymerase chain reactions (PCR), are limited. To enhance early identification and management of DF, the development of innovative diagnostic techniques, including biosensors and point-of-care analysis, is essential (Luo et al. 2019; Wilder-Smith et al. 2019; Wang et al. 2020).

6. CURRENT TREATMENT OPTIONS

6.1. SUPPORTIVE CARE

The treatment of DF largely focuses on treating the symptoms, although identifying those who are at risk of developing DHF or DSS is an important step and require hospitalisation and strict monitoring. There isn't a particular antiviral medication for DF as of now. The cornerstone of therapy is supportive care, which emphasizes symptom relief and hydration maintenance. To avoid issues like significant plasma loss and shock, adequate fluid replacement either orally or intravenously is crucial. The increased risk of bleeding makes non-steroidal anti-inflammatory medications (NSAIDs) typically contraindicated (Guarner and Hale 2019).

6.2. ANTIVIRAL THERAPIES

6.2.1. DIRECT ANTI-VIRAL AGENTS (DAA)

Numerous studies have been done so far in developing antiviral treatments for DENV that target both the structural and NS proteins. Given its critical function in promoting virus entrance into host cells, the E protein, one of the (S), has received substantial research as a possible antiviral target. In terms of NS proteins, the NS5 and NS3 proteins have been the most studied. NS5, being the largest and highly conserved NS protein in DENV, serves as the viral RNA-dependent RNA polymerase (RdRP) and possesses methyltransferase (MTase) activity. In preclinical and early clinical trials, several antiviral medications show promising results, nevertheless, this treatment is more likely to develop resistance. Balapiravir, a nucleoside derivative that prevents DENV replication, is one such medication. In vitro and in vivo studies have proven the antiviral efficacy of balapiravir. However, further research is required to assess its effectiveness and safety in humans (Do and Reau 2020).

Moreover, a wide range of naturally occurring substances, including mangiferin-punicalagin, alpha-mangostin, geraniin, curcumin-flavonoids, and quercetin derived from various plant sources have shown activity against DENV (Clain et al. 2018; Fitmawati et al. 2021; Kowalczyk et al. 2021; Santhi et al. 2021; Patil et al. 2021; Dhiman et al. 2022) .

6.2.2. HOST DIRECTED AGENTS (HDA)

HDA has the potential to effectively treat a variety of infections. Additionally, HDA offers a lesser chance of resistance, increasing their efficacy. However, it is important to note that due to their tendency to

interfere with cell homeostasis, HDA often have a limited range of safe and effective doses compared to DAA. There are several HDA antivirals that have been identified, and these all focus on various phases of viral propagation. The α-glucosidase, essential for proper protein folding and maturation, is one widely studied cellular target. Research is being done on blocking the cellular inosine monophosphate dehydrogenase, which is essential for viral replication and nucleotide production (Bhushan et al. 2020; Troost and Smit 2020; Karade et al. 2023).

7. TACKLING VECTOR CONTROL

Due to lack of antiviral medications, vector control management methods are crucial for the prevention of DF. Insecticides, mosquito repellents, and community participation are just a few of the integrated vector management strategies that have shown effective in lowering mosquito populations and, consequently, dengue transmission. Concerns about continuing to use current techniques to control these mosquitoes are being mounted. Due to their high costs, low acceptability in communities, slow implementation procedures, and widespread development of pesticide resistance in *Aedes* mosquitoes, larviciding methods such as dieldrin and DDT, mosquito fogging with 5% malathion, or Pyrethrin, are now challenged (Jones et al. 2021;Saha and Samanta 2022).

8. VACCINES

It has long been difficult for scientists to develop a dengue vaccination that is effective. In recent years the first dengue vaccine, Dengvaxia, has been approved in several countries. But it delivers partial defence against DENV serotypes 1-4, and its usage is restricted because of questions about its efficacy and safety. The goal of ongoing research is to create vaccines of the next generation with enhanced safety and effectiveness characteristics. To meet the demand for a secure and efficient dengue vaccine, currently, attempts are being made to create dengue vaccines in five main categories: inactivated virus vaccines, live attenuated virus vaccines, DNA vaccines, recombinant subunit vaccines, and viral-vector vaccines. TAK-003, CYD-TDV, and TV003/005, are the most advanced vaccine candidates which are currently under development. The genetic backbone for all four vaccine viruses is provided by TAK-003, a candidate for a tetravalent dengue vaccine that is based on a live, attenuated dengue serotype 2 virus. Phase 3 studies for TAK-003 are presently in progress, and effectiveness has been shown independent of serostatus prior to vaccination (Wilder-Smith 2020; Laydon et al. 2021; Hou et al. 2022). The NIH's National Institute of Allergy and Infectious Diseases (NIAID) developed the live, attenuated tetravalent vaccination TV003/TV005 by utilizing recombinant DNA technology. Phase 2 studies are now being conducted on it. There are also varying phases of development for other vaccination candidates from diverse classifications (Yoshimura et al. 2017; Halstead and Dans 2019; Halstead et al. 2020; Girard et al. 2020; Shukla et al. 2020; Park et al. 2022; Torres-Flores et al. 2022).

9. COMPLICATIONS OF DF

9.1. NEUROLOGICAL COMPLICATIONS

When acute febrile infections exhibit neurological signs, particularly altered sensorium, the complexity of diagnostic difficulties rises. Differentiating between dengue-associated encephalopathy and dengue encephalitis becomes challenging when people with febrile illness have altered sensorium and test positively for dengue through serology. Similar alterations may be seen in several different viral

infections that impact the central nervous system (CNS), but a positive brain neuroimaging study typically be indicative of other viral infections of the CNS and may also exhibit comparable alterations. Alterations to the sensorium in DENV seropositive patients may possibly be the result of a stroke involving an intracerebral haemorrhage or an enlarging infarct. Therefore, in suspected dengue-related cases, caution should be exercised while doing the standard procedure of analysing cerebrospinal fluid (CSF) in ill patients with altered sensorium to rule out underlying CNS illnesses (Rastogi et al. 2019;Kulkarni et al. 2021; Trivedi and Chakravarty 2022).

10. ACUTE PANCREATITIS

Pancreatitis caused by dengue is a largely unexplored complication. The onset of acute pancreatitis complicates the clinical spectrum even further and has an impact on prognosis and therapy. The risk of death and morbidity is considerably reduced when DF accompanied by acute pancreatitis is promptly identified and managed. Healthcare workers must be knowledgeable of these potentially lethal consequences that might develop alongside instances of DF that first appear to be benign. Uncertainty exists regarding the precise underlying processes of pancreatic involvement in DF. Two possibilities have been put forth. One theory is that the virus directly attacks the pancreas, inflaming it and harming its acinar cells. The second hypothesis contends that the shock from DSS might damage the pancreas, triggering either an acute infection or an autoimmune reaction against the islet cells of the pancreas. This reaction can cause the ampulla of Vater to swell, preventing the pancreatic secretions from draining. It is essential to identify pancreatitis as soon as possible using abdominal ultrasonography to avoid serious and perhaps deadly consequences (Naik et al. 2021).

11. OTHER COMPLICATIONS

DF may affect several organs in addition to plasma leakage, which can result in problems such as liver damage, myocarditis, subacute thyroiditis, gallbladder wall thickness (GWT), ascites, Isolated subdural hematoma, encephalopathy, and renal impairment. These issues call for prompt identification and adequate care since they have a major impact on patient health outcomes (Vyas et al. 2020; Mangaraj 2020; Sivanesan Uthraraj et al. 2022; Ashraf et al. 2022).

12. CONCLUSION

Millions of individuals worldwide suffer from DF a common viral infection spread by *Aedes* mosquitoes, each year. The clinical symptoms caused by the dengue virus (DENV) infection include mild DF, severe DHF, and DSS. Since DF does not currently have a particular antiviral medication, supportive care is essential for illness management. Research is mainly focused on the development of antiviral drugs, vaccines, and better diagnostic methods.A host-directed therapy and monoclonal antibodies are promising treatments for DF, while research is ongoing to develop safe and effective vaccines. Potential treatment targets have been revealed by better understanding of the pathophysiology of dengue disease.DF remains a significant public health challenge, particularly in tropical and subtropical regions. Despite the lack of specific antiviral therapy, advances in research have provided valuable insights into the virus-host interaction and potential therapeutic targets. Developing safe and effective vaccines, host-directed therapies, and monoclonal antibodies, along with effective vector control strategies, are crucial in preventing and controlling DF. The approval of Dengvaxia has been a significant breakthrough in dengue vaccination, although further research is needed to develop more effective vaccines. Continued research efforts in understanding the pathogenesis of DF, early recognition of complications

and developing novel interventions are essential to reduce the morbidity and mortality associated with this disease.

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Vaccine Strategies for Dengue Fever

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ABSTRACT

Dengue fever, a widespread viral illness transmitted by mosquitoes, is a major global health concern, especially in tropical and subtropical areas. To proactively address the disease, vaccination plans have been created to minimize its effects. Significantly, the live attenuated vaccine Dengvaxia (CYD-TDV) has been recognized as an innovative intervention. This quadrivalent vaccine introduces individuals to less potent strains of all four dengue virus types, triggering an immune reaction without inducing the illness. The main objective of these vaccines is to provide protection against all virus strains at the same time. However, due to the complicated nature of dengue and its antibody-dependent enhancement, caution is needed in the development of vaccines to prevent making the disease worse. Efforts to implement vaccinations against dengue focus on areas with high rates of transmission, customizing the approach to target specific age groups or populations at higher risk of the disease's effects. Current research is working to improve current vaccines and create new ones to address challenges in vaccine effectiveness and adaptability to different geographic and demographic conditions. The changing nature of dengue transmission and the specific factors related to different age groups highlight the need for flexible vaccine strategies. Consistent communication and advancements in science from health authorities are helping to reduce the global impact of dengue fever through successful vaccination programs.

Keyword: Dengue fever; Dengue vaccine; Tetravalent; Live attenuated; Antibody-dependent enhancement (ADE)

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1. INTRODUCTION

Dengue Fever is a viral illness propagated by the bites of Aedes mosquitoes infected with the virus. Dengue Fever is caused by a viral agent known as the Dengue Virus which encompasses four unique serotypes. It constitutes a significant issue in terms of public health across numerous tropical and subtropical territories on a global scale, such as Southeast Asia, Latin America, and the Caribbean (Kok et al. 2022).

The symptoms of Dengue Fever exhibit a broad spectrum of severity, encompassing hyperthermia, cephalalgia, arthralgia, myalgia, dermatosis, emesis, and anorexia. The manifestation of Dengue Hemorrhagic Fever, a grave variant of Dengue Fever, has been documented to have lethal consequences in certain cases (Huang et al. 2020).

At present, Dengue Fever lacks a targeted intervention, rendering vector control and personal protection the primary means for managing the disease's propagation. The quest for the creation of efficacious vaccines targeting Dengue Fever is a pivotal subject of scientific investigation, and various vaccine prototypes have been formulated and assessed through clinical trials (Pinheiro-Michelsen et al. 2020).

2. PUBLIC HEALTH INFLUENCE

Dengue Fever is a considerable health concern of utmost public importance, with the approximate occurrence of 400 million infections across the world annually. The ailment illicit significant morbidity, potentially resulting in lethality in certain cases. The development of a vaccine for the prevention or mitigation of the symptoms of Dengue Fever would constitute a substantial contribution to the field of public health, especially in regions where the disease is endemic and a considerable source of affliction (Ahmad et al. 2022).

3. ECONOMIC LOAD

Dengue Fever poses a significant economic burden, as evidenced by the substantial healthcare expenses incurred and the productivity losses suffered. The provision of a vaccine capable of averting Dengue Fever would alleviate the financial strain of the ailment on individuals, healthcare frameworks, and communities (Nasir et al. 2020).

4. VECTOR CONTROL EXPERIMENTS

The implementation of vector control measures, namely insecticide spraying and environmental management, represent vital tactics in combating the dissemination of Dengue Fever. Nevertheless, the successful implementation and long-term maintenance of such measures can pose a considerable challenge. The implementation of a vaccine that can effectively prevent Dengue Fever would serve as a supplementary approach to complement the existing vector control measures, thereby contributing towards a significant reduction in the overall disease burden associated with this affliction (Gangmei et al. 2023).

5. INFLUENCE ON TOURISM

Dengue Fever poses a significant and pressing concern for travelers visiting regions that are endemic to the virus, particularly in the context of global travel and tourism. The development of a vaccine against Dengue Fever could significantly mitigate the risk of contagion for travelers and curb the propagation of the ailment to regions where its occurrence is not endemic (Azcarate 2020).

6. EPIDEMIOLOGY OF THE DENGUE FEVER

6.1. DENGUE FEVER PREVALENCE AND INCIDENCE

Dengue Fever is a significant concern in tropical and subtropical regions. It endangers public health and is endemic in over 100 countries, with an estimated 390 million annual infections according to WHO. The number of Dengue Fever cases has increased from 2 million annually in the 1990s to over 3 million annually in recent years. Many cases may go unreported or be misdiagnosed. The prevalence of Dengue Fever varies across countries and regions, with high rates in Southeast Asia and Latin America where the Aedes mosquito is widespread. Urbanization and climate change increase disease transmission in impacted areas. Dengue Fever is a significant global health issue in endemic regions. Developing effective Dengue Fever vaccines is crucial to reducing its impact and improving public health in affected communities (Palaniyandi 2021).

7. GEOGRAPHICAL DISTRIBUTION OF THE DENGUE FEVER

Dengue Fever is caused by the Dengue virus and transmitted by Aedes mosquitoes in tropical regions. Dengue Fever is endemic in 100+ countries, with high incidence in Southeast Asia, Western Pacific, Latin America, Africa, and the Middle East. In Dengue-endemic regions, disease distribution varies greatly with some areas having frequent outbreaks and others only sporadic cases. It is limited to areas with Aedes mosquitoes, mainly Southeast Asia and the Western Pacific. We must work on prevention and vaccines in these endemic regions. Non-endemic regions may face outbreaks due to travel trends, requiring equal attention (Palaniyandi et al. 2021).

8. DENGUE FEVER AS A DISEASE BURDEN

Dengue fever is a global health concern with varying severity, including life-threatening conditions such as Dengue Hemorrhagic Fever and Dengue Shock Syndrome. The accurate measurement of dengue fever's disease burden is difficult due to underreporting and misdiagnosis. It's estimated that around 390 million people suffer from the disease every year. Around 96 million cases show symptoms of dengue fever with 20,000 deaths per year, mostly in children under 15 years. Severe forms of Dengue can lead to a 20% fatality rate. The economic impact includes healthcare costs and decreased productivity. Dengue fever outbreaks impact the local economy and healthcare system in endemic areas. Implementing measures to reduce its spread and effective immunization are crucial for community well-being (Wang et al. 2022).

9. GLOBAL HEALTH IMPACT OF DENGUE FEVER

Dengue fever can have secondary effects on global health, including increased demand for healthcare services, which burdens impacted regions. This may lead to a drop in healthcare accessibility and higher death rates for various illnesses. It has significant economic consequences, particularly in endemic regions where it results in lower productivity and higher healthcare costs. Disease outbreaks can lower tourism and hurt the economy, worsening disease-related issues. Containing dengue fever and creating effective immunizations is crucial for global health. Better surveillance can help us understand disease trends and inform public health interventions. Investing in vaccine research can help to prevent and treat the disease (Wang et al. 2020).

10. PATHOGENESIS OF THE DENGUE FEVER

10.1. FOUR SEROTYPES

The dengue virus comprises of four serotypes that exhibit discernible variations of the virus predicated on the particular proteins discovered on its surface. There are four distinct variations of the dengue virus that are characterized as serotypes (Kothai et al. 2020).

10.1.1. DENGUE VIRUS SEROTYPE I

This serotype is predominantly observed in Southeast Asia and the Western Pacific area, with sporadic occurrences in other global regions. It is correlated with a spectrum of mild to moderate disease (Filho et al. 2019).

10.1.2. DENGUE VIRUS SEROTYPE II

This specific serotype has been observed in numerous regions across the globe, spanning Asia, Africa, and the Americas. There is a significant correlation between the aforementioned condition and the manifestation of severe maladies, such as Dengue Hemorrhagic Fever (Trivedi and Chakravarty 2022).

10.1.3. DENGUE VIRUS SEROTYPE III

This serotype has been detected in numerous regions throughout the globe, spanning Asia, Africa, and the Americas. This condition is potentially linked to mild to moderate manifestations, yet possesses the ability to prompt severe afflictions in certain instances (Tahir Ul Qumar et al. 2019).

10.1.4. DENGUE VIRUS SEROTYPE IV

The aforementioned serotype has been detected across various global regions, such as Asia, Africa, and the Americas. This condition is frequently linked with a spectrum of afflictions ranging from moderate to mild; nonetheless, certain instances may result in grave morbidity (Cui et al. 2022).

11. TRANSMISSION OF DENGUE FEVER

Dengue fever is mainly spread by infected mosquitoes, specifically the *Aedes aegypti* and *Aedes albopictus* species. These mosquitoes are active during the day and commonly found in urban and suburban areas. Dengue Fever can be transmitted through blood transfusions, organ transplants, pregnancy, or childbirth. It cannot be spread through direct contact. Dengue Virus patients can spread it through mosquitoes. To prevent transmission, reduce mosquito populations, use insect repellent and protective clothing, and implement surveillance and public health interventions. Vaccination is crucial to prevent virus transmission (Anoopkumar et al. 2021).

12. REPLICATION AND MECHANISMS OF VIRUS ENTRY

The dengue virus enters host cells through receptor-mediated endocytosis, binding to glycoprotein DC-SIGN or other receptors on immune system cells. The virus enters the host cell through endocytosis and replicates. The virus releases RNA into the host cell's cytoplasm. Translation produces a polyprotein

which is cleaved by proteases, resulting in viral proteins. The virus replication cycle is complex and challenging for developing antiviral treatments. Understanding viral entry and replication is vital for developing effective interventions to stop disease spread (Sirisena et al. 2021).

13. IMMUNE RESPONSE HELPS THE DENGUE VIRUS

The immune response mounted against dengue virus is characterized by its intricate nature, which encompasses both innate and adaptive immune responses.

13.1. INNATE IMMUNE RESPONSE

The indigenous immune response represents the initial barrier of protection in opposition to the dengue virus. Upon infection, host cells are stimulated to release a diverse array of signaling molecules, such as cytokines and chemokines, which attract and trigger an immune response from various types of immune cells, including natural killer (NK) cells, macrophages, and dendritic cells. The aforementioned cells possess the ability to eliminate infected cells directly while also facilitating the activation of the adaptive immune response (DelliPonti et al. 2021).

13.2. ADAPTIVE IMMUNE RESPONSE

The adaptive immune response elicited by the dengue virus entails the generation of antibodies as well as the stimulation of T cells. Antibodies that are generated by B cells exhibit specificity and form a complex with corresponding proteins present on the exterior of the virus, referred as antigens. Antibody-antigen interactions serve as a crucial mechanism for neutralizing viruses and averting their ability to infect host cells. T lymphocytes, upon activation by antigen-presenting cells, possess the ability to identify and eradicate infected cells as well as facilitate the generation of antibody molecules (Kamgang et al. 2019).

14. DENGUE FEVER EXISTING VACCINES

14.1. LIVE ATTENUATED VACCINES

Live attenuated vaccines for dengue fever manipulate the virus for replication in human cells but without pathogenicity. This yields a potent and sustained immune response, similar to natural infection, while reducing severe morbidity. The vaccine virus reproduces and generates antigens that trigger an immune response, producing antibodies and activating T-cells. Monitoring and surveillance are crucial for safe and effective dengue fever vaccines (Jones et al. 2021).

14.2. INACTIVATED VACCINES

Inactivated dengue fever vaccines are produced by growing virus in cell culture, then rendering it inactive with heat, chemicals, or radiation. These vaccines use either the entire inactive virus or only parts, like the envelope protein. Although clinical trials have shown promise, none have been officially approved yet. Inactivated vaccines are easier to manufacture and scale as compared to live attenuated vaccines, making them more suitable for use in areas with high disease incidence (Zhu et al. 2023).

14.3. SUBUNIT VACCINES

Dengue fever subunit vaccines use virus constituents, including the envelope protein, which initiates contact with host cells and triggers an immune response. Subunit vaccines are safer than live or inactivated vaccines as these only use certain components or envelope proteins to induce a strong immune response, reducing the risk of adverse reactions. Subunit vaccines may have limited immunogenicity compared to live attenuated vaccines, as they cannot present viral antigens as effectively. Multiple dengue fever subunit vaccines, including recombinant proteins, virus-like particles, and DNA-based vaccines, are in development. Some inoculations show positive results in trials, but are not approved for use. Subunit vaccines are easier and safer to administer to at-risk individuals, such as children and those with weakened immune systems. These also show promise in high-incidence regions where these can be produced on a large scale without losing effectiveness (Meraj and Gries 2022).

14.4. CHIMERIC VACCINES

Chimeric vaccines for dengue fever combine genetic material from multiple viruses to create a hybrid that incorporates key elements of the dengue virus. This approach reduces negative reactions and enhances immune response. However, chimeric vaccines have possible disadvantages, including the risk of the vaccine virus reverting to a stronger form in areas with high virus prevalence. These vaccines are complex and expensive to produce (Nanaware et al. 2021).

14.5. DNA VACCINES

DNA vaccines for dengue fever involve direct injection of genetic material from the virus into cells, which then produce viral antigens and trigger an immune response. DNA vaccines have advantages over traditional vaccine methods. These are easy and affordable to produce, and can be quickly tailored to target specific viruses. DNA vaccination may provide longer immunity with fewer administrations. DNA vaccines for dengue fever, targeting multiple virus serotypes, are being developed. Vaccines show promise in early trials, but more research is needed for safety and effectiveness. DNA-based vaccines may be less effective than traditional methods. DNA vaccines show promise for preventing dengue fever, but more research is needed to make them safer and more effective (Nanaware et al. 2021).

15. VACCINE DEVELOPMENT STRATEGIES

15.1. TARGETS OF THE VACCINE

Vaccine objectives for dengue fever involve viral envelope protein and NS1, which activate immune response mechanisms. Vaccines targeting NS1 protein aim to produce immune response towards the conserved region present in all four dengue virus serotypes. These are usually NS1 subunit vaccines. Other vaccine targets for dengue fever include viral membrane/capsid proteins and host proteins in the immune response (Nakamura et al. 2023).

15.2. PLATFORMS OF THE VACCINE

Various vaccine platforms are currently being developed for dengue fever, with inherent strengths and limitations for each of these. Several vaccine platforms are currently under development (Verdecia et al. 2021).

15.3. TECHNOLOGIES OF THE NOVEL VACCINE

In contemporary times, a plethora of innovative vaccine technologies has surfaced, demonstrating the possibility of enhanced efficacy, safety, and cost-effectiveness of dengue fever vaccines. Several novel vaccine technologies show significant potential (Korkmaz et al. 2021).

15.4. VIRUS-LIKE PARTICLE VACCINES

Virus-like particle vaccines imitate the structural composition of the virus, yet are void of genetic material, thereby rendering them a safer alternative in comparison to live attenuated or inactivated vaccinations. These vaccines can be efficiently synthesized through recombinant DNA technology, providing a high degree of accuracy in modulating both the size and composition of the vaccine particles. Numerous virus-like particle vaccines aimed at the prevention of dengue fever are presently undergoing development (Nooraei et al. 2021).

15.5. mRNA VACCINES

The messenger RNA (mRNA) vaccines entail encoding of genetic material that specifies a definite antigen, subsequently synthesized by the host's cells. mRNA vaccines possess advantageous characteristics such as low cost and simple production procedures, and hold the potential for swift adaptation to newly evolving viral strains. At present, a number of mRNA-based vaccines intended to counteract dengue fever are undergoing preclinical development (Mukhtar et al. 2022).

15.6. NANOPARTICLE VACCINES

Nanoparticle vaccines employ diminutive, self-arranging particles that imitate the configuration of virus in order to provoke an immune system reaction. The development of nanoparticle vaccines enables the possibility of targeting distinct regions of virus, such as the envelope protein, and can be conveniently adapted to address emergent viral strains. There are presently numerous nanoparticle vaccines in progress for the prevention of dengue fever (Nguyen et al. 2021).

15.7. ADJUVANTS CHEMICAL

Adjuvants are chemical entities that are incorporated into vaccines with the purpose of augmenting the immune response. Novel adjuvants are currently in the process of development, which have the potential to augment the potency of vaccines and concomitantly minimize the number of dosing interventions requisite for optimal immunogenicity. Adjuvants have the potential to mitigate the financial burden associated with vaccines by facilitating the usage of lesser quantities. Various adjuvants are presently undergoing an investigation regarding their potential integration with prevailing vaccines for dengue fever (Eusebio et al. 2021).

16. STRATEGIES FOR THE IMMUNIZATION

Various immunization strategies can be employed to mitigate the incidence of dengue fever. There are a number of items that fall into this category.

16.1. IMMUNIZATION ROUTINE

The act of performing standard inoculation protocols entails administering vaccines to individuals residing in regions with established cases of dengue fever, irrespective of their prior exposure to the pathogen. This approach has been developed with the aim of averting the transmission of the virus in the wider community, as well as curtailing the prevailing rate of disease occurrence (Nivarthi et al. 2021).

16.2. TARGETED IMMUNIZATION

The approach of targeted immunization pertains to the administration of vaccinations to individuals who exhibit a heightened susceptibility to contracting acute illnesses, for instance, young children or persons with pre-existing medical ailments, in order to mitigate the risk of life-threatening medical complications. This strategy has been devised with the primary objective of mitigating the morbidity and mortality rates associated with dengue fever (Idris et al.2021).

16.3. TRAVELER IMMUNIZATION

The process of traveler immunization encompasses the administration of vaccines to individuals who are embarking on trips to regions where dengue fever is prevalent. The present strategy has been formulated with the aim of preventing the dissemination of the virus to other geographical regions across the world and curtailing the possibility of virus introduction into non-endemic areas (Idris et al. 2021).

16.4. MASS IMMUNIZATION

Mass immunization entails the administration of vaccines to a considerable number of individuals within a limited timeframe, typically in reaction to an epidemic of dengue fever. The present strategy is stipulated with an aim to curtail the ongoing dissemination of the virus whilst abating the prevalence of the disease cases (Aguiar et al. 2022). Different types of vaccines available against dengue fever are enlisted in Table 1.

17. PRE-CLINICAL AND CLINICAL ASSESSMENT OF DENGUE FEVER VACCINES

17.1. PRE-CLINICAL STUDIES

Prior to testing a vaccine candidate in humans, preclinical studies are conducted. The primary objective of these investigations is to assess the safety and immunogenicity of the vaccine through the use of animal models (Troost and Smit 2020). Preclinical studies generally encompass multiple stages, which include;

17.1.1. IN VITRO STUDIES

In vitro investigations comprise the assessment of the vaccine candidate's potential to elicit an immunological response by conducting tests on cell cultures. The aforementioned experiments can be employed to ascertain the most favorable quantity and composition of the vaccine (Saptawati et al. 2019).

17.1.2. ANIMAL MODEL STUDIES

The procedure of animal model experimentation entails the application of the vaccine candidate on non-human living organisms like mice or primates with the objective of assessing its safety and immunogenic

Table 1: Dengue fever vaccines

Sr. No	Vaccine name	Development stage of vaccine	Type of vaccine
1	Chimeric Yellow Fever- Tetravalent Dengue Vaccine	Licensed	Live Attenuated vaccine
2	*Takeda's Tetravalent Dengue Vaccine*	Licensed	Live Attenuated vaccine
3	Butantan-D Vaccine	Phase – III	Inactivated vaccine
4	Dengvaxia, Qdenga Vaccine	Phase – III	Live Attenuated vaccine
5	MV-D3 Vaccine	Phase – II	Live attenuated
6	DENVax-4 Vaccine	Pre-clinical	Live Attenuated vaccine
7	rDEN4 Delta 30-200, 201	Pre-clinical	Live Attenuated vaccine
8	D2/NS1-M Vaccine	Pre-clinical	Live Attenuated vaccine
9	TV003/TV005 Vaccine	Phase II	Live Attenuated vaccine
10	DENVax-2 Vaccine	Pre-clinical	Live Attenuated vaccine

capacity. The aforementioned investigations may also be employed to deduce the most advantageous course of delivery and regimen for immunization (Kayesh and Tsukiyama-Kohara 2022).

17.1.3. VIRUS TOXICOLOGY STUDIES

The field of toxicology encompasses an appraisal of the safety profile of a vaccine candidate through animal models to ascertain any potential adverse effects. The primary aim of these investigations is to ascertain any potential safety issues prior to administering the vaccine to human subjects (Moquin et al. 2021).

17.1.4. STABILITY STUDIES

Stability assessments comprise the experimental validation of the vaccine candidate's stability across variable parameters, including temperature and humidity conditions. The conduction of these studies holds considerable significance in guaranteeing the caliber and efficacy of the vaccine throughout its duration of preservation and dissemination (Chen et al. 2021).

17.2. PHASE I CLINICAL TRIALS

Phase I trials evaluate vaccine safety and immune response in humans. Phase I trials involve a small group of healthy subjects observed for negative responses to the vaccine (Alagarasu et al. 2021).

17.2.1. POTENTIAL EFFICACY SIGNALS IDENTIFICATION

The safety and immunogenicity of a given intervention. However, investigators may also scrutinize any plausible indications of efficacy. One prospective monitoring approach entails assessing the decrease in disease incidence or severity among vaccinated populations (Zeyaullah et al. 2022).

17.3. PHASE II CLINICAL TRIALS

Phase II clinical trials test vaccine safety, efficacy, and dosage in humans for dengue fever prevention. The objectives of phase II clinical trials include;

17.3.1. FURTHER ASSESSING THE VACCINE SAFETY

Phase II clinical trials are intended to conduct a comprehensive assessment of the safety profile of the vaccine candidate, particularly with regard to rare or critical adverse events that possibly eluded detection in the preliminary.

17.3.2. TO ASSESS THE IMMUNOGENICITY OF VACCINE

The immunogenic potential of a vaccine candidate in a larger and more representative cohort of study participants. One potential method for determining vaccine efficacy is to quantify the concentrations of immunoglobulins and other immunological indicators in the serum of immunized individuals (Waickman et al. 2019).

17.3.3. PROVIDING PRIMARY DATA ON EFFICACY

Phase II clinical trials are purposed to furnish initial insights into the effectiveness of the vaccine candidate for the prevention of dengue fever. This may involve surveillance of the decrease in disease incidence or severity in the population who have received vaccination in comparison.

17.3.4. PURIFYING THE OPTIMAL DOSE AND PROGRAM

Phase II clinical trials encompass the assessment of diverse doses and schedules of the vaccine candidate with the aim of identifying an optimal therapeutic regimen that can exhibit maximal efficacy while concurrently limiting the occurrence of potential adverse effects.

17.4. PHASE III CLINICAL TRIALS

Phase III trials test vaccines on a large scale in people vulnerable to dengue fever to ensure safety, efficacy, and immunogenicity for regulatory approval. The objectives of phase III clinical trials include;

17.4.1. ASSESSING THE SAFETY OF VACCINE

Phase III clinical trials are specifically structured to appraise the safety of prospective vaccine by enrolling a substantial number of individuals within diverse population groups. The process entails vigilance in the surveillance of potential untoward occurrences or adverse reactions linked to the vaccination (Torres-Flores et al. 2020).

17.4.2. MEASURING THE EFFICACY OF VACCINE

The effectiveness of the vaccine candidate for the prevention of dengue fever. This entails the surveillance of any decrease in the frequency or severity of the illness in immunized individuals when compared to those who have not been vaccinated.

17.4.3. APPROVING THE IMMUNOGENICITY OF VACCINE

The confirmation of the immunogenicity of vaccine candidate by administering the investigational product to a vast population of human subjects. The assessment encompasses quantifying the concentrations of antibodies and other immunological indicators present in the peripheral blood of recipients who have been immunized.

17.4.4. CALCULATING THE LONG-TERM SAFETY AND EFFICACY OF VACCINE

Phase III clinical trials may additionally comprise prolonged observation of immunized individuals in order to assess the consistency of their immune response, as well as to oversee the occurrence of exceptional or belated adverse events linked to the vaccination (Torres-Flores et al. 2022).

18. EXPERIMENTS AND LIMITATIONS IN EMERGING DENGUE FEVER VACCINES

18.1. HETEROLOGOUS IMMUNITY AGAINST DENGUE VIRUS

Heterologous immunity recognizes antigens similar to prior exposure. In dengue fever, it impacts the response to different virus serotypes. When infected with dengue virus, the immune system creates specific antibodies to neutralize that serotype. However, antibodies can cross-react with other serotypes of virus, causing a problem with heterologous immunity. Cross-reactive antibodies from previous infections may worsen dengue virus infection, known as antibody-dependent enhancement (ADE), which complicates dengue fever vaccine development. ADE happens when antibodies in infected person's blood can't fully neutralize a different serotype of virus. They may aid virus entry and impact vaccine development for dengue fever. Vaccine must generate immune response to all 4 dengue virus serotypes, with low risk of ADE (Balz et al. 2020).

18.2. PRIVATION THE CONTACTS OF PROTECTION

A key challenge for a dengue fever vaccine is undefined protection measures. The vaccine's ability to trigger an immune response is crucial for its effectiveness. No prevention method currently exists for dengue fever. The immune response to dengue virus involves antibodies and T cells. Notably, protection against one serotype does not guarantee protection against others, hindering dengue fever vaccine evaluation. It's challenging to determine whether a vaccine protects against or enhances immune response for a disease like dengue fever. Researchers are investigating possible protective factors like antibodies, T cells, and genes. More research is needed to confirm and improve protection measurement methods (John et al. 2019).

18.3. CONCERNS OF VACCINE SAFETY

Vaccine safety is critical for dengue fever vaccines. There are risks that need careful consideration. Dengue fever vaccines may cause severe disease due to ADE. Vaccines must be carefully designed and tested to reduce this risk. Dengue fever vaccines may pose safety concerns due to potential adverse events like fever, headache, and injection site reactions reported by some participants in clinical trials. Monitor dengue fever vaccine safety and theoretical harm risk to non-infected individuals. Incomplete protection from the dengue virus vaccine could potentially increase severe disease risk in subsequent infections, but this is yet to be observed in clinical trials (Wilder-Smith et al. 2019).

18.4. DEVELOPED AND DISTRIBUTION EXPERIMENTS

Production of dengue fever vaccine is critical, especially for large-scale distribution to effectively protect against all four serotypes of the virus. Vaccine production is costly and complex, requiring multiple components. Additionally, the cold chain for storage and transport adds further difficulty. Vaccines require refrigeration or freezing to stay stable, but maintaining the cold chain can be difficult. Researchers and manufacturers seek new ways to produce and distribute vaccines; adjuvants may be key to making production cheaper and more scalable. Manufacturers may use drones to deliver vaccines to remote areas (Gaobots et al. 2022).

19. FUTURE GUIDELINES FOR DENGUE FEVER VACCINE IMPROVEMENT

19.1. NOVEL VACCINE APPLICANTS

Multiple novel vaccine candidates for dengue fever are currently undergoing diverse phases of development and clinical experimentation. The aforementioned vaccine attained regulatory approval as the foremost immunization against dengue fever. This vaccine is a live attenuated formula specifically formulated to elicit a protective response against all four serotypes of the virus. Clinical investigations have demonstrated the efficacy of vaccine against severe cases of dengue fever; however, its potential in mitigating milder forms of the disease remains relatively uncertain.

19.2. MODIFIED VACCINES

Custom vaccines adjust to an individual's genetics and pathogen exposure, creating better immunity for non-traditional vaccine recipients. Dengue fever vaccines can be personalized according to immunity or gene tendencies. UCLA is creating a dengue fever vaccine personalized for severe illness by targeting specific virus regions. This method can produce individualized vaccines for illnesses like dengue fever, which may transform vaccination methods with precise remedies. Personalized vaccines face challenges including accurate prediction of immune response and efficient manufacturing (Meganck 2021).

19.3. IMPLEMENTING THE STRATEGIES OF VACCINE

The implementation of efficacious vaccination strategies for the deployment of dengue fever vaccines represents a pivotal element in the prosperous outcome of any immunization initiative.

19.4. TARGET POPULATIONS AT HIGH RISK

Prioritizing to target the populations that are highly susceptible to contracting dengue fever is of utmost importance. This encompasses populations residing in regions that are endemic or currently undergoing an outbreak.

19.5. PARTICIPATE VACCINES INTO ROUTINE VACCINATION PLANS

The incorporation of the dengue fever vaccine within mainstream immunization programs has the potential to enhance its accessibility to all individuals necessitating its administration.

19.6. MAIN PUBLIC EDUCATION AND AWARENESS MOVEMENTS

The implementation of public education and awareness campaigns holds significance in the enhancement of disease awareness, promotion of vaccination benefits, and resolution of any vaccine hesitancy queries.

19.7. MATE WITH LOCAL HEALTHCARE SUPPLIERS

They have the capacity to furnish continual surveillance and assessment pertaining to the efficacy of vaccine.

19.8. CONFIRM ADEQUATE VACCINE SOURCE

The maintenance of an adequate supply of vaccines stands as a crucial determinant of the success of any vaccination program. The aforementioned plan pertains to the enhancement of proficient manufacturing and distribution networks.

19.9. DEPORTMENT POST-LICENSURE INVESTIGATION

It is imperative to carry out post-licensure surveillance of vaccination for the purpose of monitoring both its safety and efficacy. This approach can facilitate the interpretation of unfavorable occurrences and enable the evaluation of the efficacy of vaccine in mitigating the impact of dengue fever.

19.10. COOPERATE WITH INTERNATIONAL ADMINISTRATIONS

The facilitation of partnerships with global entities, including the World Health Organization (WHO), has the capacity to furnish essential assets and specialized knowledge in order to bolster the creation and implementation of a vaccination program (Meganck 2021).

20. CONCLUSION

Dengue fever is a significant public health concern in tropical and subtropical areas. The virus has four serotypes, and infection with one does not provide immunity for the other three. Dengue virus is mostly transmitted by infected mosquitoes, but there are other ways too. A vaccine is hard to develop due to its complex immune response. Various vaccine types have been developed, including live attenuated, inactivated, subunit, chimeric, and DNA vaccines. Dengue fever cases are expected to keep rising due to urbanization, globalization, and climate change. A vaccine could help stop the disease and save lives. Vaccines can ease dengue fever's financial burden by lowering healthcare costs and productivity losses, thus promoting economic reduction. However, creating and executing vaccines for dengue pose significant challenges. Vaccine safety, lack of protection indicators, manufacturing and distribution difficulties, and potential heterologous immunity hazards all need attention. To improve dengue vaccine effectiveness, focus on research, targeted vaccination, and global accessibility. Prioritize vaccine production and dissemination for public health initiatives.

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Potential Treatment of Anthrax Infection

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ABSTRACT

Anthrax, which is caused by the bacteria Bacillus anthracis, presents a major risk to the health of both humans and animals. Anthrax requires a thorough and quick treatment plan due to its ability to be transmitted through different means such as breathing it in, consuming contaminated food, or direct contact with the skin. The main approach is to use antibiotics like ciprofloxacin, levofloxacin, and doxycycline to eliminate the bacteria. The length of antibiotic treatment depends on the type of anthrax, with inhalation cases typically needing a longer course of treatment. Antitoxins are essential in minimizing the harmful impact of anthrax toxins, in addition to antibiotics. Anthrax immune globulin (AIG) when combined with antibiotics, works to deactivate toxins, minimizing tissue damage and improving the overall effectiveness of the treatment. Vaccination plays a vital role in providing both prevention and treatment benefits. It is advised to give regular vaccinations to people who are at risk of being exposed to anthrax. If someone has been exposed, they can start taking the anthrax vaccine and antibiotics to prevent the disease from developing. Additionally, patients with anthrax infection will receive supportive care such as pain relief, help with breathing, and fluids to manage symptoms and complications. It is crucial to isolate infected individuals and implement strict infection control measures in order to control the spread of the disease. It is essential to closely monitor the patient's reaction to treatment using both clinical and laboratory evaluations, in order to make necessary adjustments to the therapeutic methods. The timely identification and treatment of suspected anthrax cases are crucial, highlighting the importance of prompt medical intervention. Continued care guarantees the infection is fully resolved, reducing the chance of any additional problems. Continued research into new ways of treating and preventing anthrax is essential as infectious diseases change, in order to improve our ability to fight it and protect public health.

Keyword: Anthrax; Bacillus anthracis; Antibiotics; Antitoxins; Vaccination

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1. INTRODUCTION

1.1. OVERVIEW OF ANTHRAX AS A DEADLY DISEASE

Anthrax, an exceedingly virulent contagious ailment, is attributed to the pathogenic bacterium *Bacillus anthracis*, constituting a longstanding menace to the well-being of both human and animal populations throughout history. Anthrax is an exceptionally virulent pathogen, elucidating its diverse modes of transmission and the multiple clinical manifestations it can manifest in both humans and animals (Hiko and Malicha 2016).

1.2. IMPORTANCE OF ANTHRAX TREATMENT DEVELOPMENT

Anthrax presents a significant public health issue given its ability to induce severe illness and mortality in both human and animal populations. In addition, the utilization of Anthrax as a bioterrorism instrument in previous incidents has established its significance as a subject of utmost national security concern (Goel 2015). The development of efficacious therapeutic interventions for Anthrax assumes significant significance in safeguarding the populace from potential occurrences and acts of bioterrorism. The implementation of a timely and suitable medical intervention has the potential to considerably mitigate mortality rates and enhance the overall well-being of patients. Hence, the focal objective of this chapter is to underscore the pressing nature of continual research endeavors in addressing the threat of Anthrax and the imperative for novel therapeutic approaches (Bouzianas 2009).

1.3. REASON AND SCOPE OF THE CHAPTER

The objective of this chapter is to offer a comprehensive exposition on possible therapeutic approaches for mitigating Anthrax infection. This paper will explore contemporary treatment strategies, their inherent drawbacks, and the increasing prevalence of antimicrobial resistance. Furthermore, this chapter will analyze the most recent advancements in scientific research pertaining to Anthrax and assess the potential future therapies that exhibit promising prospects in effectively combatting this ailment The primary emphasis will encompass conventional strategies encompassing antibiotics and vaccines, alongside innovative therapeutic modalities spanning gene-based therapies, nanotechnology-based treatments, and immunomodulatory approaches. Moreover, this chapter will elucidate the dynamics of host-pathogen interactions and examine the pivotal role of the immune system in the context of Anthrax infection. Comprehending these intricate interactions holds great significance in the development of specialized therapeutic interventions capable of disrupting the virulence mechanisms employed by the pathogen, while simultaneously bolstering the host's defense mechanisms (Uludag 2021).

2. *BACILLUS ANTHRACIS*: UNDERSTANDING THE PATHOGEN

2.1. FOUNDATION ON *BACILLUS ANTHRACIS*, THE CAUSATIVE OPERATOR OF *BACILLUS ANTHRACIS*

Bacillus anthracis, a bacterium with a gram-positive classification and a rod-shaped morphology, represents the pathogenic etiological agent responsible for the occurrence of Anthrax. The identification of this phenomenon can be attributed to the renowned German physician and scientist, Robert Koch, in the year 1876. *Bacillus anthracis* possesses the distinctive capacity to produce exceedingly durable spores, which have the ability to endure severe environmental conditions over

prolonged durations (Hugh-Jones and Blackburn 2009). The spores function as the principal means of dissemination for anthrax. The bacterial species is frequently encountered in terrestrial ecosystems, primarily within soil, and exhibits a capacity to affect a diverse array of fauna, specifically herbivorous species such as cattle, sheep, goats, and deer. When infected animals become dead and undergo decomposition, they emit Anthrax spores into the surroundings, potentially resulting in subsequent infections of other animals or humans who come into contact with tainted soil, animal derivatives, or cadavers (Carlson et al. 2018).

2.2. DISTINCTIVE SHAPES OF *BACILLUS ANTHRACIS* DISEASE (CUTANEOUS, INWARD BREATH, GASTROINTESTINAL)

Anthrax can present in three ways depending on how spores enter the body. Cutaneous anthrax occurs when spores come into contact with skin imperfections such as cuts, scrapes, or bug bites. Spores enter the body through orifices, causing infection. Cutaneous Anthrax is a skin condition that starts as an itchy bump and develops into a painless ulcer with a black scab. Untreated infection may lead to septicemia. However, the mortality rate for this type of Anthrax is low compared to other forms of the disease (Bower et al. 2015). Pulmonary Anthrax is the deadliest type of the disease. Inhalation/ pulmonary anthrax are caused by inhaling spores into the lungs, usually from contaminated dust or aerosols. The spores are engulfed by macrophages, leading to tissue damage and respiratory failure. The early symptoms closely resemble influenza, making it difficult to identify the illness quickly. As the ailment gets worse, people may experience high body temperature, severe breathing issues, and circulatory failure. Inhaling anthrax without prompt treatment shows high fatality rate (Thomas 2013). Gastrointestinal anthrax is rarely seen and occurs after consuming tainted meat infected with spores. After ingestion, spores germinate in the gastrointestinal tract, producing toxins that cause severe gastrointestinal symptoms. Symptoms include severe abdominal pain, nausea, vomiting, and bloody diarrhea. Gastrointestinal anthrax causes septicemia and has a high fatality rate unless promptly identified and treated (Coggeshall et al. 2013).

2.3. ANTHRAX INFECTION: PATHOGENESIS AND MECHANISMS

The pathogenesis of anthrax encompasses a cascade of mechanisms that enable bacterial colonization and the subsequent production of harmful toxins. When anthrax spores infiltrate the human body via any of the aforementioned routes, they meet with conducive circumstances for their activation and proliferation (Al-Obaidi and Desa 2018). The spores undergo phagocytosis by macrophages subsequent to entering the host and they undergo a transformative process, transitioning into vegetative bacteria. The vegetative cells of *Bacillus anthracis* undergo proliferation and subsequently secrete toxins, constituting vital virulence factors of the species. *Bacillus anthracis*, commonly known as anthrax, is a gram-positive bacterium that causes a severe and potentially fatal infectious disease in humans and animals (Nielsen-LeRoux et al. 2012). *Bacillus anthracis*, the causative agent of anthrax, is known to produce toxin which is attributed to the induction of localized swelling and accumulation of fluid called edema. The lethal toxin elicits cellular death and leads to significant tissue harm. The protective antigen serves to facilitate the internalization of edema and lethal toxins into the host cells. These toxic substances disrupt the normal functioning of the immune response and induce significant harm to the surrounding tissues, consequently worsening the overall severity of the associated pathological condition. Furthermore, the toxins are capable of disrupting the host's capacity to mount a proficient immune response, thereby enabling the bacterium to elude the immune system and initiate a systemic infection (Yang et al. 2021).

2.4. CLINICAL SYMPTOMS AND DISEASE PROGRESSION

The clinical manifestations of Anthrax exhibit variability, contingent upon the specific type of infection. Commencing symptoms encompass the emergence of a painless, pruritic papule that subsequently progresses into an ulcer featuring a black, necrotic core. Lymphadenopathy may manifest in close proximity to the ulcerative lesion. The affliction typically does not result in mortality when expeditiously addressed with suitable antibiotics (Bower et al. 2015). The main signs are similar to flu symptoms: high body temperature, general discomfort, breathing problems, and muscle pain. As the disease progresses, severe respiratory problems and instability may occur. Without interventions, inhalational Anthrax has a high fatality rate. Initial symptoms include severe gastrointestinal distress, such as abdominal pain, vomiting, and bloody diarrhea. The illness can quickly progress to septicemia, leading to shock and high fatality rates if not treated promptly (Li et al. 2017). In every manifestation of Anthrax infection, prompt identification and therapeutic intervention play a vital role in enhancing patient prognosis. Antibiotics such as ciprofloxacin, doxycycline, and penicillin have become widely utilized in the therapeutic management of Anthrax. The manifestation of antibiotic-resistant strains underscores the significance of cultivating alternative treatment modalities, encompassing vaccines and innovative therapeutic interventions, in order to address this issue effectively (Doganay et al. 2023).

3. STRATEGIES OF CURRENT TREATMENT

3.1. ANTIBIOTICS FOR ANTHRAX TREATMENT

Antibiotics stand as the fundamental pillar for the treatment of Anthrax, demonstrating their efficacy in effectively handling the disease, particularly through timely administration at the onset of infection. The selection of appropriate antibiotics is contingent upon the type and severity of the anthrax infection. Frequently employed antibiotics encompass ciprofloxacin, doxycycline, and penicillin. The pharmaceutical compounds in question are specifically designed to target the actively proliferating bacterial cells, with the primary objective of eradicating the pathogenic microorganisms before they have the opportunity to produce life-threatening toxins (Roche et al. 2021). In cutaneous Anthrax, antibiotics like ciprofloxacin or doxycycline are given orally for 7 to 10 days. Compared to other types of anthrax, Inhalation anthrax treatment is more challenging due to its rapid progression. In this case, antibiotics like ciprofloxacin or doxycycline are used with other agents like clindamycin or rifampin to enhance bacteria elimination. Management of gastrointestinal anthrax requires the use of IV antibiotics (ciprofloxacin, doxycycline, or penicillin) for at least 14 days or more (Kayabas et al. 2012).

3.2. LIMITATIONS & CHALLENGES OF CURRENT TREATMENTS

The utilization of antibiotics, while undeniably efficacious, is accompanied by an array of constraints and difficulties. Inhalation Anthrax, particularly, may exhibit nonspecific symptoms, resulting in the potential delay of diagnosis and commencement of treatment. The postponement of treatment can result in a less favorable prognosis (Omidfar and Daneshpour 2015). The emergence of antibiotic-resistant strains of *Bacillus anthracis* is a subject of considerable concern. The excessive or improper utilization of antibiotics has the potential to exacerbate the emergence of resistant bacterial strains, thereby diminishing the efficacy of certain antibiotics in addressing the medical condition known as Anthrax. The diagnosis and treatment of Anthrax in regions characterized by restricted healthcare facilities and diagnostic capabilities pose notable challenges, potentially resulting in increased mortality rates (Rather et al. 2012).

3.3. ANTIMICROBIAL RESISTANCE AND IMPLICATIONS

The rise of antimicrobial resistance in Anthrax is concerning and could hamper treatment. Bacterial evolution leading to antibiotic resistance reduces treatment options. Consistent monitoring of Anthrax strains is necessary to identify resistance pattern evolution. The knowledge helps adjust treatment protocols. Extensive investigation and advancement of antibacterial agents or alternative therapies are crucial in combating resistant strains efficiently (Fair and Tor 2014).

3.4. SUPPORTIVE THERAPIES IN ANTHRAX MANAGEMENT

Supportive therapies are crucial in managing Anthrax and its symptoms. These therapies are used with antibiotics to improve patient outcomes. IV fluid is crucial for severe Anthrax patients with inhalation or GI symptoms to prevent dehydration and shock. Patients of inhalation anthrax may need mechanical ventilation if their health declines (Green et al. 2019). To prevent secondary infections, proper wound care and bandaging are crucial for managing cutaneous Anthrax. Anthrax can cause distress, especially when it appears on the skin. Administering drugs effectively to reduce pain is essential for improving patient comfort. Proper nutrition is crucial for patients with gastrointestinal Anthrax, who may face severe digestive problems and struggle to eat normally (Begelman 2018).

4. DEVELOPING THERAPEUTIC METHODS

4.1. NOVEL ANTI-MICROBIAL AND ANTIMICROBIAL SPECIALISTS

The rise of antibiotic-resistant *Bacillus anthracis* has prompted the search for new antibiotics to fight Anthrax. Researchers are studying new types of antibiotics or altering them to boost effectiveness against infections. Combining different antibiotics with complementary mechanisms can enhance bacteria elimination and reduce resistance emergence. This study aims to determine the effectiveness of approved drugs used to treat infectious diseases in combating Anthrax. The study of antimicrobial peptides against *Bacillus anthracis* is actively researched (Lu et al. 2020).

4.2. IMMUNIZATIONS AND IMMUNOTHERAPY FOR *BACILLUS ANTHRACIS* AVOIDANCE AND TREATMENT

Vaccines are highly effective in preventing anthrax infection. The Anthrax vaccine contains protective antigen, an important component of *Bacillus*. anthracis toxins studied extensively. The vaccine triggers an immune response that generates antibodies to protect against anthrax toxins and lessen the severity of infection (Hajj Hussein et al. 2015). Researchers are now exploring new immunotherapy methods in addition to traditional vaccinations. These vaccines use inactivated Anthrax toxins to stimulate the immune system and produce protective antibodies. Genetic engineering can generate protective antigens that act as vaccines and elicit an immune response. Implementing pre-existing antibodies against anthrax toxins for prompt protection in high-risk situations, like after exposure to the pathogen (Coggeshall et al. 2013).

4.3. TARGETING VIRULENCE FACTORS AND TOXIN-NEUTRALIZING TECHNIQUES

An alternative strategy for Anthrax infection is focused on *Bacillus anthracis* virulence factors. Researchers have studied strategies to reduce anthracis' harmful effects, including weakening its toxins

in order to minimize harm to the host. Scientists are studying ways to counteract anthrax toxins. The goal of this study is to develop antibodies that neutralize anthrax toxins and prevent them from binding to host cells and causing harm. This study aims to identify molecules that disrupt Anthrax toxins, reducing their toxicity (Carlson et al. 2018).

4.4. NANOTECH THERAPIES FOR ANTHRAX INFECTION

Nanotech offers potential for advancing Anthrax treatment. Nanoparticles have the potential to target and deliver therapies to infected cells, enhancing treatment effectiveness while reducing non-specific interactions. Various nanotech approaches have been developed. Using nanoparticles to incorporate antibiotics or other therapeutic agents has shown potential in enhancing drug stability, increasing bioavailability, and improving drug delivery precision to the infection site. The current research involves synthesizing and characterizing nanoparticles that can selectively associate with anthrax toxins and inhibit their harmful activity. Developing nanoscale sensors to quickly and accurately detect anthrax spores or toxins, aids in early identification and prompt intervention (O'Brien et al. 2021).

5. HOST-PATHOGEN INTELLIGENT AND RESISTANT REACTIONS

5.1. IMMUNE RESPONSE TO ANTHRAX INFECTION

When *Bacillus*. anthracis spores enter the body, the immune system plays a key role in recognizing and responding to the pathogen. The immune response to anthrax infection includes innate and adaptive mechanisms. The innate immune system is crucial in the early response to anthrax. Immune cells, called macrophages and neutrophils, can phagocytose invading spores. *Bacillus*. anthracis spores evade phagocytes and spread. As infection progresses, immune response activates. APCs process Anthrax antigens to induce T cell activation and antibody production. The adaptive immune system's ability to modulate immune responses is crucial in regulating bacterial dissemination and infection eradication (Hess and Jewell 2020).

5.2. STRATEGIES OF *BACILLUS ANTHRACIS* TO ESCAPE IMMUNE SYSTEM

Bacillus anthracis may escape the immune system of the host. The mechanism of evasion of immune system includes a subset. *Bacillus anthracis* produces poly-D-glutamic acid, encapsulating the bacteria. The generation of capsule stops the process of phagocytosis via immune cells, thus making the bacterium capable to avoid destruction. The bacterium toxins disturb the response of host immune system. The released toxins disturb signaling of immune cell, thus damaging their capability to produce an effective immune reaction against bacterium (Lopes Fischer et al. 2020).

5.3. DETERMINING THE INTERACTIONS BETWEEN HOST-PATHOGEN FOR TARGET SPECIFIC TREATMENT

It is highly important to understand the highly complicated interaction of the bacterium and the host for developing therapy with target specificity. By understanding the process of immune response, we may enhance its ability to eliminate the infection. Immunomodulatory agents can boost innate and adaptive immune responses, enhancing their ability to fight Anthrax. Targeting Anthrax toxins is a way to lessen their harmful effects on host cells. Therapeutic interventions can reduce Anthrax severity and improve prognosis. Vaccines can target evasion strategies used by *Bacillus*. anthrax enhances host's ability to

detect and eliminate the pathogen. Using immune-targeted therapies alongside antibiotics or other modalities shows promise for enhancing treatment outcomes (Perera et al. 2012).

6. ANIMAL MODELS & CLINICAL TRIALS

6.1. IMPORTANCE OF ANIMAL MODELS IN ANTHRAX RESEARCH

Animal models are key for anthrax research, shedding light on disease development, evaluating therapies, and assessing vaccine efficacy. The study of anthrax in humans is constrained by ethics and low disease occurrence, but animal models allow systematic investigation of Anthrax infection. Animal models help researchers understand how *Bacillus anthracis* infects various host tissues and organs, aiding in the comprehension of pathogenesis. This knowledge is crucial for therapy and interventions. Animal models are crucial for preclinical assessment of new antibiotics, immunotherapies, and treatments prior to human testing. The preclinical phase is crucial for risk identification and safety evaluation. Animal models are crucial for anthrax vaccine testing. The data shows how the vaccine generates effective immune responses against the pathogen (Esteves et al. 2018).

6.2. PRECLINICAL STUDY OVERVIEW

Animal models contributed to anthrax research. Various animals, like mice, guinea pigs, rabbits, and primates, have been used by researchers to study anthrax and test therapies. *Bacillus*. anthracis spores enter the host, germinate, spread, and cause disease. These investigations uncovered valuable findings on toxins, bacteria, and host responses in anthrax progression. Preclinical research studied the effectiveness of antibiotics, peptides, and novel therapies in managing anthrax in animal models. These studies have led to potential treatment alternatives, which need further investigation in clinical trials. Animal models played a key role in evaluating Anthrax vaccine efficacy. The data on neutralizing antibodies and immune responses has helped vaccine development (Twenhafel 2010).

7. COMBINATION TREATMENTS AND MULTI-MODAL APPROACHES

7.1. COMBINATION THERAPIES IN ANTHRAX TREATMENT

Combination therapies entail the concurrent or sequential administration of multiple therapeutic modalities in order to combat Anthrax infection. The justification underlying the adoption of combination therapies in the treatment of anthrax is to augment the effectiveness of treatment, surmount resistance, and focus on various facets of the infection. The pathogenic mechanisms implicated in anthrax, including toxin synthesis and immune evasive tactics, exhibit a multifaceted nature. Researchers and clinicians endeavor to comprehensively address the intricacies by integrating diverse therapeutic approaches (Bouceiro Mendes et al. 2022).

7.2. CHALLENGES AND BENEFITS OF UTILIZING DIFFERENT RESTORATIVE MODALITIES

The co-administration of multiple drugs may precipitate drug interactions, resulting in compromised therapeutic efficacy or heightened potential for adverse effects. Establishing the suitable dosage and regimen for individual therapeutic modalities can present difficulties, given that specific medications have the potential to interact or impede one another. The concurrent administration of multiple

therapies may heighten the potential for unfavorable outcomes or complications, necessitating meticulous surveillance of patients (Bellosta and Corsini 2012).

7.3. CASES OF EFFECTIVE COMBINATION TREATMENTS

Extensive investigation has studied the use of diverse antibiotic combos to fight anthrax. Enhanced therapeutic effectiveness in severe inhalation anthrax can be achieved with combined ciprofloxacin and clindamycin treatment, rather than ciprofloxacin alone. The combined use of immunotherapies and antibiotics has shown promising results in animal experiments for anthrax toxin neutralization. Using vaccines and antibiotics together after possible anthrax exposure is a viable way to protect individuals (Murray et al. 2021). Vaccines activate and prepare the immune system, producing antibodies and memory cells for long-term immunity against pathogens. Antibiotics shield the body from infection while the vaccine builds immune protection. The investigation of nanoparticles as carriers of antibiotics aims to enhance drug delivery to the infected area and improve treatment effectiveness. In recent studies, scholars have investigated the combined impact of different antitoxin agents, particularly monoclonal antibodies that target various anthrax toxins. The aim is to improve the ability to neutralize these harmful substances (Diamant et al. 2015).

8. POSSIBLE FUTURE THERAPIES

8.1. GENE-EDITING AND GENE-BASED TREATMENTS

Gene-editing and gene therapies show promise for treating anthrax. With gene-editing technologies like CRISPR-Cas9, researchers can now target specific genes in *Bacillus anthracis* or manipulate host genes to strengthen the immune response to this pathogen. Bacteriophages have multiple potential applications as viral agents that target and eliminate bacteria. Scientists are studying bacteriophages that target *Bacillus anthracis* as a potential therapy. Gene-editing can be used to manipulate important virulence genes in B. Therefore, this tech can be used to disable or change said genes. *Bacillus anthracis* with reduced virulence, limiting its pathogenicity and toxin production. Gene therapies have potential to boost host immune response against anthrax. Researchers aim to boost the body's ability to fight infection by enhancing immune-related gene expression or introducing specific immune-stimulating genes (Arabi et al. 2022).

8.2. ADVANCES IN ANTHRAX TREATMENT PERSONALIZATION

Personalized medicine customizes treatment based on genetics, health records, and other factors. In anthrax treatment, personalized medicine improves outcomes and reduces side effects. Potential applications include genetic screening to identify variations that impact anthrax susceptibility or tailored therapy response. This info can shape treatment decisions. Personalized treatment plans could be made by considering an individual's genetic profile and other clinical factors, including suitable antibiotics, dosages, and treatment duration. Personalized vaccine approaches can enhance efficacy and reduce adverse reactions by customizing based on individual immune responses (Bayer and Galea 2018).

8.3. IMMUNOMODULATION AND POTENTIAL

The implementation of immunomodulatory approaches encompasses the utilization of agents capable of modulating the immune response in order to augment its efficacy in counteracting anthrax. Several

immunomodulatory strategies have been identified as potential means to enhance the immune system's ability to combat anthrax infection. One such strategy involves the administration of specific cytokines, which act as signaling molecules responsible for regulating the immune response. By introducing these cytokines, it is possible to strengthen the immune system's capacity to defend against Anthrax infection. TLR agonists refer to chemical compounds capable of activating immune cells, thereby bolstering the inherent immune response of the host organism against the pathogenic agent known as Anthrax. These agents selectively target immune checkpoint molecules that modulate immune responses, enhancing the ability of immune cells to launch a more vigorous attack against cells infected with the bacterium *Bacillus anthracis*, also known as anthrax. The incorporation of adjuvants into vaccines has been shown to augment the immune response elicited by the vaccine antigens, thereby resulting in enhanced defense against anthrax infection (Marquardt and Li 2018).

9. BIODEFENSE AND PREPARATION

9.1. *BACILLUS ANTHRACIS* AS A BIOTERRORISM DANGER

Anthrax holds a prominent place among bioterrorism dangers as a result of its capacity to inflict widespread casualties, induce panic, and disrupt societal order. The demonstration of employing anthrax spores as a biological weapon occurred in 2001 when letters, containing a powdered form of these spores, were dispatched to media entities and government authorities in the United States. Consequently, this event led to multiple casualties and a substantial number of individuals being infected. This event emphasized the necessity of implementing substantial and effective biodefense strategies in order to mitigate the risks associated with anthrax and other potential bioterrorism hazards (Jansen et al. 2014).

9.2. ANTHRAX OUTBREAK READINESS

Preparedness strategies for Anthrax outbreaks require a comprehensive and coordinated approach, including prevention, detection, and response. An imperative approach monitors anthrax outbreaks in humans and animals. Such systems would help detect outbreaks earlier and expedite the response. Educating people about symptoms of anthrax, transmission, and infection control can raise awareness and encourage early reporting. Improving lab diagnosis for anthrax is important for prompt verification and appropriate interventions. Administering vaccines to high-risk populations, like military personnel and lab workers, can provide pre-exposure prophylaxis and enhance their readiness. Implementing emergency response strategies at all governance levels can ensure efficient action during an Anthrax epidemic. Preserving antibiotics and other medical supplies ensures quick access in emergencies (Ghai et al. 2022).

9.3. COLLABORATIVE ENDEAVORS IN BIODEFENSE INQUIRE ABOUT AND IMPROVEMENT

In biodefense research and development, the importance of collaborative endeavors cannot be overstated, particularly when addressing intricate issues such as anthrax preparedness. The act of collaborating with foreign nations and international organizations facilitates the exchange of information, surveillance efforts, and coordination of responses when confronted with global health hazards such as Anthrax. The involvement of the private sector in biodefense research and development has the potential to harness expertise, resources, and innovative approaches, thereby

expediting the advancement of novel therapies and countermeasures. Promoting synergy among scientists, public health experts, clinicians, veterinarians, and other relevant stakeholders embodies a promising avenue towards attaining an encompassing comprehension of Anthrax and its subsequent administration. The prompt highlights the significance of timely dissemination of research findings, data, and best practices among scientists and institutions in bolstering collective knowledge and enhancing preparedness strategies. Collaborative endeavors may concentrate on initiating training initiatives geared towards enhancing workforce capability in anthrax diagnosis, surveillance, and response. Through collaboration, governments, organizations, and researchers have the potential to enhance global biodefense capabilities and readiness, encompassing not only anthrax but various emerging infectious diseases and bioterrorism hazards. The significance of preparedness and collaboration is pivotal in adopting a proactive stance aimed at protecting public health and bolstering national security (Bidwell and Bhatt 2016).

10. MORAL CONTEMPLATIONS AND OPEN WELLBEING SUGGESTIONS

10.1. MORAL CHALLENGES IN *BACILLUS ANTHRACIS* INQUIRE ABOUT AND CLINICAL TRIALS

When conducting research or clinical trials on anthrax, it is imperative for researchers to meticulously evaluate the associated risks and potential advantages for the individuals participating in such endeavors. It is imperative to strike a careful balance between the prospective advantages of progress in understanding and developing efficacious interventions, and the potential hazards faced by those involved. The principle of informed consent holds paramount importance in the realm of research and clinical trials due to its ethical underpinnings. It is imperative to guarantee the comprehensive comprehension of participants regarding the essence of the study, the potential hazards associated with it, and their entitlement to voluntary cessation. Ethical considerations are pertinent when assessing the utilization of animal models in the context of anthrax research. It is imperative for researchers to adopt measures aimed at reducing the quantity of animals utilized and guaranteeing their well-being throughout the entirety of the study. Ethical considerations may arise pertaining to the fair and equal availability of treatments for anthrax, particularly in situations wherein resources are scarce or particular areas are experiencing outbreaks. The inclusion of vulnerable populations in accessing potentially life-saving therapies is of utmost importance (Bauchner et al. 2020).

10.2. ADJUSTING OPEN WELLBEING NEEDS AND PERSON RIGHTS

Public health authorities bear the responsibility of safeguarding the populace against potential infectious diseases such as anthrax. The containment of disease transmission may encompass the enforcement of strategies such as quarantine, isolation, or the administration of vaccines in order to mitigate its dissemination. The moral challenge of keeping up a fragile adjusts between open wellbeing needs and person rights requires cautious consideration. The principles of individual autonomy, privacy, and freedom must be respected while prioritizing public health measures for the betterment of society. Preservation of the privacy and confidentiality of those affected is of paramount importance in the management of anthrax outbreaks, as it serves as a crucial measure to mitigate the potential for stigmatization and discrimination. During outbreaks of anthrax or incidents of bioterrorism, ethical complexities may arise in the process of allocating resources. The prioritization of resource allocation in order to optimize positive outcomes while minimizing negative consequences poses a noteworthy challenge (Bloom and Cadarette 2019).

10.3. ARRANGEMENT SUGGESTIONS AND DECISION-MAKING IN *BACILLUS ANTHRACIS* TREATMENT IMPROVEMENT

The development of Anthrax treatment necessitates the provision of robust regulatory frameworks and oversight to substantiate ethical decision-making, thereby upholding the protection of human subjects and the public. In the context of public health crises, such as instances of anthrax outbreaks or occurrences of bioterrorism, policymakers may find it necessary to deliberate on the option of emergency use of authorization for novel treatments, in order to expedite their access and distribution, all while ensuring the implementation of suitable safety protocols. The ethical dimensions surrounding the development of Anthrax treatments transcend national boundaries. In order to ensure fair access to treatments and efficient responses to potential outbreaks, it is imperative to establish global collaboration and harmonize policies. Transparency in decision-making processes should be accorded utmost priority by policymakers, who bear the responsibility of ensuring that public health decisions are grounded in robust evidence, guided by ethical principles, and driven by unwavering commitment to the larger welfare of the public (Tin et al. 2022).

11. CONCLUSION

In this chapter, we discussed anthrax treatment, anthrax as a deadly infection and the need for effective treatments due to bioterrorism. We researched *Bacillus anthracis* and anthrax infections cutaneous, inhalation, and gastrointestinal. The disease was discussed. The chapter covered anthrax treatment, antibiotics, and antimicrobial resistance challenges. Supportive therapies vital for anthrax management. The discussion covered new therapies: antibiotics, vaccines, toxin-neutralization, and nanotechnology. Improving anthrax treatment. We studied anthrax host-pathogen interactions & immune responses for therapy development. Smart research focuses on the treatment of anthrax and the potential of personalized medicine. Future research on anthrax treatment: exploring novel approaches to combat resistance and enhance outcomes. Enhancing anthrax vaccines focuses on efficacy and safety. Gene editing and therapies could be effective against anthrax. Surveillance and preparedness for anthrax outbreaks are vital for quick detection and response. Despite anthrax's threat, there is hope for improved survival rates in the future. Advancements in anthrax treatment research provide hope for challenges. Through therapy research, anthrax understanding, and global collaboration, hope for better anthrax management exists. Scientific progress lessens anthrax risks, fostering a safer future.

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Epidemiological Trends of Lymphochoriomeningitis Virus Infection

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ABSTRACT

Lymphocytic choriomeningitis virus (LCMV) a member of family Arenaviridae genus Mammarenavirus, discovered in 1933 from a patient with meningoencephalitis, persists as a significant zoonotic threat, primarily harbored by house mice and linked to aseptic meningitis in humans. Its global impact ranges from mild flu-like symptoms to severe neurological complications, particularly perilous in immunocompromised individuals and pregnant women, leading to fetal abnormalities and mortality. Human transmission primarily occurs through contact with rodents or exposure to contaminated aerosols, highlighting house mice (Mus musculus), especially persistently infected ones, as key agents in human infections. M. musculus and Mus domesticus are the natural and reservoir host of LCMV virus. Except for vertical transmission from infected pregnant women to foetus and organ donation, there is no evidence of human-to-human transfer. The LCMV targets the endothelial and lymphatic cells and replicate there or settle down in lymphatic tissues like spleen or lymph nodes and further replicate there leading to viremia to various organs. In the 1950s virus has been detected about 8% of the patients suffering with neuroinvasive disease. Diagnosis remains challenging due to limited diagnostic tools, Serological tests like IFA and EIA target immunoglobulin M and G, RT-PCR, and viral isolation being employed. Therapeutic options, notably ribavirin, show promise but remain limited, while ongoing vaccine research investigates candidates like reverse genetically altered recombinant LCMV and replicating LCMV-based vectors. LCMV's global prevalence, though constrained by diagnostic limitations, underscores its continued public health impact, necessitating sustained research into diagnostics, treatments, and vaccines to mitigate its multifaceted threats.

Keywords: Choriomeningitis; Aseptic Meningitis; Meningioencephalitis; Arenavirus; Encephalitis

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1. INTRODUCTION

Lymphocytic choriomeningitis virus (LCMV) was the first time isolated by Lillie and Armstrong in 1933 from cerebrospinal fluid of a patient suffering with meningoencephalitis (Bonthius 2009). House mouse (*Mus musculus*) recognized as a natural reservoir host of the virus in year 1935 by Traub (Vilibic-Cavlek et al. 2021). In the studies after the discovery of LCMV, it was recognized as the main reason of aseptic meningitis in human beings (Meerburg et al. 2009). Virus was detected in 58 cases out of 713 in the years between 1953 and 1958 from USA. Along with these massive cases were reported from Germany (47 cases) in years between 1968 to1971 and USA (181 cases) in years 1973 to 1974 (Sarute and Ross 2021). LCMV is a neglected rodent-borne zoonotic virus due to limited diagnostic aids. Although cases were reported from round the globe, or the virus was also isolated from the rodents of Americas, Africa, Asia, and Europe. Though the diagnostic tools are limited still the LCMV is an important cause of meningitis in humans (Taniguchi et al. 2020).

Lymphocytic choriomeningitis virus (LCMV) is a member of family *Arenaviridae* genus *Mammarenavirus*. Old-world and new-world arena viruses are the two categories into which *Mammarenaviruses* are separated. In the same way as Lassa virus (LASV), the cause of Lassa fever, belongs to the old-world arena virus group, so does LCMV (Anesi et al. 2019). Two negative-sense single-stranded RNA segments, designated S and L, make up the LCMV genome. A viral nucleoprotein (NP) and glycoprotein precursor are encoded by the S segment, which is about 3.4 kilobases (kb) long. In contrast, the L segment, which is about 7.2 kb long, encodes a viral RNA-dependent RNA polymerase (L) and a polypeptide that contains a tiny zinc finger-domain (Z) (Baker 1998). Noncoding areas are responsible for LCMV's virulence, but they can also be used as targets to encourage viral attenuation for vaccine development (MacNeil et al. 2012).

2. TRANSMISSION

Arena viruses often spread horizontally, however some species of arenavirus can also spread vertically (Mims 1981). Although Wnzhu virus vertical transmission has not yet been experimentally shown, pups and dams were determined to be the source of horizontal transmission (Blasdell et al. 2016). The virus might behave as a possible teratogen, which is referred to as any environmental element that can cause a permanent aberration in form or function, a limitation of growth, or the death of the embryo or foetus, if it infects the embryo or foetus by vertical transmission (Gilbert-Barness 2010).

2.1. SIGNS AND SYMPTOMS

In Humans LCMV causes nausea, flu-like fever, headache, neck stiffness, sometimes photophobia and in severe cases meningitis and encephalitis (Vilibic-Cavlek et al. 2021). LCMV also infect the fetus in the comb of mother leading to its role as an emerging fetal teratogen. In congenital infection it leads to chorioretinitis, Hydrocephalus and periventricular calcifications. Mortality rate in children which are infected congenitally is about 35% and 70% of among them shows long-term neurologic sequelae (Bonthius 2009). In the result of LCMV directly acquired from rodent's leads to a highly fatal hepatitis in captive Callitrichid primates, this kind of hepatitis also occurs as sporadic outbreaks among many species

of tamarins and marmosets (Anesi et al. 2019). In individuals with strong immunity LCMV infection is usually asymptomatic or self-limited febrile disease although it occurs in about one third cases only and recovers in two to three weeks (Jamieson et al. 2006). On the other hand, in patients with compromised immunity like organ transplant recipients, LCMV can leads to a failure of multiple organs with a high fatality rate (Doherty et al. 1992). LCMV also play a role as a teratogen pass on to fetus in the comb of mother transplacentally and leads to ocular or CNS malformation, abortion, or intrauterine death of fetus (Welsh et al. 1991). In immunocompetent patients one third of the patients that acquire LCMV are a symptomatic while from the remaining two-thirds half of the cases shows non-specific febrile condition while the remaining suffer with central nervous system infection and in them symptoms appear about 6 to 20 days after the initial exposure (McLay et al. 2013).

LCMV shows a biphasic course in infected individuals starting from nonspecific conditions like nausea, headache, vomiting, malaise, and myalgia. While in the second phase main target is nervous system showing nervous signs like nuchal rigidity, photophobia, and headache and in some cases may leads to serious outcome like myelitis hydrocephalus or encephalitis or in rare cases LCMV can also leads to orchitis, parotitis, pneumonitis and, myocarditis. In acquired cases the rate of mortality is as low as 1%. On the other hand, immunocompromised patients are on higher risk (McLay et al. 2013).

LCMV can be transferred from infected person to non-infected through organ transplant. Cases of LCMV have been reported from the patients that received liver and kidney from the infected individual. But LCMV did not develop in patients that received cornea from infected individuals (Louten 2016). LCMV leads to multiple organ failure in recipients in terminal stages, at early stages after the transplant symptoms like flu, fever leukocytosis, abdominal pain, coagulopathy has been noted. It leads to a high mortality rate in patients up to about 71%. The patient that survived required ventriculoperitoneal shunt placement (Welsh et al. 1991).

In congenitally infected LCMV, leads to abortion in early first trimester of age. In about 88% of the PI cases it leads to hydrocephalus, neonatal meningitis, chorioretenitis and periventricular calcification (Anesi et al. 2019). Usually, Persistent infection occurs during the viremic stage of the disease when the virus is present in huge amount in the blood of the mother and cross the placental barrier to infect the fetus (19). High mortality rate up to 35% has been noted in persistently infected infants while the survivors suffer with neurological disorders for a long period (Blasdell et al. 2016).

3. LCM VIRAL PROTEINS AND THEIR FUNCTION:

With a bisegmented RNA genome that encodes two proteins on each segment in an ambisense orientation L polymerase protein and the small matrix protein Z on the L segment and glycoprotein GPC and nucleoprotein NP on the S segment arena viruses are a diverse family of negative-strand enveloped RNA viruses (Buchmeier 2007). Humans can contract a wide range of illnesses from arena viruses, but there are few preventative or curative measures available (McLay et al. 2013; Zapata and Salvato 2013). Neurologic illnesses can be brought on by the lymphocytic choriomeningitis virus (LCMV) (Bonthius). Organ transplant recipients who passed away from a febrile illness had the Dandenong virus (DANV) isolated from them (Palacios et al. 2008). Arena viruses that cause hemorrhagic fever (HF), including the Lassa virus (LASV), the Lujo virus (LUJV), the Junin virus (JUNV), the Machupo virus (MACV), the Sabia virus (SABV), the Guanarito virus (GTOV), and the Chapare virus (CHPV), can result in multisystem organ failure and death. In several West African nations, LASV is an endemic illness that results in 500,000 infections and 5,000 yearly fatalities (McCormick et al. 1987). There isn't a licensed vaccine for human use now, except for Candid#1, which is used as the JUNV vaccine in Argentina. There aren't many therapeutic choices, thus supportive care is generally used. A broad-spectrum antiviral drug called ribavirin has only

been proven to be somewhat effective when given at the insidious early stages of viral infection (McCormick et al. 1986). Argentine HF (AHF), which is caused by the JUNV, has been treated with moderate effectiveness by immune plasma transfusion (Enria et al. 2008) but not hemorrhagic fever from Lassa. Other arena viruses, such as Mobala virus (MOBV), Mopeia virus (MOPV), Ippy virus (IPPYV), Amapari virus (AMAV), and Pichinde virus (PICV), have been isolated from the same host species and belong to the same serogroups as the other arenaviral pathogens. However, it is unknown why these viruses are not linked to human diseases (Zapata and Salvato 2013).

The 15-kDa arenavirus Z protein serves a variety of purposes (Kleinschmidt-DeMasters and Beckham 2015), including helping to create the virions' matrix layer (Salvato et al. 1992; Neuman et al. 2005), mediating virus budding (Perez et al. 2003; Strecker et al. 2003), and regulating viral genome replication and transcription (Cornu and de la Torre 2002; Kranzusch and Whelan 2011). According to studies, the Z protein of New World (NW) pathogenic arenaviruses, such as MACV, JUNV, SABV, and GTOV, but not of Old World (OW) pathogenic ones (LASV and LCMV), can bind RIG-i and reduce the generation of IFN (Fan et al. 2010). Here, we provide a unique finding: all known human arenavirus infections' Z proteins, but not those of nonpathogens, suppress RLRs by binding to RLRs and preventing RLR-MAVS interactions. The N-terminal domain (NTD) of pathogenic Z proteins has been identified as the key regulator of RLR binding and inhibition. When a pathogenic Z NTD is switched out for a nonpathogenic Pichinde virus (PICV) genome, viral proliferation in Vero cells is unaffected, but type I IFN responses are markedly suppressed, and viral replication in primary human macrophages is increased. Our study identifies a universal innate immune-system suppressive mechanism shared by all pathogenic arenaviruses, which may shed light on arenavirus pathogenesis.

3.1. SOURCES OF INFECTION

Common house mice serve as both the reservoir and the LCMV's primary rodent host. In persistently infected mice that fails to develop immune response again the virus during the intrauterine period leads to long lasting asymptomatic infection ad results in the shedding of large amount of virus in all body secretions and excretions like in nasal secretion, milk, semen, saliva, and urine (Blasdell et al. 2016).

Human beings exposed to infection through the exposure of mucosa to rodents dropping contaminated aerosols or through the direct contact with rodents just like in case of rodent bite or licking. Pets rodents also play a role in the spread of infection to humans. Many out breaks were directly linked with the exposure to PI pet hamsters (Kleinschmidt-DeMasters and Beckham 2015).

Except for vertical transmission from infected pregnant women to foetus and organ donation, there is no evidence of human-to-human transfer. When exposed to the bodily fluids of infected house mice (*Mus musculus*), which serve as the virus's natural reservoir, humans may get infected with LCMV (Zapata and Salvato 2013).

4. PATHOGENESIS

Rodents are the targets of LCMV, especially hamsters and common house mice. The virus gets entry into the human body through direct contact with rodents like licking or biting or indirectly by inhaling the virus that is present in rat excretions and secretions (Taniguchi et al. 2020). After the entry into the human body, the virus targets the endothelial and lymphatic cells and replicate there or settle down in lymphatic tissues like spleen or lymph nodes and further replicate there (Kleinschmidt-DeMasters and Beckham 2015).

In response to targeting macrophages and lymphatic cells body immune system leads to the activation of innate immune response and body makes interferons or pro inflammatory cytokines against the virus (Blasdell et al. 2016).
In viremia, virus spreads to multiple organs like liver, spleen, lungs, kidney but the main tropism is towards the cell of CNS, where they target almost all types of nervous cells including neurons or microglia (McCormick et al. 1986).
In immunocompetent patient's virus leads to an asymptomatic disease, while in the immunocompromised patients it may leads to serious outcomes. The main signs of the disease are due to body own immune response against the virus that may leads to inflammation or excessive tissue damage (Djavani et al. 2000). Natural killer or cytotoxic T lymphocytes are the main player that leads to the clearance of virus from the body but also affect body own tissues (Kleinschmidt-DeMasters and Beckham 2015).
In immunocompetent patient's virus just show flu like symptoms while in compromised patients leads to serious nervous signs like meningoencephalitis, encephalitis or aseptic meningitis or involvement of multiple organs of the body. In pregnant mother's virus can infect the fetus and play a role as a teratogen or may leads to abortion in first trimester. Signs and symptoms vary from a no serious flu like condition to seizures, blindness neurologic deficits, hepatitis, or hemorrhagic fever (Djavani et al. 2000).

4.1. EPIDEMIOLOGY OF LCMV

M. musculus and *Mus domesticus* are the natural and reservoir host of LCMV virus. Persistently infected mice (infected in the comb of mother) fail to develop immune resonse against LCMV and become a a-symptomatic, chronic carrier, and shed virus during whole life through natural secretions or excretions. Hamsters and pets' mice also work as a carrier of virus. Human-beings directly gets the infection from rodent bites or mucosal exposure of infected secretions of rodents. Large number of outbreaks of LCMV have been reported that are directly linked with the exposure of infected hamsters. As human-to-human transmission is not documented except through organ transplantation or through the uterus of infected dam.
Rodents are the targets of LCMV specially hamsters and common house mice. The virus get entry into the human body through the direct contact with rodents like licking or biting or indirectly through the inhalation of the virus present in the secretions and excretions of rodents.

4.2. LCMV PREVALENCE IN HUMANS

As the reservoir host for LCMV is distributed worldwide, the virus has been reported from worldwide, but due to lack of diagnostic facilities, some mild or asymptomatic infection, true picture remains un-known. In the 1950s virus has been detected about 8% of the patients suffering with neuroinvasive disease and these cases mostly reported in winter season when the interaction of rodents with human beings increased.
A study during the last decade shows that in Finland 5% of the cases suffering with neroinvasive disease were screened positive for the IgG of LCMV. In these studies, they noticed that the virus infect humans irrespective of gender, with the 5-10 years age group being infected more than any other. Additionally, 5.1% of cerebrospinal fluid (CSF) samples taken from individuals with neuroinvasive illness in southern Iraq (Nasiriyah region, 2012–2013) contained virus. On more investigation from the same area reveals the prevalence of the virus in neurologically infected or healthy individuals both. About 12.2% seroprevlance was recorded in healthy groups. A seroprevalence investigation was conducted in overall population that shows that up to 15% of population is infected with the virus.
Cases of LCMV were also reported from Argentina with2.3%, Canada with 4%, Albama with 5.1%, spain with 1.7% and in Argentina with the 3.3% of seroprevalance. Although limited data available on the

seropervalence of the virus in the pregnant women, 1.6% of pregnant women were found positive in Argentina and 3.9% Croatian women, but in both scenario IgM antibodies were not found suggwsting a history of past infection. According to studies, the number of instances among humans who had intimate contact with rats is greater. According to an Austrian study, 13% of the personnel at the Vienna Zoo were LCMV seropositive.

4.3. DIAGNOSTIC AIDS

We can isolate virus from the nasopharyngeal secretions and blood during the early stage of disease. There is a time restriction in finding virus form the nasopharyngeal secretions as the virus is present for a short period of time. We can detect the virus by growing the sample in different cell lines like vero cells, L-929 or BHK-21.
LCMV can also be detected by the inoculation of CSF or blood of infected individual into newborn mice, if it leads to development of convulsive disease during a short duration of a week is pathognomonic for the virus. For further confirmation RT-PCR or IFA can be performed on the brain of mice. By the help of RT-PCR viral RNA can be detected from the sample of blood or CSF fluid. Serological tests like IFA and EIA target immunoglobulin M and G, but these facilities are limited.
Congenitally infected children have a difficult time being diagnosed with LCMV since most newborns were free of the virus when they were born, making diagnosis difficult. In these circumstances, the mother and foetus' IgG and IgM titers should be evaluated.

4.4. THERAPY OF LCMV INFECTION

There are limited therapeutic options for LCMV in humans. In majority of the cases main line of treatment is symptomatic or the use of already available options for viral treatment. Ribavirin is among the first purposed anti-viral for LCMV infected patients. Ribavirin has a complex mechanism of action that directly leads to inhibition of virus growth by inhibiting inosine monophosphate dehydrogenase that will ultimately leads to the depletion of GTP, it’s an analogue of guanosine. Ribavirin also acts as immunomodulatory drugs that will help in differentiation of of native CD4 T-cells to helper T cells that increses the antiviral activity. Ribavirin can be given through oral or intravenous route to the patients.
In addition to ribavirin, favipravir that inhibit the growth of various RNA viruses by inhibiting the growth of RdRp, also being used to treat LCMV infected patients on trial basis. This drus is clinically approved by japnese government for the treatment of influenza infection or currently being used to treat the COVID patients. Lab trials on acute disseminated LCMV infected mice, shows excellent results of drug. In less severe cases of animals infected with LCMV, it leads to permanent inhibition of virus growth with complete protection from mortality.
Currently umifenovir is being used for the treatment of influenza infected patients, is also being studied for the treatment of covid-19. It works by inhibiting various lifecycle stages of the viruses by interacting with virion lipids or protein. Umifenovir, according to Herring et al. (2021), can reduce the proliferation of numerous arenaviruses, including LCMV, in vitro, opening the door for future use of this medication to treat LCMV-infected individuals.

5. VACCINE RESEARCH IN LCMV

Reverse genetically altered recombinant LCMV (rLCMV), in addition to serving as a significant research model in immunology, is a significant potential for the creation of vector-based vaccines. In immunosuppressed mice, who are deficient in a functioning type I IFN receptor, Krolik et al. (2021)

recently published the findings of a safety and effectiveness examination of a non-replicating rLCMV vector producing ovalbumin as a model antigen. When mice was immunised, this resulted in the development of multifunctional cytotoxic CD8+ T-cells and memory T-cells, which cleared the rLCMV-ovalbumin vector 7 days after vaccination (Krolik et al. 2021). Non-replicating rLCMV-based vectors appear to be a good choice for vaccine development due to the rLCMV viral vector's outstanding safety profile and retained effectiveness in immunocompromised animals.

Replicating LCMV-based vectors have been investigated as potential therapeutic cancer vaccines with the goal of eliciting antitumor T-cell mediated immunity and long-term tumour control. A novel vaccine called TT1-E7E6 was developed by Schmidt et al. (2020) using replicating attenuated LCMV that encoded a non-oncogenic form of the oncoproteins E7 and E6 of human papillomavirus type 16 (HPV-16). The mouse model used to evaluate TT1-E7E6 demonstrated vector clearance, induction of CD8+ T cells specific for HPV-16, and tumour reduction, indicating that the LCMV-based TT1-E7E6 vaccine would represent a great prospect for the immunotherapy of HPV-16-positive malignancies (Schmidt et al. 2020).

6. VACCINATION OF LCMV

6.1. APATHOGENIC ARENAVIRUSES AS LIVE VACCINES

With the introduction of the vaccinia virus for the prevention of smallpox or the 17D strain of the yellow fever virus, the use of live-attenuated strains or similar apathogenic viruses for immunisation has a long history (Riedel ; Frierson 2010). Both successfully target cellular adaptive immunity as well as a potent immune response that produces neutralising antibodies against the chemical (Wrammert et al. 2009).

6.2. REASSORTMENT OF LASV AND MOPV

Promising outcomes were obtained when a plaque-purified clone (ML29) was used as a LASV vaccination (Lukashevich et al. 2005). Only animals that had received the MOPV vaccine, which was likewise protective, did not exhibit a brief rise of liver enzymes in plasma following LASV exposure.

6.3. INACTIVATED OR DEAD VACCINES

After transiently transfecting expression plasmids into HEK-293T cells, virus-like particles comprising GP1, GP2, NP, and Z were created. ELISA was used to measure the binding antibodies that were elicited. In order to determine whether or not this strategy will be effective, further functional trials will be required (Branco et al. 2010).

6.4. MUCOSAL VACCINATION

Additionally, oral administration requires little to no physical exertion, making immunisation campaigns possible. To express LASV NP and LCMV NP, S. typhimurium and the vaccinia virus underwent genetic modification. Recombinant vector-injected mice displayed LASV NP-specific IgA and particularly reactive splenocytes, and the results were good (Djavani et al. 2000).

6.5. RECOMBINANT VIRUSES EXPRESSING ARENAVIRUS PROTEINS

Since the early 1980s, recombinant viral vectors have been in use. They are a great tool and have a number of benefits over other vaccination platforms when used as vaccine vectors for the expression of foreign antigens (Thummel et al. 1981; Mackett et al. 1992)

6.6. DNA VACCINE

Target genes can be expressed and delivered into the host using plasmid DNA to stimulate immunity. Plasmid DNA is taken up by antigen-presenting cells and other body cells, and the subsequent protein synthesis from the plasmid DNA results in the presentation of peptides encoded by the plasmid DNA by MHC I and II (Huygen 2005). In addition to their considerable work on LCMV, Whitton et al. have also studied the extremely pathogenic LASV. After giving mice plasmid DNA expressing LASV or LCMV NP, the immune response and protective capacity in response to LCMV or Pichinde virus (PICV) challenge were evaluated (Rodriguez-Carreno et al. 2005).

7. CONCLUSION

The lack of commercially accessible serologic tests has contributed to the fall in the percentage of meningitis cases attributable to LCMV, yet this virus continues to be a significant cause of meningitis in humans. However, there is little clinical interest in the condition, and LCMV hasn't been used very much. The discovery of fatal LCMV infections in multiple groups of solid organ transplant recipients who got organs from donors who passed away from causes that appeared to be unrelated to infection further demonstrated the pathogenic potential and clinical importance of this underappreciated human pathogen. LCMV should also be regarded as a developing teratogen in pregnancy. Obstetricians should be aware of the increasing role of LCMV as a TORCH agent that can affect maternal, foetal, and neonatal health even though only 82 cases of congenital LCMV infection have been documented so far.

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Chikungunya Fever: Clinical Perspective

47

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ABSTRACT

Chikungunya virus is the arthropod born virus. Aedes aegypti is recongnized as primary vector. The virus is transmitted from one to another vertebrate host. The individuals having compromised immune system like new born babies are at higher risk of Chikungunya fever. Chikungunya fever is divided into three genotypes. West Africa genotype (waf) and other two are East\Central\South Africa genotype. The incubation period of Chikungunya virus is 1 to 2 weeks. On the basis of Clinical perspective, disease has two stages. During the acute stage patient feel Pyrexia, Polyarthralgia along with these muscle pain also noticed. Diarrhea is the primary GIT symptom in acute stage. Clinical stage of disease involve various body system like nervous system, respiratory system and muscloskeleton. RT-PCR, RT-LAMP and also various serodiagnostic techniques like immunofluorescence assay, haemogglutatin assay can be used for the diagnosis purpose. There is no specific treatment for the Chikungunya virus but in order to alleviate the pain and other symptoms, symptomatic treatment is given. The most important is the management of the disease. By giving appropriate analgesia, pain can be reduced. It is acute febrile disease associated with increasing prevalence and impact on public health. Chikungunya virus spreads very rapidly and cause the contamination of the large population. The only way to control the spread is the proper management by completely destroying the vector habitat. Vaacination is available against chikungunya virus, but before vaccination personal protective measurements is crucial. Besides of all these, awareness among the community play a vital role for the Control of disease.

Keywords: Aedes aegypti, Incubation period, Genotype, Polyarthralgia, serodiagnosis, RT-PCR, Vaccination.

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INTRODUCTION

Chikungunya virus (CHIKV) is spread by Aedes (Ae.) mosquitoes and belongs to the arthropod-borne virus category. Back in 1952, the CHIK virus was primarily recognised in the Makonde Plateau, previously known as Tanganyika, located in the southern province of Tanzania. CHIKV is propagated through a transmission cycle involving female mosquitoes. Aedes mosquitoes feed on the blood-containing virus from a affected vertebrate host and become infected. After an appropriate extrinsic incubation period, the virus is then transmitted from one to another vertebrate host when the mosquitoes feed again (Solignat et al. 2009). Chikungunya is a viral disease transmitted by vectors, primarily causing significant outbreaks, particularly in tropical and subtropical regions. (Weaver et al. 2012). Chikungunya fever is distinguished by an significantly elevated viraemic load, accompanied by specific abnormalities like significant lymphopenia and mild thrombocytopenia. (Thiberville et al. 2013). Chikungunya fever (CF) presents as a highly symptomatic acute illness, with severe arthralgia during the acute phase that may progress to chronic arthritis. The term "Chikungunya" originates from the Makonde language spoken in some areas of Mozambique and translates to "that which bends up," directly alluding to the arthritic symptom's characteristic of the disease (Kucharz et al. 2012). The transmigration of Chikungunya virus (CHIKV) primarily arises through mosquitoes, mainly *Aedes aegypti* and Aedes albopictus. Nevertheless, in certain regions, transmission by other mosquito species like Culex, Mansonia, and Anopheles has also been documented. Besides affecting humans, CHIKV is found to circulate within natural sylvatic environments, where it involves primates and possibly rodents as hosts and reservoirs (Pialoux et al. 2006). In Pakistan, the Chikungunya virus (CHIKV) was identified to be circulating in rodents as far back as 1983 (Darwish et al. 1983), still only a limited number of human cases have been reported. In 2011, several patients were found to have CHIKV antibodies in their bodies, during a dengue outburst in Lahore. Later, in 2016 in Karachi CHIKV emerged, and an outbreak was officially announced, once evidence of local transmission was confirmed (Aamir et al. 2017).

2. RISK FACTOR

Certain risk factors have been related to the development of a severe chikungunya fever. Females have a higher risk of progressing to a severe chronic stage of the disease compared to males. Individuals who smoke are more likely to experience a severe chronic stage of Chikungunya fever. Moreover, Patients who experience severe joint pain during the early grade of Chikungunya fever are at a greater possibility of developing a severe recurrent stage (Delgado-Enciso et al. 2018). The study indicating that newborn babies and infants (under one year of age) are highly affected to intense forms of CHIKV infection and have a higher degree of viral load are significant and have important implications for public health policies. This highlights the need for special attention and protection for this vulnerable age group, potentially through CHIKV vaccination strategies.

Given that neonates bear the greatest relative economic and health burden of CHIKV disease, the development of an effective vaccine becomes even more critical. The presentation of CHIKV infection in children can be diverse and sometimes challenging to diagnose accurately, especially in younger age groups like infants. While fever and skin rash are more apparent and easier to identify, joint-related symptoms such as arthralgia and arthritis may be less obvious, leading to potential delays in diagnosis and appropriate management, particularly in infants (Pinzón-Redondo et al. 2016).

3. VECTOR

In the Asian and North Pacific Ocean regions, the Chikungunya virus is spread through the sting of Aedes mosquitoes, which are also responsible for transmitting the dengue virus. Among these mosquitoes,

Aedes aegypti is recognized as the primary vector, while Aedes albopictus has newly arisen as an front page vector as well, which is commonly known as the Asian Tiger mosquito. *Aedes aegypti* (primary vector) primarily flourished in reservoirs of freshwater resources such as air coolers, plant pots, and water cans. These mosquitos can be found in peri-domestic areas, which include wasted household stuff like vehicular tires, coconut shells, pots, cans, and bins in rural, town and suburban areas. These flourishing sites provide favourable habitats to the mosquitoes for the completion of their life cycle (WHO 2009; Samuel et al. 2009).

4. EPIDEMIOLOG

CHIKV is considered to have its origins mainly in Central/East Africa (Powers et al. 2000). Notably, *Aedes aegypti* and *A. albopictus* mosquitoes are the main carriers accountable for the civil spread of Chikungunya fever (Powers and Logue 2007). CHIKV stands out as the most widespread alphavirus conveyed to vertebrate hosts (Zaid et al. 2021; Kril et al. 2021). While the precise details remain unclear, advanced understanding suggests that CHIKV flourished within a wild animals and vectors in both Asia and Africa, and it involves primates other than humans and Aedes mosquito's residency in forested areas. However, the transition to urban areas and subsequent human-to-human transmission is driven by two Aedes mosquitoes of the genus that possess a strong affinity for human blood over that of other animals (Weaver et al. 2020; Azar et al. 2020).

In 1952, in Tanazania outbreak of chikungunya virus has occurred and it caused a large no of both emerging and re-emerging cases of chikungunya virus across different areas of Tanazania. Notable outbreaks occurred in the following areas and periods:

A chikungunya outbreak was reported in Uganda during the 1960s and 1990s (Schuffenecker et al. 2006; Lanciotti et al. 1998). The virus caused an outbreak in Zimbabwe (Lanciotti et al. 1998) and in Senegal (Halstead et al. 1969; Diallo 1999). Countries in Central Africa, such as the Central African Republic, Democratic Republic of the Congo and Cameroon,also experienced chikungunya outbreaks (Barrett and Weaver 2012; Jupp and McIntosh 1988; Pastorino et al. 2004). Apart from these regions, chikungunya outbreaks have been reported in many other regions of the world, making it a global health concern. On the basis of their geographical distribution, Chikungunya virus has been classified into three definite forms of their genotype. The first genotype, known as the West African genotype (WAf). The other two are East/Central/ South Africa and Asia (Powers et al. 2000).

Studies conducted by Lanciotti et al. (1998) and phylogenetic analyses presented by Powers have provided genetic evidence that ONN (O'nyong-nyong virus) and CHIKV are genetically different from each other (Powers et al. 2000). The African CHIKV viruses exhibit a paraphyletic grouping suggesting past affirmation shows that the virus first appeared in Africa and then in Asia. These genetic findings shed light on the evolutionary history and geographic spread of CHIKV, showing how different strains have emerged in various other regions over time and providing valuable insights into its transmission dynamics (Powers et al. 2000; Presti et al. 2012).

5. CLINICAL SIGNS AND SYMPTOMS

Whenever a person comes in contact with chikungunya fever, there is a plethora of signs and symptoms displayed by the infected individual. The disease is marked by a sudden and abrupt onset of high fever accompanied by severe pain in joints, which can endure for weeks to even years (Suhrbier et al. 2012). The incubation period of chikungunya virus is usually between I to 2 weeks. On the base of illness duration, chikungunya fever can be divided into two forms. It can be either acute illness or chronic/late-stage illness.

5.1. ACUTE STAGE

Symptomatic individuals typically experience a sudden onset of the disease, characterized by pyrexia, pain in different joints of the body, back pain, cephalalgia, and tiredness. High-grade Fever and the distinct pathological indication manifest within one week.

Polyarthralgia, which is the pain affecting multiple joints, is recorded in 89% to 99% of cases and stands as the highly distinctive indication. The arthralgia is usually symmetrical, on both sides, and commonly affects external joints like carpus, tarsus, and appendages, along with a few larger joining of the body like shovel, arm and leg. Arthritis, on the other hand, is less common, observed in 25 to 42% of cases. Additionally, discomfort in ligaments (such as pubic inguinal pain syndrome, musculus sternocleidomastoideus, occipital inclusion, and heel pain), articular temporomandibularis and tendonitis have been reported.

In recent prospective studies, myalgia (muscle pain) was seen in 46 to 59% of cases, while contemplative studies showed greater frequency (almost 94%). Muscle pain tends to affect the elbow and legs, and pain in the back portion of the lower leg without causing inflammation of the muscles. Muscularmaculopapular or Maculopapular rashes characterized these cutaneous manifestations. Hypersensitivity, hypermelanosis, dermatitis and photosensitivity are also seen. Such complications are transient and subside soon. A general pruritus is also observed in one-fourth of the total cases. If a person already suffers from dermatoses, then there will be a sudden flare-up in that particular skin condition, as in psoriasis. In about 15-47 per cent of the reported cases presented at clinics, there are symptoms related to the gastrointestinal tract. They are specifically seen in the acute stage of disease. People affected with chikungunya fever have to suffer from stress and depression, not because the disease affects the nervous system but mainly due to the declining quality of life. Diarrhea is a primary gastrointestinal symptom in the acute stage (Thiberville et al. 2013).

5.2. CHRONIC STAGE

Now that we have talked about the different signs and symptoms accompanying with the acute stage of the disease. Let us take a close look at the symptoms of the late-stage or chronic phase of chikungunya fever. The most frequent and prolonged problem is musculoskeletal pain. Patients are also reported to have chronic rheumatic manifestations. Rheumatoid arthritis is also diagnosed in accordance with chikungunya fever. Spondylarthopathy is often interpreted as well. There are so many atypical cases with a variety of displays of signs and symptoms. It is to be noted that people who have a history of alcoholism or epilepsy display episodes of seizures. Encephalopathy and encephalitis are some major and well-known signs of nervous anomalies. Subarachnoid cerebral haemorrhages are observed as well. Symptoms such as fever, fatigue, cerebral disorders, bursitis, dysesthesia, and paraesthesia are seen, but they are not very abundant. But there is one thing that must be repeated: people report a poor quality of life after contracting the disease. Haemorrhagic symptoms are less presented, usually in only 1-7 per cent of cases. Minor bleeding from gums can be reported and that is one of the reasons not to use certain medications which will be discussed in the treatment section. Clotting abnormalities are not associated. Conjunctivitis, neuroretinitis, dry cough, pneumonia and pericarditis are also seen. Children show a very interesting pattern of symptoms of the disease. In children there is more involvement of cutaneous signs than rheumatological signs. Most commonly we can see maculopapular rashes, generalized erythema and hyperpigmentation in children when it comes to the neurological symptoms,menengial syndrome is observed. For pregnant women, this disease has no observable growing teratogenic effects fetus. Vertical transmission is a significant cause of the spread of intrapartumviremia (Thiberville et al. 2013). Chronic CHIKV disease can lead to substantial debilitation, and when large epidemics occur, the severe economic consequences underscore the significant public health threat posed by CHIKV (Mohan 2006).

6. CLINICAL SIGNS AMONG TRAVELLERS

Between January and October 2006, a group of 69 travellers with symptoms suggestive of CHIKV infection and a compatible medical history were investigated. Among them, 41 were female, and 48 experienced joint pain. A confirmed diagnosis of chikungunya fever was established in 20 patients, with 14 of them being female. The average life of those patients was 45 years, varying from 13 to 65 years.
Out of the 20 confirmed cases, 45% (9 patients) had travelled from Mauritius, 15% (3 patients) from India, and 10% (2 patients) each from Réunion, Malaysia, and the Seychelles. Additionally, 5% of the cases each were from Madagascar and Indonesia. Among these patients, 19 were German tourists on vacation, while one patient was on a student exchange in Réunion. The mean period of travel was three weeks, ranging from 2 to 26 weeks. The symptoms typically started during the travel period in 14 patients, while in 6 patients, they emerged 1 to 3 days after their return. These symptoms included fever, fatigue, headache, and myalgia (muscle pain) (Taubitz et al. 2007).

7. DIAGNOSIS

The most common and excellent procedure for determining Chikungunya fever culture media of the virus involves inoculating mosquito cell cultures, mosquitoes, mammalian cell cultures, or mice with patient samples (Simon et al. 2008; Sudeep and Parashar 2008; Chevillon C et al. 2008; Powers et al. 2007). Viral culture has the advantage of being able to detect a broad range of viruses. Alternatively, molecular tools such as RT-PCR and RT-LAMP have also been very efficient for rapid diagnosis of CHIKV. In clinical settings, serodiagnostic methods are more commonly employed for detecting Chikungunya virus infection. These methods determine the presence of several immunoglobulins like immunoglobulin M (IgM) and immunoglobulin G (IgG) against the CHIKV in acute and convalescent serum samples. Some of the serodiagnostic techniques used include enzyme immunoassay, indirect immunofluorescence microscopy, hemagglutination assay, or neutralization techniques. After two days of infection, IgM antibodies become detectable, as measured by enzyme immune assay or immunofluorescence microscopy, and can remain for 3 to 12 weeks. IgG antibodies, on the other hand, are detectable in recovering specimens and can stay for an extended period. It has been discovered that approximately 40% of symptomatic patients may still have detectable IgM antibodies even 18 months after the onset of the disease (Borgherini et al. 2008; Grivard et al. 2007). Therefore, the interpretation of these serological tests should be done cautiously, as they may need to be fully standardized.

8. TREATMENT AND MANAGEMENT OF CHIKUNGUNYA

The mild acute cases of chikungunya fever can be managed by simple measures such as resting, maintaining oral hydration, and providing appropriate analgesia. These steps help alleviate the symptoms and support the body's natural recovery process during the intense stage of the infection (Simon et al. 2015). Indeed, it is crucial to differentiate patients who have mild, uncomplicated chikungunya fever from those who present with severe forms of the disease, which necessitate medication and examination in a specific medical setting. The standard for determining the severity that requires hospitalization includes:
1. Haemodynamic failure: When there are signs of instability in the circulatory system, such as low blood pressure or poor perfusion.
2. Uncontrolled pain: If the patient's pain is not adequately managed using level 1 analgesics like aspirin or ibuprofen and level 2 analgesics like tramadol PO/IM/slow infusion.
3. Indication of haemorrhage: If there are indications of abnormal bleeding, such as injury, pinpoint haemorrhage, usually red, brown, and purple on the skin, or bleeding from a mucous membrane.

4. Comorbidities with decompensation: If the patient has pre-existing health conditions that worsen due to the chikungunya infection.
5. Atypical chikungunya fever symptoms: When the disease manifests with unusual symptoms affecting the respiratory system, heart, nervous system, liver, blood, or kidneys.
6. Patients meeting any of these criteria require immediate hospitalization and specialized medical care to manage the potentially severe complications associated with chikungunya fever (Webb et al. 2022).

9. MANAGEMENT OF PAIN

Intense pain is the most debilitating indication experienced during the acute phase of chikungunya fever. To assess and quantify pain levels, healthcare professionals routinely use verified pain estimation scales, such as the numeric rating scale (NRS). The NRS allows patients to figure their pain on a continuum from zero to ten, where zero represents no pain, and ten indicates the unfavorable pain. This range rate helps healthcare providers understand the severity of pain experienced by the victim and aids in determining appropriate analgesic interventions for pain management during the intuitive phase of chikungunya fever (Brito et al. 2016). During clinical examination of a patient with chikungunya fever, neuropathic pain is suspected, and it may be characterized by specific symptoms such as allodynia (pain triggered by an ordinarily non-painful stimulus), neuropathic pain or nerve pain, burning sensation, or numbness. In such cases, optimizing pain management requires a comprehensive evaluation using validated tools like the DNA questionnaire.
The DNA questionnaire includes both sensational description and indications associated with bedside sensory examination. It comprises four questions aimed at identifying signs of neuropathic pain, such as burning sensation, numbness, or pain from non-painful stimuli. By using this questionnaire, healthcare providers can assess the presence and severity of neuropathic pain and tailor the analgesic treatment accordingly. Identifying and addressing neuropathic pain is essential for providing effective pain relief and improving the overall management of chikungunya fever in patients experiencing these specific pain symptoms (Bouhassira et al. 2005). According to WHO guidelines, daily hydroxychloroquine or chloroquine administration for four weeks is recommended for patients experiencing musculoskeletal symptoms that are not responding well to conventional symptomatic treatment (WHO 2008). However, it is important to note that the effectiveness of hydroxychloroquine and chloroquine for treating chikungunya fever has not been definitively proven. Additionally, many other expert societies do not support the use of hydroxychloroquine and chloroquine for chikungunya fever. Their recommendations are not in favour of using these medications due to the need for substantial evidence supporting their efficacy in managing the symptoms of the disease. As with any treatment, it is the first and foremost duty of medical management staff to attentively measure the possible advantages and disadvantages before administering hydroxychloroquine or chloroquine to patients with chikungunya fever. The choice to use these medications should be according to the requirement and the medical condition of the patient, considering individual patient factors and the most up-to-date clinical evidence available (Webb et al. 2022; Lamballerie et al. 2008).

10. FUTURE STUDIES OF CHIKV

CHIKV infection leads to an acute febrile illness, with a significant number of patients experiencing persistent polyarthralgia *(*Zaid et al. 2021; Kril et al. 2021; DE Lima Cavalcanti et al. 2022; Hoarau et al. 2010). The pathogenesis of chikungunya fever is a complex process characterised by a delicate coaction of both human and viral factors. Over the past decade, significant advancements have been made in identifying the primary molecules of the host involved in CHIKV infection and immune pathophysiology

(Liu et al. 2022; Suhrbier 2019; Ekchariyawat et al. 2015). However, further research is still necessary to certify this discovery related to anatomical systems.

Despite the significant knowledge acquired from the current outburst and examination, additional research is required to deepen our understanding of CHIKV transmission. Specifically, studies exploring carrier ability and possible spread can shed light on why this Central/East African strain was exceptionally efficient in transmission. Developing susceptible and precise models that incorporate ecological, entomological, and virological factors may aid in predicting disease spread and potential future CHIKV outbreaks. Similar models have proven valuable for other phlebovirus diseases, like Rift Valley Fever (Linthicum et al. 1999).

Physicians play a crucial role in determining cases, and they should acknowledge CHIKV infections in victims with pyrexia and arthralgia, especially if there's recent travel to or exposure to individuals from CHIKV outbreak regions. Swift notification of suspected cases to local health departments is essential to facilitate early detection and implement combative carrier monitoring procedures and correspondence to prevent local transmission. It is imperative to continue researching the pathological process of consistent joint pain and explore possible medicinal, such as anti-virus, to cure CHIKV infection and mitigate its high viremia and significant morbidity. While a live, attenuated vaccine showed promise in stage 2 human tests, its growth was discontinued due to reactogenicity and low demand (McClain et al. 1998; Edelman et al. 2000). Revisiting the study of live attenuated vaccines and other immunization production, such as chimeric alphavirus vaccines, is crucial and public health officials are essential to prevent further spread—the appropriate awareness of correct detail. In the meantime, physicians should seriously educate patients travelling to the areas which are at higher risk of chikungunya infections and preventive measures involving plans to reduce the bite of mosquitoes.

Chikungunya virus has displayed its potential to spread rapidly and contaminate a considerable number of populations during recent epidemics. Taking measures to improve disease recognition, control vector populations, and promptly apply community health data to carrier management procedure experimentation can play a pivotal role in controlling the degree of future CHIKV outbursts.

11. PREVENTION

Before the availability of vaccines, the primary effective measures to prevent infection consist of personal protection against mosquito bites and controlling mosquito populations. The approach used for controlling both adult and larval mosquitoes is similar to that employed for managing dengue and has demonstrated considerable success in various countries and environments (WHO 2009). Mosquito control remains the most viable method for preventing CHIKV infection, necessitating the elimination, destruction, regular emptying, and cleaning or treatment with insecticides of breeding sites (WHO 2007).

In order to protect against mosquito bites, it is highly recommended to wear clothing that reduces skin exposure to daytime-biting vectors. Following the specific instructions written on the product label, it is helpful to use mosquito repellent against the vectors to the exposed skin and clothing. Effective repellents should contain DEET (N, N-diethyl-3-methylbenzamide), IR3535 (3-[N-acetyl-N-butyl]-amino propionic acid ethyl ester), or icaridin (1-piperidine carboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester). Further protection against indoor mosquito biting can be achieved by using mosquito coils or other insecticide vaporizers (WHO 2014).

In order to combat Chikungunya fever outbreaks effectively, it is imperative to raise awareness among public health officials and the community. For the effective vector control measures, it is essential to dispose of the nature sites, and the application of insecticides and repellants should be implemented at both in-person and population levels, as they can yield significant benefits. The effective control of vectors and surveillance play a role in minimising fever epidemics. To achieve this, it is vital to actively appoint the

community and collaborate with public health authorities to promote hygiene practices and mosquito control measures. Integrated vector management strategies aimed at reducing or interrupting disease transmission should be actively pursued.
However, due to the extensive nature of these measures, they are beyond the scope of this review. For more comprehensive information, readers are encouraged to refer to (Bhatia and Narain 2009).

12. CONCLUSION

It is typically a short-lived illness, yet during significant outbreaks, it can result in a public health and economic impact. Effective disease prevention hinges on a meticulously planned approach that also incorporates awareness regarding early warning signals. The adoption of an integrated strategy for vector management, entailing the removal of breeding sites, the use of adult and larval control measures, and the promotion of personal protective measurements, is vital in thwarting the occurrence of outbreaks. The active involvement and mobilization of communities are pivotal in the quest to prevent and manage Chikungunya.

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Rift Valley Fever: Insights into Abortive and Zoonotic Disease

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ABSTRACT

RVFV, also known as the Rift Valley fever virus (genus Phlebovirus family Phenuiviridae), is an arbovirus infection that causes Rift Valley fever (RVF). Whenever RVFV shows up, it spreads epidemics among the local population and causes epizootics in livestock. Animals and people in Africa and the Arabian Peninsula have been affected by RVF, a disease spread by mosquitoes and caused by the RVFV. In RVF epidemics, animals contract the virus through mosquito bites, leading to substantial viral amplification and spread to nearby regions through livestock movement and mosquito migration. Following animal slaughter or the handling of embryonic materials, direct contact with infected animals or mosquito bites are the subsequent ways in which the virus is transmitted to humans. Real-time polymerase chain reaction (RT-PCR) reverse transcription can be used to identify RVFV. The most common symptom of RVF in pregnant animals is an abrupt, violent abortion. Animals with the virus may have up to 100% abortion rates because it directly targets the developing embryo. In young animals, the mortality rate can reach 100%. When this disease progresses from apparent to acute, it causes fever, weakness, and bloody diarrhea in adults, but it causes fever, loss of appetite, and death in young animals. RVFV infections in humans usually show no symptoms at all and go away on their own. After an incubation period of 4-6 days, symptoms of RVF, including fever, chills, fragility, headache, and joint and muscular pain, become apparent. An almost simultaneous, marked increase in the number of abortions performed on pregnant ruminants is the telltale sign of an RVF epizootic. Known as "abortion storms," these widespread abortion occurrences allow one to distinguish RVF from several other common infectious causes of abortion in ruminants, including toxoplasmosis, salmonellosis, chlamydiosis and Q fever (Coxiella burnettii). The one health approach is essential in combating this rapidly spreading infection. RVF can be effectively managed and prevented by focusing on the interconnectedness of human, animal, and environmental health.

Keywords: RVFV, Zoonosis, Abortion, Vector borne, RT-PCR, One-health.

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1. INTRODUCTION

The Rift Valley fever virus (genus Phlebovirus family Phenuiviridae; RVFV) is an arbovirus infection that causes rift valley fever (RVF). RVFV appears regularly, causing epizootics in livestock and epidemics in people living nearby. Furthermore, RVFV transmission is vertical among human and vector mosquito populations (Ahmed et al. 2020). The RVFV causes RVF, a mosquito-borne disease that has impacted both humans and animals across Africa and the Arabian Peninsula. The World Health Organization (WHO) views RVF as a priority for research and intervention since previous RVF epidemics have caused devastating public health catastrophes in affected nations. RVFV is highly contagious and has been associated to abortion and infant death in cattle, goats, and sheep (De Glanville et al. 2022).

Vector-borne transmission of RVFV is widely acceptable (Rissmann et al. 2017). Animals become infected with the virus by mosquito bites during RVF epidemics, which results in significant viral amplification and dissemination to neighboring areas via livestock and mosquito migration. The virus is subsequently spread to people by mosquito bites or direct contact with infected animals, such as during animal slaughter or the handling of embryonic materials. The symptoms of RVF in ruminants include a high fever, hemorrhagic diarrhea, high mortality among young animals, and abortion storm among pregnant animals. (Halawi et al. 2019). Pregnant animals frequently abort, which makes post-infection herd recovery difficult, and many generations of animals are lost during the outbreaks. For families and communities that rely on the sale of animal foods, milk, and byproducts as a source of revenue, rapid herd size reductions can also result in severe resource and financial pressure (Grossi-Soyster et al. 2019).

Even after 10 days, RVFV can be detected by using RT-PCR (reverse transcription real-time polymerase chain reaction). The levels of the antibodies immunoglobulin M (IgM) as well as immunoglobulin G (IgG) grow on days 4 and 7, respectively, after the onset of symptoms, and are identifiable by serological assay for at least 42 days for IgM and several years for IgG, respectively (Paweska et al. 2003). The three segments that make up the RVFV genome are short (S), medium (M), and large (L). The non-structural proteins (NS) and nucleocapsid (N) proteins are made by translating the overlapping open reading frames (ORF) that make up the S segment. The M segment encodes two glycoproteins (Gn and Gc) as a non-structural protein (NSm). The L segment also contains the RNA-dependent RNA polymerase (RDRP) gene (Ikegami 2012).

Modern RVF research aims to learn more about the disease's abortive and zoonotic nature. This includes determining the molecular mechanisms underlying the virus's propensity to cause fetal mortality and birth abnormalities in pregnant animals its ability to be transmitted from animals to people. Other goals include the development of new diagnostic tools and therapeutic interventions, assessing the risk of RVF outbreaks, and implementing early detection and response strategies to prevent disease spread. The purpose of this chapter is to increase knowledge about RVF and its effects in order to better protect human and animal populations.

2. EPIDEMIOLOGY

The epidemiology of RVF is poorly understood, particularly in terms of viral maintenance during inter-epizootic intervals (IEPs). A single species of *Aedes*, mistaken as *Aedes lineatopennis* before 1985 and later identified as *Aedes* (Neomelaniconion) McIntosh, has demonstrated the ability to transmit the virus to its offspring (Wright et al. 2019). It is reasonable to believe that RVFV can survive in the eggs of these species during the dry season and then hatch whenever the rains arrive (Linthicum et al. 1985).

Flooding caused by severe rainfall results in massive increases in mosquito populations that can lead to RVF epizootics, affecting vast numbers of livestock. Because of the relationship between RVFV infection and weather conditions, rainfall and changes in vegetation have been used to forecast RVF epidemics (Anyamba et al. 2010). Massive increases in mosquito populations due to flooding caused by excessive rains can produce RVF epizootics, impacting large numbers of animals. Due of the correlation between RVFV infection and climate, meteorologists have used precipitation and plant growth patterns to predict RVF epidemics. (Lumley et al. 2017). According to research on those insects, more than 53 varieties of mosquitos caught in the wild during an epizootic proved positive for RVFV (Kenneth J Linthicum et al. 2016). Even though more than 65 species have been identified as potential vectors, most of them are *Aedes* and *Culex* species (Mansfield et al. 2015).

Following the 1930s discovery of RVFV, outbreaks began to occur frequently from the 1950s (McMillen and Hartman 2018). In 1950s and 1951s, there were significant epidemics in South Africa and Kenya(Murithi et al. 2011). A second outbreak in South Africa in 1974-1975 led to the first human fatalities there. About 110 human cases were reported, culminating in seven fatalities (McIntosh and Gear 1980). Egypt experienced the greatest RVF outbreak between 1977 and 1979, with an estimated 200,000 human cases leading to 598 verified deaths (Laughlin et al. 1979). Due to unusual high rains, a significant epidemic in East Africa in 1997-1998 led to an estimated 89,000 human cases and 478 fatalities (Hebdomadaire 1998).

Heavy rains in 2018 resulted in an unexpected increase in RVFVs in East African countries like Rwanda, Kenya, Uganda, and Tanzania. This RVF outbreak was the deadliest in Rwandan history, resulting in the loss of two veterinarians and a large number of ruminant lives. Nomadic by clinical signs, not genetic approaches, were used for the majority of diagnoses of RVF in Cattle because of the tiny ruminant's limited economic and cultural relevance in Rwanda (Dutuze et al. 2020). According to RVF geographical distribution, the disease was confined to Sub-Saharan Africa until the year 2000, and then spread to the Arabian Peninsula and the rest of North Africa in 2008 and 2009. Serological research in ruminants and human populations in the Sahrawi refugee camps (Tindouf Province) along the Western Sahara (Algeria) border, in Mauritania, and southern Morocco found RVF-specific IgG antibodies in camels and goats. Geographical distribution of RVFV is shown in Fig. 1.

3. CLINICAL MANIFESTATIONS

3.1. ANIMALS

In pregnant animals, RVF manifests mostly as a sudden and violent abortion. Abortion rates in infected animals may be as high as 100% since the virus attacks the developing embryo directly (Michel Pepin et al. 2010). Animals of different ages and species have different mortality and morbidity rates. The mortality rate was as high as hundred percent in young animals (Gerdes 2002). Fever, loss of appetite, and death occur in young animals with this disease, while fever, weakness and bloody diarrhoea occur in adults as the disease advances from apparent to acute (Busquets et al. 2010). Due to their immature immune systems, young animals are more susceptible to RVF infection and its related consequences. As a result, they become more vulnerable to viral infections, and the virus has a greater potential to harm their growing tissues. Young animals may also be more susceptible to contracting RVF because they are more likely to come into contact with mosquitoes or other vectors that carry the virus.

3.2. HUMANS

In humans, RVFV infections typically cause no symptoms and resolve on their own (Archer et al. 2013). Symptoms of RVF, such as fever, chills, fragility, headache, and joint and muscular pain, become noticeable

Table 1: Symptoms caused by RVFV in animals and humans.

Species	Symptoms of RVFV
Animals	Diarrhea, Decreased milk production, Loss of appetite, Abdominal pain, Weakness, Nasal discharge, Abortion or being born dead.
Humans	Headache, Muscle pain, Joint pain, Encephalitis, Vision disorders, Bleeding from nose gums and skin, Hepatitis.

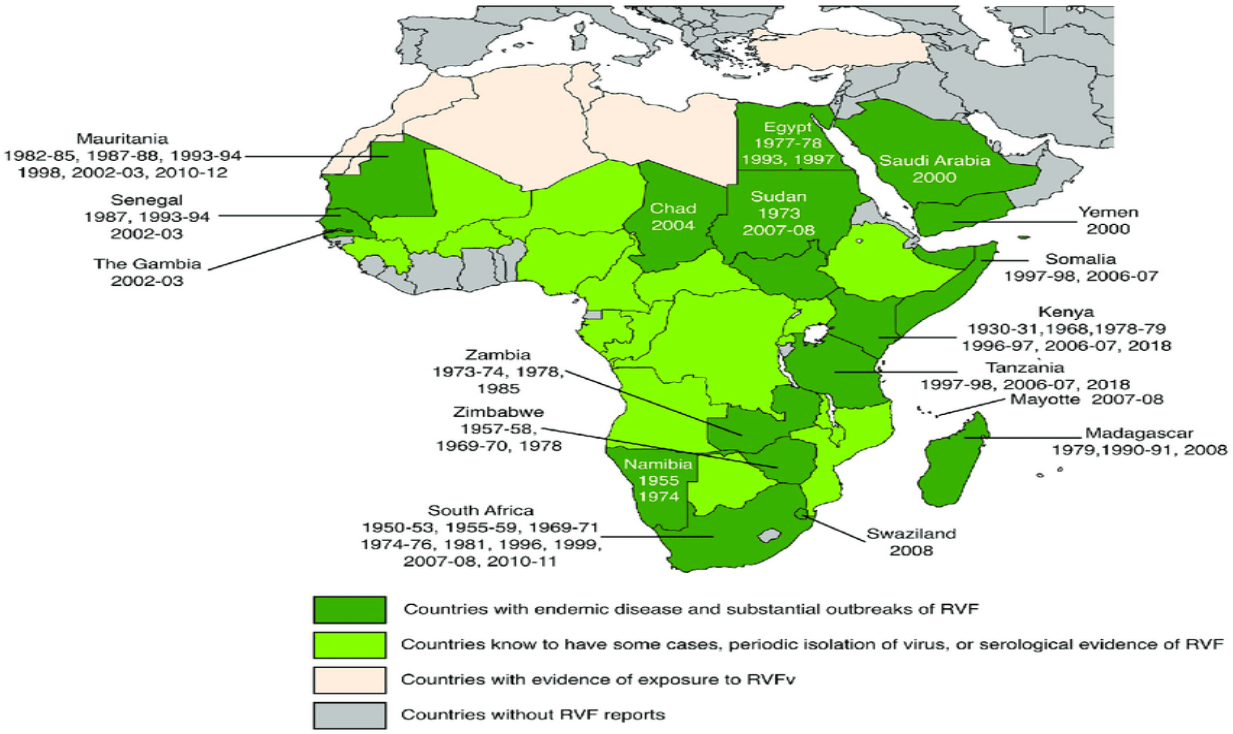

Fig. 1: Geographical distribution of Rift Valley fever (Gerdes 2004).

after an incubation period of 4-6 days. These symptoms will be followed by jaundice, red eyes, vomiting, diarrhea, and an inability to sleep (Seufi and Galal 2010). In addition to these symptoms, RVFV infection can cause blood loss, low haemoglobin levels, low platelet counts, rashes, and general malaise (Baudin et al. 2016). About 1-2% of instances have serious repercussions, and among those are 1. Headaches, irritability, haziness, confusion, coma, encephalitis, and visual hallucinations are all symptoms of a neurological disorder (Seufi and Galal 2010). 2. Ocular abnormalities like retinitis and vision loss (Yoser et al. 1993). 3. Symptoms of hemorrhagic fever with abnormalities in the liver include high body temperature, muscle pain, and bleeding from the mucous membranes(Kahlon et al. 2010). Acute RVFV infection and miscarriages are significantly associated with pregnant women with fever (Baudin et al. 2016). The summary of various symptoms caused by RVFV in animals and humans is shown in Table 1.

4. DIAGNOSIS OF RVF

RVF is diagnosed using a variety of approaches, including virus isolation (Anderson Jr et al. 1989), antigen detection (Meegan et al. 1989) and nucleic acid amplification techniques (Garcia et al. 2001) and by detection of specific antibodies (Swanepoel et al. 1986). In the acute phase of the illness, when a fever is present, RVFV is readily isolated from serum or whole blood samples as well as from the liver, spleen, and

brain of freshly decomposed carcasses/cadavers as well as aborted fetuses. Cell cultures, newborn mice, and hamsters are used to detect the virus (Stear 2005). However, the procedures required to isolate viruses are expensive and time-consuming. An RVF pandemic could present significant challenges for regulatory healthcare authorities due to diagnostic delays caused by the use of conventional virus isolation and identification techniques, especially in countries outside the virus's natural geographical borders. So, researchers are currently working on nucleic acid techniques for rapid RVFV detection and diagnosis.

RVFV detection and quantification PCR assays with high sensitivity, such as RT-PCR, have been reported (Sall et al. 2002) and real-time detection PCR (RTD-PCR) based on TaqMan probe technology (Bird et al. 2007). Real-time reverse-transcription loop-mediated isothermal amplification assays (RT-LAMP) targeting the big RNA segment were created and tested more recently for identifying a variety of RVFV isolates and clinical samples (Le Roux et al. 2009). The detection limit of RT-LAMP was reported to be 0.065 TCID50 per reaction volume (Le Roux et al. 2009) as well as 10 RNA copies per test (Peyrefitte et al. 2008), and there was complete agreement between the RT-LAMP, TaqMan-based RTD-PCR, and virus isolation data (Le Roux et al. 2009). Similar results were found when the assay was used to screen multiple clinical samples from humans as well as animals that had been exposed to the virus in the wild during earlier RVF outbreaks in Africa. Positive clinical specimens can be tested for particular viral genomic targets in less than 30 minutes using the RT-LAMP. Because it may be performed using simple and affordable equipment, the LAMP assay is well-suited for usage in low-resource environments and as a portable device during RVF epidemics in remote regions. In addition to its high levels of analytical and diagnostic dependability, as well as its rapid detection speed (Peyrefitte et al. 2008). During the RVF outbreak that occurred in Kenya in 2006, researchers utilised quantitative real-time RT-PCR, also known as qRT-PCR, to identify individuals with high viremia, which is connected to a bad prognosis (Njenga et al. 2009). In this study, RVFV-RNA levels obtained by qRT-PCR were compared to infectious virus titers to confirm the case. Compared to non-fatal cases, fatal RVF cases exhibited infectious virus concentrations of 105.2 infectious virus particles/mL of blood and viral RNA levels that were over 3-fold higher (mean = 8.6 106 viral RNA copies/mL of serum). The findings in Kenyan (Njenga et al. 2009) and Saudi Arabian(Bird et al. 2007). Patients that were collected during the RVF outbreak in 2000 show that qRT-PCR can quickly identify patients who have a high viral infection and a bad prognosis. This makes it possible for these patients to be prioritized for special or extensive clinical care.

However, it should be emphasized that the conclusive diagnosis or confirmation of RVF, as well as any other suspicious VHF case, should not be solely on a single PCR result. This is because RVF can cause symptoms that are similar to those of VHF. The tests for the identification of nucleic acids need to be carried out in conjunction with other processes, such as the detection of type-specific antibodies for RVFV. In this respect, it is crucial to remember that viremia in RVFV-infected persons is very short-lived, and the majority of infected patients and adult ruminants have subclinical or mild illnesses; nonetheless, IgM and IgG antibodies are easily detectable quickly after viral exposure (Paweska et al. 2005). In addition, the majority of the techniques involving nucleic acids require highly specialized equipment for laboratory use, pricey reagents, and properly educated laboratory people, all of which may only be accessible sometimes if outbreaks arise in far-flung places and prompt detection is necessary.

Several immunological methods allow for the rapid identification of viral antigens in blood and other types of tissue. Some of these methods are immunodiffusion on agar gel with homogenized tissues and immunostaining on liver, spleen, and brain impression smears or cryostat slices. With these tests, it is possible to find the RVFV antigen in affected cells. Histopathological analysis of liver tissue from affected animals reveals a distinct cytopathology (Stear 2005). Antigen detection ELISAs (enzyme-linked immunosorbent assays) for RVFV have also been described. However, the majority of these experiments utilized chemicals that were both costly to produce and posed a biohazard risk to laboratory workers (Zaki et al. 2006). Recently(Zaki et al. 2006) Multiple virus-specific antigens (Gs, Gn, N, NSs) were put to use in immunofluorescence tests with a collection of rat IgG monoclonal conjugates. It has a high sensitivity for

RVFV detection in patient samples, however its utilization requires working with amplified virus in tissue culture. Several RVFV infections in laboratories have been documented, indicating that the virus is extremely infectious for humans (Smithburn et al. 1949). Recently, a completely risk-free approach for antigen detection using a sandwich ELISA (sAg-ELISA) was reported as a potential solution. With its recombinant nucleocapsid protein (recNP)-based internal controls for monitoring regular test performance, this kit can be used for surveillance and diagnosis outside of places where the virus is endemic (P Jansen Van Vuren and Paweska 2009). After inactivation at 56 °C for 1 hour in the presence of 0.5% Tween-20 (v/v), the nucleo capsid protein (NP) of RVFV was identified using the assay. RVFV strains obtained in different parts of the world over the course of 53 years were successfully identified using the sAg-ELISA because of its lack of cross-reactivity with related African phlebo viruses or other members of the family *Bunyaviridae*. The limit of detection was determined to be between log10(102) and log (103) TCID50/reaction volume. The sAg-ELISA was 67.7% sensitive, 97.97% specific, and 100% specific when compared to the results of virus isolation in serum from experimentally infected sheep and RVF patients. The approach demonstrated perfect accuracy when testing organ tissues from both naturally infected buffalo fetuses and artificially infected mice. The presence of NP antigens in infected culture supernatants was analyzed as soon as 8 hours post-inoculation with 105.8 TCID50/mL RVFV. The assay's speed makes it ideal for first-pass viral detection during in vitro isolation. Because of its excellent specificity, security, and convenience of use, the sAg-ELISA is an invaluable diagnostic tool that may be utilized in African laboratories that are less well-equipped as well as for the regular differential diagnosis of VHF (Jansen Van Vuren and Paweska 2009).

RVF diagnosis frequently uses serum samples. In domestic ruminants, viremia titers between 105.6 and 109.0 mouse LD50/mL have been observed (Swanepoel et al. 1986), and humans have a mouse LD50/mL of 108.6 while an adult African buffalo has a TCID50/mL of 105.4(Davies et al. 1981). Although viremia in RVFV-infected individuals can reach high titers, this state of infection only lasts for a short period of time. As a result, its utility in viral detection methods for RVF epidemic detection is limited. The use of an ELISA panel that tests for both viral antigens and IgM antibodies is recommended for detecting recent RVFV infection. Alternatively, RVFV can persist in elevated titers in the ovine brain and liver lasting 21 days, and in the spleen for up to 30 days(Swartz et al. 1981). While the sAg-ELISA has a high degree of diagnostic precision for detecting RVFV in tissues that have been infected, these samples typically contain virus levels that are 10- to 100-fold above the detection limits of the assay (Morrill et al. 1987). Therefore, it is suitable for testing products made from human corpses and aborted foetuses. In the midst of an RVF epidemic, unexpectedly high rates of abortion and mortality among young animals are noticeable.

Infectious diseases can be diagnosed using serological testing, clinical observations, epidemiological history or when seroconversion is proven. Sero diagnostic techniques are also commonly utilized in epidemiological studies to demonstrate disease freedom. Traditional techniques for determining whether or not a patient has RVFV antibodies include haemagglutination inhibition, complement fixation, indirect immunofluorescence, and viral neutralization tests (VNT) (Stear 2005). The disadvantage of these techniques include health risks to laboratory personnel (McIntosh and Gear 1980) and restrictions on their use in regions of the world where RVF is not prevalent. Recent infection can be confirmed by testing for IgM antibody expression in an ELISA or by observing seroconversion, which is defined as a 4-fold or greater increase in antibody titer in paired serum samples (Paweska et al. 2007).

Although it is the gold standard, the VNT is laborious, costly, and takes 5-7 days to perform. It can be done using just tissue cultures and regular stocks of live viruses. As a result, it is infrequently employed and only in extremely specialized reference laboratories. However, from the perspective of using the VNT as a diagnostic discriminator in validation studies, it is crucial to remember that RVFV infection induces lifelong neutralizing immunity and that there is no evidence for the existence of serological subgroups or major antigenic variation between virus isolates of different chronologic or geographic origins (Coetzer and

Tustin 2004). With minimal cross-neutralization with other *phleboviruse* , the VNT is quite accurate (Tesh et al. 1982). However, work with a live virus requires the use of dedicated biocontainment labs.

Recent advances in ELISA technology have resulted in a number of formats that are proving to be invaluable in disease monitoring and control initiatives, import/export veterinary certification, as well as monitoring of immune response in vaccinations, and they are based on inactivated antigens extracted with sucrose and acetone and obtained from either tissue culture or mouse brain(Pepin et al. 2010). They are able to replace existing diagnostic methods, which pose hazards to one's health and need isolation in high security institutions outside of RVF-endemic areas, with techniques that are extremely reliable, safe, and accurate. Nonetheless, bio-containment facilities are required to lessen the likelihood of infecting laboratory personnel during the production of the antigen for these tests. In order to overcome these obstacles, the recNP of RVFV is the basis of a novel indirect ELISA for the detection of particular antibodies in human as well as animal serum. (Paweska et al. 2008). The nucleocapsid protein appears to have significant levels of conservation among members of the *Bunyaviridae* family. (Gauliard et al. 2006) and studies on antigenic cross-reactivity in animals (Swanepoel et al. 1986) and the indirect ELISA based on recNP (Paweska et al. 2007) failed to offer proof that additional African phleboviruses could make it difficult to reliably diagnose RVF. Since NP is the most abundant and immunogenic viral element in the RVFV virion, it seems to be the best candidate for creating immunological reagents for antigen detection testing. The simplicity of mass-producing a recombinant RVF NP that is both soluble and very pure (Petrus Jansen van Vuren et al. 2007) will enable fully automated, less expensive sera bulk screening. The development and validation of next-generation diagnostic immunological reagents and tests, such as those based on RVFV recombinant antigens and implemented in ELISA formats, is strongly encouraged. The test reagents have been made safe for routine use in RVF-free environments by cloning and expressing RVFV antigens, which eliminates the possibility of laboratory infections and residual viruses. Although it has not yet been shown through rigorous validation trials, it is expected that recombinant antigen-based ELISA will be at least as precise as ELISA based on the virus's full inactivated antigen for identifying the virus in livestock populations from different areas.

5. PATHOGENESIS

Human illnesses, often acquired through contact with contaminated animal tissues, pose a hazard to their jobs as veterinarians, farm workers, and abattoir staff (Archer et al. 2013), manifesting as mild febrile sickness or subclinical infection. However, the infection can occasionally progress to a serious illness manifesting as hemorrhagic fever syndrome, encephalitis, retinal degeneration, or other consequences. The effects of these disease kinds are typically severe, with high mortality or long-term vision and brain function damage. There is a viremia in the early stages of the disease, 1-4 days post infection, which decreases as levels of antibodies rise. A vasculitis associated with viremia can cause thrombosis and other vascular problems, frequently appearing days to weeks after the original infection. In highly vulnerable species like sheep and mice, liver infection plays a significant role in infection; this develops within the acute infection phase and may become the main pathological characteristic (Bingham and van Vuren 2020).

RVF hemorrhagic fever syndrome is characterized by haemorrhages and multi-organ failure. It is brought on by fulminant hepatic necrosis and vasculitis, two conditions that cause disseminated intravascular coagulopathy by preventing the renewal of clotting factors in the liver (hepatic necrosis) and depleting them in the vasculature (vasculitis), respectively. Clinical symptoms include diarrhea, jaundice, hematemesis, bleeding from the gums, conjunctivae, and other mucous membranes, as well as vomiting (Swanepoel 2004). Viral load, cytokine responses, and coagulation pathways significantly

influence disease severity (Jansen van Vuren et al. 2015). In a tiny percentage of instances, encephalitis may appear days or weeks after the first feverish episode, and its clinical manifestation may depend on the location of infection foci in the brain (Ikegami and Makino 2011). An area of localized necrosis with mononuclear cell perivascular cuffing is seen on histological examination (Van Velden and McIntosh 1977).

RVFV antibodies are typically present even when encephalitis occurs, suggesting that the illness is caused by immunologically mediated injury in response to lingering infection. Like many viral encephalitis, recovery might take a while and have different results. Local ocular vascular thrombosis is likely followed by retinal degeneration, which can develop during the first febrile illness or up to four weeks later (Swanepoel 2004). It may be connected to uveitis and retinal detachment. Different types of vision loss can be persistent and frequently permanent (Ikegami and Makino 2011).

Sheep, and especially young lambs, are particularly susceptible to RVFV infection. Abortions are typically the first sign of infection in a herd, and they can be quite common, with up to 100% of pregnant ewes losing their lambs (Swanepoel 2004). Infection of several fetal tissues, including the placenta's fetal-maternal interface, results in abortion (Oymans et al. 2020). Lambs that are infected and live to adulthood are typically feeble and only live a few days. Animals exposed to experimentally transmitted diseases develop viremia from days 1 through 7, peaking around day 2 (Wilson et al. 2016).

However, adult sheep may occasionally experience fatal sickness, primarily brought on by hepatic necrosis, vasculitis, and related conditions. However, this is less common because of adult sheep's relative tolerance. Clinical symptoms include bloody diarrhea, congested mucous membranes, lethargy and weakness (Swanepoel 2004). Hepatic necrosis, vasculitis, renal tubular necrosis, and lymphoid necrosis are among the main lesions (Odendaal et al. 2019). While usually not as severe, the sickness in other ruminants can be similar to that in sheep. The most frequent result of infection is abortion in pregnant cattle, goats, and camelids, while young animals seem extremely susceptible (Rippy et al. 1992). Rodents and non-human primates are used as laboratory models to study human infection and vaccination (Ross et al. 2012). Replication cycle of RVFV is shown in Fig. 2:

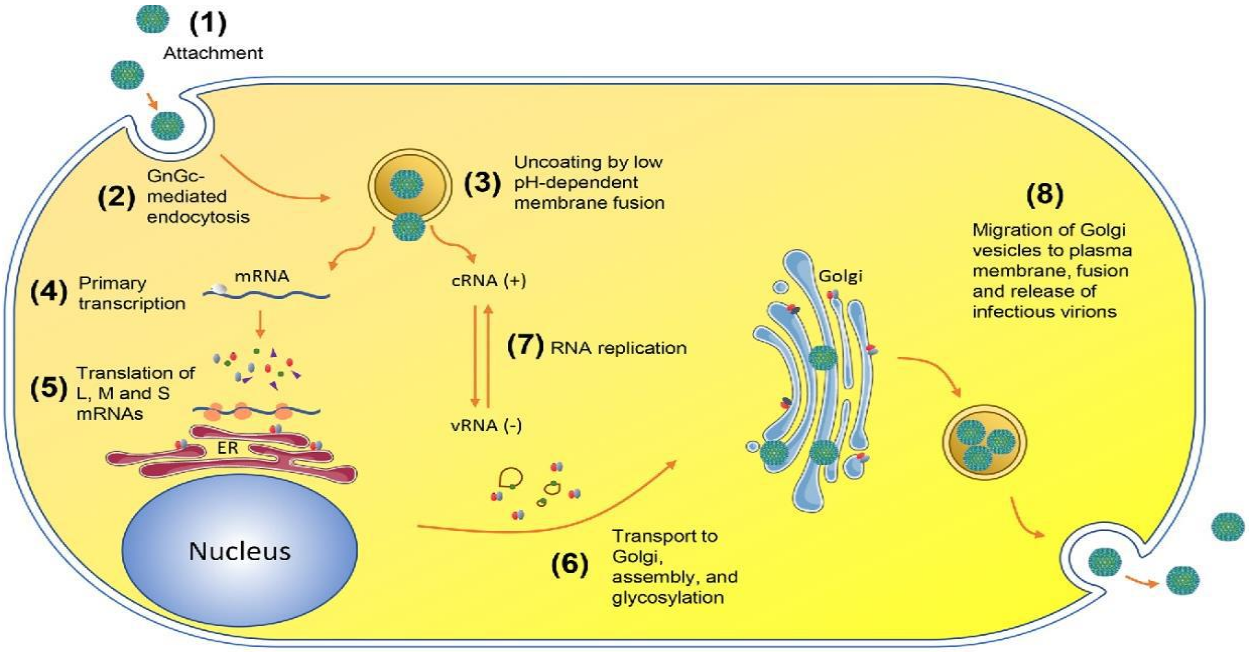

Fig. 2: Replication cycle of RVFV (Wright et al. 2019).

6. ZOONOTIC NATURE

RVFV infection can spread to people by mosquito bites or contact with contaminated blood, tissue, or bodily fluids. Additional ways to become infected include handling contaminated placentas, fetal and maternal blood from animals that have been put to death, and consuming raw milk or uncooked meat from sick animals (Helmy et al. 2017). Around 240 of the 400 recognized zoonotic illnesses are transmitted from animals to humans, accounting for around 60% of all pathogen-caused human infections. Millions of fatalities and an astounding billion incidences of human illness arise from this year, costing the economy hundreds of millions of dollars over only the last two decades. Most newly emerging infectious diseases during the past 70 years have been zoonotic. Additionally, endemic zoonosis has grown. Some zoonosis are becoming increasingly or solely dependent on humans as the transmission host as a result of new diseases, ecological changes, and social pressures (Seetah et al. 2020).

Human fatalities have been high during RVF epidemics due to a variety of causes, including contact with newly slaughtered diseased sheep meat and a lack of awareness about public health. Risk factors for human RVF infection include but are not limited to: age, sex, occupation (via contact with animal blood or bodily fluids), water, nutrition, social status, and poor sanitation (Nyakarahuka et al. 2018). Camel, wild animal, and vulnerable cattle host populations exist in Egypt without immunization (Gad et al. 1995),the ongoing of sick slaughter animals for human food and the ongoing importation of animals, particularly camels, from enzootic nations like Africa and Sudan. Humans can become infected with RVF by eating meat infected with RVFV (Fawzy and Helmy 2019).Transmission of RVFV from animals to humans is shown in Fig. 3:

7.REPRODUCTIVE IMPLICATIONS

There were indications of reproductive failure, including abortions, the ejection of healthy, macerated, and mummified fetuses, the delivery of frail and stillborn piglets, and neonatal fatalities. Several samples of live piglets tested positive for RVFV antibodies and antigen/RNA, whereas a small number of aborted fetuses did. Both viral and non-infectious factors, as well as their pathophysiology, may contribute to these reproductive failures (Pozzi and Alborali 2012). It was established that RVFV was the most likely cause since the pigs were taken from an enclosed breeding herd that adhered to stringent biosecurity and disease control laws and regulations. These circumstances, which are helpful against management causes, led to the conclusion that RVFV was the most likely culprit. This is because to the fact that widespread pathogenic diseases that have been associated to stillbirth, embryonal deaths, mummies and infertility were not likely to be the reason. During the epidemic of RVF in South Africa in the 1950s, pregnant sows and ewes both experienced abortions, which our data confirm, supporting Weiss' field observations from that time period (Weiss 1957).

Teratogenicity in pig farms, which can be brought on by hereditary factors, nutritional factors, toxins, or infectious agents, is a widespread problem around the world, with documented incidence rates ranging from 0.11% to 4.96% (Straw et al. 2009). In this study, 9% of the piglets had congenital abnormalities in both the neonates and the aborted fetuses (Coetzer 1980). The researchers made this discovery after observing that the mouse brain passaged and live-attenuated Smith burn vaccine strains when administered to pregnant sheep between the ages of 42 and 74 days into their pregnancies, caused spontaneous abortions and teratogenic outcomes such as arthrogryposis (Coetzer and Barnard 1977).

8. IMPACT ON PREGNANCY

The hallmark sign of an RVF epizootic is a significant increase in the number of abortions that take place in pregnant ruminants almost simultaneously. These widespread abortion occurrences, also known as "abortion storms," make it possible to differentiate RVF from a number of other common infectious

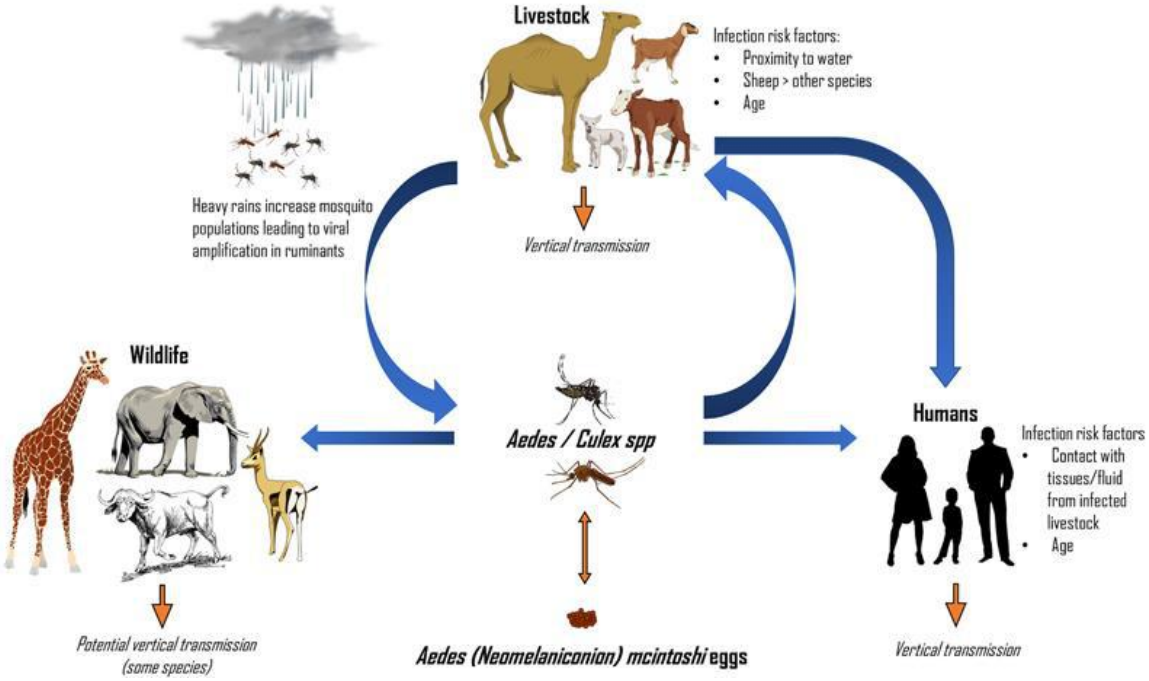

Fig. 3: Rift Valley fever virus cycle (Wright et al. 2019)**.**

causes of abortion in ruminants, such as Q fever (*Coxiella burnettii*), salmonellosis, chlamydiosis, listeriosis, or toxoplasmosis. This differentiation is made possible by the fact that widespread abortion occurrences have been given the name "abortion storms." An active surveillance technique using sentinel herds is unaffordable in non-endemic nations. On the other hand, reliable passive surveillance-based processes that depend on the detection and prompt reporting of significant abortion occurrences to national authorities (for example, more than twenty percent of pregnant animals in a herd suddenly aborting with accompanying signs and symptoms of jaundice within survivors) could provide an inexpensive means to detect the increase of this major veterinary and human health threat (Michel Pepin et al. 2010).

Large quantities of virus particles are present in aborted fetal tissues and placental membranes, and these particles have the potential to either directly contaminate the environment or infect nearby animals. It is possible for animals to contract RVFV either by the bite of a mosquito that is already infected with the virus or through direct contact with infected tissue from animals, bodily fluids, or fetuses. This is especially true in situations that are associated with abortions(Theiler and Medicine 1957). A study looking at the prevalence of abortion during the 1977 epidemic in Egypt found no rise above the average frequency of abortions, indicating that the relationship between RVFV infection and human abortion is less obvious than in ruminants(Abdel-Aziz et al. 1980). However, a study published in 2016 revealed for the first time a significantly elevated risk of miscarriage following laboratory-confirmed RVFV infection during pregnancy. However, compared to cattle, people have a decreased risk of abortion. Additional research is required to better understand the mechanisms driving pregnancy loss brought on by RVF (Wright et al. 2019).

9. CONTROL OF RVFV

The One Health strategy advocated by RVFV requires the participation of the following groups: The danger of further transmission of the disease among all affected species can be reduced by (1) Prompt diagnosis,

alert, treatment of the affected individuals and animals, and provision of alerts by medical and veterinary physicians, diagnosticians, epidemiologists, and public health specialists, (2) Wildlife experts who need to know how the disease spreads among animals and what role it plays in animal populations, (3) Entomologists to learn about the vector's biology, its role in RVFV epidemiology, and to provide direction on vector control, (4) The disease's impact on ecology and the natural world must be evaluated by ecologists, (6)It is the responsibility of governments and policymakers to implement the policies and provide the funding essential to One Health's focus on prevention and control. The economic and social implications of RVF sickness on populations should be assessed, according to economists and social scientists, (7) Vaccinologist to develop and supply antiviral vaccinations medical treatment (for both humans and animals) and vector control (through insecticides, acaricides, and larvicides) are provided by the eighth sector: the pharmaceutical industry. According to the One Health strategy, in order to decrease outbreaks in people, it is necessary to (1) provide a safe and effective RVFV vaccine to susceptible animals under government supervision, (2) set up a reliable surveillance system with a rapid reporting programme for the disease, and other measures, (3) conduct epidemiological research to identify risk factors, and (4) instruct veterinary and medical health professionals on the diagnosis and treatment of suspected cases (Fawzy and Helmy 2019).

10. PREVENTION OF RVFV

RVFV infections in livestock are now thought to be prevented only by vaccination. However, a lot can still be done to improve the current livestock vaccines. Additionally, the lack of any licensed human vaccinations makes it difficult to use techniques to prevent spillover into humans (Faburay et al. 2017). It would be desirable to replicate the durable protection from exposure to nature. In the USA, MP-12 and TSI-GSD-200 are the two vaccines now recognized as investigational new human drugs (Dungu et al. 2018). The US Army developed TSI-GSD-200, a formalin-inactivated vaccine, to protect those whose work may expose them to infection. It has a great safety profile, but it requires numerous boosters to be effective, and even then, over 10% of vaccines have low nAb titers or fail to seroconvert (Pittman et al. 1999).

The most frequently used commercial vaccination for livestock, named after its creator Smith burn, is a live-attenuated RVFV that develops long-lasting immunity after a single injection (Faburay et al. 2017). However, the Smith burn vaccination cannot be given to pregnant animals because residual virulence increases the chance of abortion (Botros et al. 2006). Genetic reassignment with wild-type RVFV is also possible, but this is unlikely to result in a pathogenicity rise beyond that of the wild-type virus. A novel RVFV vaccine would have the added benefit of distinguishing between infected and vaccinated animals (DIVA). The antibody profile obtained by utilizing live-attenuated RVFV as a vaccine, such as Smith burn, is identical to natural infection, making outbreak mapping challenging in the face of vaccination. The advantage of subunit vaccinations is that they do not contain all RVFV antigens. It is feasible to distinguish between animals that have been naturally exposed and those that have been vaccinated by assessing reactions to the N protein, which is not present in the vaccine (Wright et al. 2019).

Clone 13 was one of several viral clones identified from a human patient infected with the 74HB59 strain in the Central African Republic. It was discovered to be naturally attenuated due to a significant loss in the NSs gene, the key virulence factor, and subsequent infection in mice demonstrated that it did not cause disease (Muller et al. 1995). Clone 13 has been shown in cattle, sheep, and goats to be safe and immunogenic after a single injection (Njenga et al. 2015). On the other hand, overdose tests in pregnant ewes have revealed that clone 13 can pass the placental barrier and generate teratogenic

consequences (Makoschey et al. 2016). Several promising vaccine candidates are now being developed to overcome the shortcomings of current vaccinations, especially single dose efficacy and safety issues. In sheep, a subunit vaccination based on the GnGc glycoproteins demonstrated 100% effectiveness (Faburay et al. 2016). Another vaccine, RVFV-4s, which has the M segment separated into two portions that encode Gn and Gc independently, has provided sterile immunity in lambs after a single inoculation (Schreur et al. 2015). Furthermore, vaccinated pregnant sheep revealed no teratogenic effects or presence of the RVFV-4s virus in their fetuses' blood or organs (Schreur et al. 2017).ChAdOx1 RVF is another possibility, a replication-deficient chimpanzee adenovirus vectored vaccine encoding the Gn and Gc glycoproteins. In sheep, goats, and cattle, ChAdOx1 RVF showed 100% effectiveness against RVF viral challenge (Warimwe et al. 2016). The ChAdOx1 RVF is also intended for use in humans, where the ChAdOx1 vector expressing additional antigens has shown a great safety profile (Stylianou et al. 2015).

11. FUTURE DIRECTIONS

11.1. FUTURE DIRECTION ACCORDING TO THE ONE HEALTH APPROACH IS

11.1.1. COLLABORATIVE AND INTERDISCIPLINARY RESEARCH

Future research on RVF should be collaborative and interdisciplinary, bringing together experts from environmental science, public health, and both human and veterinary medicine. Through such initiatives, the causes of the disease's origin and spread will be found, and practical control strategies will be created.

11.1.2. PREVENTION AND CONTROL STRATEGIES

The creation of RVF prevention and control strategies must be prioritized. These covers creating novel diagnostic instruments, vaccinations, and antiviral medications. Effective surveillance and control measures must also be implemented if the disease is to be stopped from spreading.

11.1.3. ENHANCING REPRODUCTIVE HEALTH

Future RVF research should aim to enhance animal reproductive health, emphasizing the one-health approach. This entails figuring out the molecular processes that lead to fetal demise and birth abnormalities and creating fresh preventative measures.

11.1.4. RAISING AWARENESS

To implement effective control measures, there must be a greater understanding of RVF and its effects on the health of people, animals, and the environment. Raising public knowledge will make it easier to put early detection and quick response measures into place, lessening the effects of RVF outbreaks.
Overall, the fight against RVF as a zoonotic and abortive illness will require a one-health approach. It will be essential to conduct collaborative and multidisciplinary research and effective preventative and control strategies, improve reproductive health, and create awareness.

12. CONCLUSION

There were clear distinctions between the clinicopathological outcomes of RVFV infection in domestic pigs, sheep, and cattle, as well as parallels in these outcomes, according to this study and earlier ones

as well. Similarities included reproductive problems, the ability to transmit the virus vertically, the capability to detect anti-RVFV antibodies and viral RNA in the offspring born to infected sows, the absence of clinical indications in immature and non-pregnant animals, and the presence of macroscopic lesions typical of RVFV infection, particularly in the liver, spleen, and kidneys. Between this investigation and others carried out in pigs, lambs, and rats, there were a lot of inconsistencies with clinicopathological results and laboratory analysis of samples from experimentally infected animals. These contradictions were characterized by negative results for several, but one or two analytes. On histology, liver lesions in infected pigs were most commonly characterized by mild necrosis and non-lipid glycogen-filled vacuoles. These lesions differed from their counterparts in domesticated ruminants in that neonatal piglets were subclinically infected with the virus. In contrast to what may be observed in domestic ruminant animals, where significant pan-necrosis can be found, wild ruminants do not suffer from this condition.

In conclusion, Rift Valley fever (RVF) is a viral infection that has the potential to be zoonotic as well as abortive. Insights have been gained into the molecular mechanisms behind the virus's abortive character and the elements that lead to its genesis and dissemination in humans. Even though RVF research has made great strides, there is still much to be done in terms of creating efficient defence and enhancing animal reproductive health. The one health approach is essential in combating this developing infectious illness by highlighting the interdependence of human, animal, and environmental health and encouraging interdisciplinary and collaborative efforts in prevention, control, and treatment. It is hoped that by continuing to concentrate on these areas, RVF may be effectively managed and prevented, safeguarding both animal and human populations from this significant virus.

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AIDS: Treatment Strategies for AIDS Patients

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ABSTRACT

Initial cases of acquired immune deficiency syndrome were identified among homosexuals in 1981 in the United States. The human immunodeficiency virus was identified in 1983, and in 1984, it was linked to AIDS. There are two strains, HIV-1 HIV-2, HIV-1 is more common in humans. Antiretroviral therapy is the primary treatment used for AIDS. There are 23 antiretroviral drugs currently available with different modes of action. These drugs are categorized based on the stage of viral life cycle that they hinder. Non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors are the two distinct categories of these drugs. The primary function of these drugs is to improve the quality of life of these patients and provide them with mental security to have an everyday life among other people. There are some adverse effects of antiretroviral therapy in both short-term and long-term usage, but they are nothing compared to the issues AIDS causes. Gastrointestinal tract toxicities, rash, anemia and renal dysfunction are some common side effects of antiretroviral therapy but they are relatively easy to manage. Pre-exposure prophylaxis and post-exposure prophylaxis are two types of treatments used for patients, health workers and any individuals at risk of getting exposed to HIV, like family members of patients. Poor adherence to the drugs is the most common cause of contact and spread of HIV among patients, health workers and exposed individuals. Management of patients affected by AIDS is much easier now than it used to be, and it's getting even better with time.

Keywords: AIDS, HIV, Antiretroviral therapy, Non-nucleoside reverse transcriptase inhibitors, Nucleoside reverse transcriptase inhibitors

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1. INTRODUCTION

In 1981, the initial cases of AIDS were identified among male homosexuals, IV drug abusers, and hemophiliacs in the United States, as well as sexually active heterosexuals in several nations in equatorial Africa. The human immunodeficiency virus (HIV) was initially identified in 1983, and by 1984, it had been clearly linked to AIDS patients and high-risk populations. Prospective epidemiological studies documenting the absolute necessity for HIV infection for the development of AIDS provide the strongest evidence that HIV causes AIDS. Multiple studies have demonstrated that AIDS does not exist in nations where no residents test positive for the virus, but flourishes in nations where many residents test positive. Not only that, but the arrival of AIDS in a nation follows closely on the heels of the introduction of HIV to that country (Fauci and Lane 2020).

Over 25 years ago, HIV was a completely new virus. Early patients usually had a baffling array of neurological signs and symptoms suggesting central nervous system involvement in addition to systemic opportunistic infections. These severe illnesses are now understood to be the last manifestation of an initially hidden and symptomless infection. Before the advent of highly active antiretroviral treatment (HAART), anyone infected with HIV would almost certainly advance from an asymptomatic years-long pre-symptomatic stage to the symptomatic and ultimately lethal end stages (AIDS) (Anthony and Bell, 2008).

HIV responsible for Acquired Immune Deficiency Syndrome (AIDS), and the virus has spread to over 65 million people all over the world. About 14,000 people are infected with HIV every day, and more than 95% of them live in underdeveloped nations. About 12,000 people between the ages of 15 and 49 (mostly women) get infected each year, and 80% of these cases are the result of heterosexual transmission. Twenty-five million of them have already perished (Sudharshan and Biswas 2008).

2. CAUSATIVE AGENT

HIV-1 and HIV-2 are two strains of the HIV, both of which are human retroviruses with RNA genomes and the distinctive 'Reverse transcriptase enzyme. HIV-1 is the primary pathogen in human illness. The virion, measuring 100-120 nm in diameter, is composed of several components. These include an outer envelope, a protein shell forming the core, and an inner core that takes on a cone-shaped structure. Within this inner core, one can find the RNA genome, the enzyme known as "reverse transcriptase", and various core polypeptides. In contrast, HIV-2 is recognized for its comparatively less severe and gradual impact on the immune system. Individuals who exhibit symptoms resembling those of AIDS but yield negative results for HIV-1 should undergo testing for HIV-2 (Sudharshan and Biswas 2008).

There are two distinct categories of helper T cells, known as CD4 T cells, which exhibit varying profiles of cytokine production. The cells primarily impacted in HIV infections are CD4 and CD8 cells. The typical range for CD4 counts is 300 to 1000 cells per cubic millimeter but decreases during the infection (Mosmann and Coffman 1987).

3. MODE OF ACTION OF HIV

Upon cellular infection by HIV, the viral RNA undergoes a process of conversion into viral DNA, facilitated by the enzyme reverse transcriptase. Subsequently, this viral DNA is replicated and integrated into the DNA of the host cell. Subsequently, the viral DNA provides instructions to the host cell, prompting it to engage in replication of the genetic material of the HIV. The protease enzyme facilitates the assembly of replicated viral genetic material into progeny viruses, subsequently enabling their egress from the host cell for the purpose of infecting neighboring cells. The initial category of ARV reverse-transcriptase inhibitors functions during the early stages of HIV life cycle, effectively halting the replication of the virus subsequent to HIV infection (Oguntibeju 2012).

4. TREATMENT STRATEGIES

There are different strategies used for the treatment of HIV patients, they are discussed below.

5. ANTIRETROVIRAL THERAPY

Recent studies have provided evidence that during the initial stages of infection, HIV exhibits a preference for infecting CCR5, CD4 and memory T lymphocytes located in the gastrointestinal tract. This phenomenon leads to a swift, extensive, and potentially irreversible depletion of CD4 cells leading to disruption of the intestinal mucosa and infiltration of microbial translocation products into the systemic circulation (Brenchley et al. 2004). Currently, there are 23 antiretroviral agents available, each with distinct mechanisms of action. These agents can be combined in various ways to optimize treatment outcomes (Palmisano and Vella 2011). Long-term antiretroviral therapy has demonstrated efficacy in reducing the burden of inflammation associated with HIV infection. However, it is essential to note that complete elimination of inflammation is not achievable through this treatment. The presence of inflammation remains causatively linked to various complications, including cardiovascular diseases, which have emerged as a significant concern within the HIV-infected population (Grinspoon and Carr 2005).

Antiretroviral drugs are categorized based on the specific stage of the viral life cycle that they impede. One possible basis for subclassification is the chemical structure of the organisms in question. One significant development in the chronology of HIV disease has been the emergence of novel drug categories during the years 1995-96. This advancement facilitated the implementation of combination HAART and subsequently led to the progressive transformation of HIV infection into a chronic state, typically without fatality (Palella et al. 1998). Until 2010, over 20 antiretroviral agents have been granted licenses, often through an expedited approval process. These licenses were granted based on not only the clinical effectiveness of the agents, but also their impact on plasma HIV RNA concentration. This concentration serves as a validated surrogate marker for measuring HIV activity (Palmisano and Vella 2011). The conventional approach to ART involves the administration of a minimum of three antiretroviral medications in order to effectively suppress the human immunodeficiency virus and halt the advancement of HIV-related illness (Oguntibeju 2012).

The utilization of a strong combination of ART, predominantly comprising a minimum of three antiretroviral medications, has exhibited significant enhancements in the well-being and longevity of individuals afflicted with HIV in regions where ARVs are readily available. Furthermore, there are several preparations available in fixed-dose combinations. These components can be integrated to formulate various efficacious treatment plans for both initial and subsequent therapy. Despite its limitations, ART plays a crucial role in preserving lives and enhancing the functionality of the immune system. Additionally, it mitigates the likelihood of various HIV-related complications, as well as those unrelated to AIDS (Shen et al. 2008).

Furthermore, ART effectively reduces the risk of HIV transmission. There is a growing body of evidence that suggests the potential advantages of ART for individuals with elevated CD4 counts. The utilization of HAART has proven effective in managing the replication of HIV-1. However, when treatment is not administered optimally, it can lead to the emergence of resistance and subsequent resurgence of viral activity (Yang et al. 2020).

6. MODE OF ACTION OF ART DRUGS

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are the two distinct categories of these pharmaceutical compounds. Typically, NNRTIs interact with the reverse transcriptase enzyme to hinder the conversion of HIV RNA into DNA. Consequently, this

impedes the replication of the virus within the cell's DNA. On the other hand, NRTIs become part of the viral DNA, obstructing its ability to generate viral copies. NRTIs disrupt the replication cycle of HIV by competitively inhibiting the activity of HIV reverse transcriptase enzyme and causing premature termination of the DNA chain (Cox et al. 1994).

7. QUALITY OF LIFE OF PATIENTS USING ART

Given the widely acknowledged significance of health as a primary determinant of overall quality of life (QOL), there has been a proposition positing that QOL might be distinctly influenced by particular diseases, such as HIV/AIDS (Oguntibeju 2012).

Research findings indicate that individuals diagnosed with HIV/AIDS encounter a range of psychological challenges, including but not limited to stigma, poverty, depression, substance abuse, and cultural beliefs. These factors have the potential to impact not only their physical well-being but also their mental and social well-being, thereby compromising their overall quality of life. Consequently, these issues can significantly disrupt the individuals' ability to engage in essential activities and pursue their personal interests (Aranda-Naranjo 2004).

The assessment of clinical progress in individuals with HIV infection who are receiving antiretroviral therapy frequently involves evaluating the decrease in mortality rates, rates of opportunistic infections, or the severity of symptoms associated with advanced AIDS. However, there has been an increasing interest in evaluating the quality of life among individuals who are living with HIV/AIDS, particularly with the availability of more effective and easier treatment regimens. Scientific and clinical research has consistently demonstrated the high efficacy of ART in producing significant benefits for individuals living with HIV and AIDS. Despite the presence of some negative effects, the overall impact of ART on the quality of life and general health of these individuals is positive on a global scale (Burgoyne 2008).

Significant enhancements in the average quality of life were observed among HIV patients who participated in two multicenter clinical trials for antiretroviral therapy. These improvements were evident after 1 and 4 months of receiving new ART regimens, and they remained consistent for a duration of 12 months (Mannheimer 2005). The researchers conducted an assessment of patients' quality of life for a duration of 4 months following the initiation of ART, taking into account the subjective perceptions, values, and preferences of the individuals. The findings revealed that a considerable percentage of patients (66.4%) reported a positive or highly positive QOL after approximately 4 months of ART. Moreover, a significant disparity was observed when comparing these results to the baseline values prior to the commencement of ART treatment (Campos 2009).

8. ADVERSE EFFECTS OF ART

ART exhibits both short-term and long-term adverse effects on the patients that also need avoiding or managing.

9. SHORT TERM EFFECTS

9.1. GASTROINTESTINAL TOXICITIES

The primary causes for discontinuation during the acute phase of treatment, as observed in a retrospective analysis of the HOPS database, were gastrointestinal (GI) toxicities, specifically vomiting, nausea, and diarrhoea (O'Brien et al. 2003).

10. RASH

A skin rash occurs when skin becomes red, inflamed and bumpy. Rash is a frequently observed transient adverse event that can be attributed to a wide range of pharmaceutical agents. However, NNRTIs are primarily implicated as the principal culprits in HAART. The rash commonly observed in individuals taking NNRTIs typically presents as erythematous, maculopapular and exhibits a widespread distribution. Rash has been documented in a range of 10-17% of patients who have been administered NNRTIs (Carr and Cooper 2000).

11. HYPERSENSITIVITY REACTION

Hypersensitivity reactions (HSR) may manifest in response to certain antiretroviral drugs, particularly Abacavir (ABC) and Nevirapine (NVP). HSR is distinguished by a constellation of symptoms including fever, rash, myalgia, abdominal pain, elevated liver transaminases, fatigue, breathing problems, muscle and joint pain, paresthesia and edema. In severe cases, HSR may lead to renal or hepatic failure. A notable characteristic of drug HSR is the potential occurrence of a severe and potentially life-threatening anaphylactic reaction upon re-administration of the causative drug to the patient (Mallal et al. 2008).

12. CNS TOXICITY

The occurrence of Central Nervous System (CNS) toxicity is frequently observed in relation to the NNRTI Efavirenz (EFV). This phenomenon has been evidenced in various research studies, most notably in a specific sub analysis of the AIDS Clinical Trials Group (ACTG) 5095 trial, specifically referred to as ACTG 5097 (Hawkins 2010).

13. ANEMIA

Anemia is a detrimental occurrence primarily linked to ZDV and its myelosuppressive impact. According to the findings of the GS 934 study, it was observed that a proportion of 6% of patients belonging to the Zidovudine (ZDV) group had terminated their participation in the study after 48 weeks due to the presence of anemia (Pozniak et al. 2006).

14. LONG TERM ADVERSE EFFECTS

14.1. CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) continues to be the primary cause of mortality on a global scale. A substantial multinational cohort consisting of 33,000 patients was established with the primary objective of investigating the correlation between HAART and adverse effects (AEs). There is an increased probability of experiencing myocardial infarction (MI) by 16% for every year of combination HAART, primarily attributed to the utilization of protease inhibitors (PIs). (DAD Study Group 2007).

15. HEPATOTOXICITY

Several antiretroviral agents have the potential to induce hepatotoxicity. NVP is linked to the development of acute liver disease through a HSR. The examination of the ATHENA cohort, focusing on pre-therapy and

current CD4+ cell counts, revealed a 6.2% incidence rate of NVP associated HSR. This risk was found to be comparable between patients who were treatment-naive and those who had prior treatment experience (Hawkins 2010).

15. RENAL DYSFUNCTION

The primary association of renal dysfunction has been observed with TDF, as the parent NRTI tenofovir is actively accumulated in the proximal renal tubule through the activity of renal-specific organic anion transporters 1. The utilization of TDF has been linked to modest yet statistically significant alterations in creatinine clearance, typically ranging from 6 to 10 ml/min. Typically, these alterations do not hold significant clinical relevance when normal renal function is present initially. However, they may acquire significance if renal disease is present (Gallant 2006).

16. LIPODYSTROPHY

Lipodystrophy encompasses various conditions, such as lipoatrophy and/or lipohypertrophy, which are frequently linked to dyslipidemia and insulin resistance. These symptoms have the potential to manifest either in conjunction or independently. Lipoatrophy refers to the condition characterized by the reduction of adipose tissue in specific regions of the body, including the facial region (cheeks), extremities, buttocks, and subcutaneous abdominal fat. Many patients frequently express dissatisfaction with the visibility of their veins, which can be attributed to a decrease in adipose tissue in the surrounding area. Lipohypertrophy refers to the pathological condition characterized by the accumulation of adipose tissue in various regions of the body, including the visceral abdominal area, dorsal cervical region, parotid area, and the development of lipomata or breast enlargement in females (Grinspoon and Carr 2005).

17. DISTAL SENSORY PERIPHERAL NEUROPATHY

Distal sensory peripheral neuropathy is characterized by subjective sensations of numbness and/or pain primarily affecting the extremities, particularly the feet. Clinical manifestations encompass the absence of ankle reflexes, as well as diminished sensory perception of vibration and pinprick stimuli. In recent times, a number of cohort studies have provided confirmation regarding the existence of DSPN, wherein a minimum of one sign or symptom is observed in approximately 30-57% of patients. Among these individuals, symptoms are reported in the range of 5-40% (Ellis et al. 2009).

18. PROPHYLAXIS TREATMENTS

18.1. PRE-EXPOSURE PROPHYLAXIS

Given the significant worldwide spread of HIV, the World Health Organization has emphasized the critical need for innovative, efficacious, and safe interventions in the realm of HIV infection prevention. This phenomenon is particularly prevalent among individuals who are deemed to be at a heightened risk, as a result of the inconsistent implementation of these precautionary measures (Weinhardt et al. 1999).

Pre-exposure prophylaxis (PrEP) represents a formidable instrument in the containment of HIV transmission, whereby the individual undertakes the daily ingestion of an ARV tablet, in conjunction with the implementation of supplementary preventive behavioral strategies, with the ultimate aim of averting

HIV infection. This particular protective mechanism is employed by individuals who have not received a diagnosis of HIV, yet find themselves at a significant risk of contracting the virus due to their lifestyle choices or as a partner in a sero-discordant relationship (Castilla et al. 2005).
The findings derived from clinical trials provide evidence supporting the effectiveness of PrEP, whether utilized as a standalone intervention or in conjunction with other behavioral preventive strategies. These trials have demonstrated that PrEP has the capacity to significantly decrease the occurrence of HIV by as much as 86% or potentially higher, contingent upon strict adherence to the prescribed regimen (Molina et al. 2015).

19. DRUGS COMMONLY USED FOR PREP

On July 16, 2012, the US Food and Drug Administration (FDA) granted approval for [tenofovir (TDF) 300 mg/emtricitabine (FTC) 200 mg] based on the outcomes and evidence obtained from PrEP trials. This medication was deemed effective in preventing sexually acquired HIV as well as other potential modes of HIV transmission, including the use of injectable drugs (Holmes 2012).
The ARV medications currently recommended for oral PrEP consist of either tenofovir (TDF) alone or a combination of TDF and emtricitabine (FTC) (Louissaint et al. 2013). These medications have demonstrated high potency, a favorable resistance profile, and are alleged to have minimal adverse effects, thereby establishing their efficacy and safety for pre-exposure prophylaxis (Baeten et al. 2012).
Several studies have also evaluated the effectiveness of a 1% vaginal gel formulation of Tenofovir Disoproxil Fumarate (TDF) and have reported a reduction in HIV transmission by 39% (Sokal et al. 2013).
Subsequently, the US Centers for Disease Control (CDC) issued guidelines pertaining to the implementation of PrEP in clinical settings. The WHO has recently released guidelines that align with the aforementioned recommendations, advocating for the use of PrEP as a viable preventive measure for individuals who face a significant risk of contracting the Human Immunodeficiency Virus (Tetteh et al. 2017).

20. SUCCESSFUL TRIALS OF PREP

The FEM-PrEP study, which involved a total of 2120 participants, observed 56 new cases of HIV infection after 14 months of study initiation. Notably, these infections were evenly distributed between the Truvada® and placebo groups, with 28 cases occurring in each arm. This finding strongly suggests that the use of Truvada does not provide effective protection against HIV transmission. The overall level of adherence, as reported by participants, was found to be 95%, with no discernible disparity in adherence observed between the two experimental groups (Van Damme 2012).
The study on PrEP conducted in the United States involved a total of 373 participants, with 186 individuals assigned to the TDF group and 187 individuals assigned to the placebo group. The study yielded positive results, as only four individuals from the placebo group and three individuals from the delayed-arm participants experienced seroconversion. The estimated adherence rate based on pill load was found to be 92%, while the adherence rate determined through the use of a medication event monitoring system was 77%. The oral administration of TDF was found to be well-tolerated, with no notable renal issues observed. Furthermore, there were no statistically significant differences in the occurrence of adverse drug events between the TDF and placebo groups (Grohskopf et al. 2019).

21. ADVERSE EFFECTS OF PREP

The combination of TDF/FTC or TDF monotherapy commonly exhibits a favorable tolerability profile when utilized for PrEP. In the majority of studies, there was no significant difference observed in the

incidence of experienced side effects between participants receiving active treatment and those receiving a placebo. The adverse events or side effects primarily stem from the gastrointestinal tract and tend to be more common during the initial period of usage, although they typically diminish within one month of use. The gastrointestinal disturbances typically manifest as abdominal discomfort, accompanied by symptoms such as nausea, vomiting, or diarrhea. Additional adverse events that have been reported, which are not related to GIT origin, include symptoms such as dizziness, headache, loss of weight, fatigue, shortness of breath, cough, anxiety, fever, and joint and muscle pain. In the majority of studies, the incidence of side effects or adverse events did not exhibit a statistically significant difference when compared to the rates observed among participants who were administered a placebo (Tetteh et al. 2017).

Several risk factors have been identified in relation to long-term use of the medication. These factors include the patient's age, the duration of treatment with TDF, elevated levels of baseline creatinine, and the use of protease inhibitor combinations that are boosted with ritonavir. Additionally, individuals of African descent have been found to be at higher risk compared to Caucasians (Mugwanya et al. 2016).

The incidence of nausea and vomiting was found to be greater among individuals receiving TDF compared to those receiving a placebo during the initial two-month period in the Bangkok Tenofovir Study (Choopanya et al. 2013).

The safety trial conducted in the United States on homosexual men did not reveal any significant disparity in the overall occurrence of adverse events between the groups administered TDF and those given a placebo. However, a specific group of men at a site in San Francisco exhibited a slight yet statistically significant reduction in bone mineral density (BMD) at the femoral neck (1.1%) and total hip (0.8% decrease) when using TDF. It is important to note that no instances of bone fractures were observed in this subset (Grohskopf et al. 2013).

22. RESISTANCE TO PREP TREATMENT

In the context of HIV infection, the occurrence of resistance to PrEP among individuals who contract the virus subsequent to randomization is infrequently observed. Participants who exhibit resistance are more likely to be attributed to the presence of pre-existing resistance in the population rather than being solely caused by the use of PrEP. In the PROUD trial, there were no instances of participants developing resistance to Tenofovir Disoproxil Fumarate (McCormack et al. 2016).

23. POST EXPOSURE PROPHYLAXIS

PEP refers to the implementation of short-term ART with the aim of mitigating the likelihood of contracting HIV infection subsequent to exposure. The accessibility of HIV testing has expanded significantly in both occupational and nonoccupational settings. The detection of HIV in regional lymph nodes may require a time frame of up to 72 hours, while detection in blood may take up to 5 days. Detection in the cerebrospinal fluid, on the other hand, may require approximately 8 days. The early initiation of ART presents a valuable opportunity to mitigate the acquisition of HIV infection by impeding viral replication or hindering the spread of infection. (Sultan et al. 2014).

The swift beginning of ART immediately following the diagnosis of HIV infection is of significant importance in the global management of HIV for two primary reasons. In the context of managing the HIV epidemic in the absence of a vaccine or cure, it is important to note that the concept of an undetectable virus corresponds to an untransmissible virus. Furthermore, in order to enhance the well-being of individuals afflicted with HIV (Boyd et al. 2019).

24. ROLE IN VERTICAL TRANSMISSION

Research studies have demonstrated a decrease in the transmission of HIV from mother to child through vertical transmission when pregnant women receive antiretroviral treatment. These findings further validate the effectiveness of PEP. The AIDS Clinical Trials Group (ACTG) 076 study demonstrated a decrease in the occurrence of HIV infection among newborns who were administered a six-week course of zidovudine within 48 hours of birth. This intervention was specifically targeted at women who had not undergone any ART prior to giving birth (Sperling et al. 1996).
Recent empirical findings indicate that neonates born to pregnant women who did not undergo ART exhibit a higher efficacy in preventing mother-to-child transmission when subjected to dual or triple ART, as opposed to monotherapy (Nielsen-Saines et al. 2012).

25. POOR ADHERENCE

Historically, the efficacy of four weeks of post-exposure prophylaxis (PEP) among health-care workers and individuals exposed non-occupationally has been hindered by low adherence and completion rates. The influence of factors beyond pill burden and side-effects, such as psychological distress or the re-evaluation of risk over time, on adherence and completion rates remains uncertain. The completion rates of a study conducted on 401 individuals who were administered dual nucleoside therapy for PEP following non-occupational exposure were found to be 78% (Benn et al. 2011). Participants were provided with a total of three adherence sessions and five risk reduction sessions, which potentially contributed to the observed enhancement in completion rates. The virological outcome in individuals with chronic HIV infection is closely linked to the level of adherence to combination ART. Theoretical consequences of inadequate adherence to PEP regimens include the potential acquisition of a drug-resistant strain of the virus in the event of HIV infection (Benn et al. 2011).

26. OCCUPATIONAL EXPOSURE TO HIV

Prospective randomized controlled trials assessing the efficacy of PEP are lacking, primarily due to ethical considerations surrounding the withholding of a potentially effective treatment and the challenges associated with recruiting a sufficiently large number of participants for such a study.
The justification for the utilization of PEP in human subjects largely stems from an investigation involving health care workers who were occupationally exposed to the HIV. This study revealed that a 28-day regimen of zidovudine exhibited a protective effect (Sultan et al. 2014).
There have been documented instances of PEP failure in occupational settings, with a minimum of 24 reported cases. These failures have predominantly occurred following the administration of zidovudine monotherapy (Tomkins and Ncube 2005).

27. PREVENTION AND TREATMENT OF OPPORTUNISTIC INFECTIONS IN HIV

A considerable body of research has extensively documented the notable decrease in the occurrence of HIV-associated opportunistic infections (OIs) within populations of patients who possess consistent and dependable availability to efficacious ART. Antiretroviral therapy effectively mitigates the risk of developing OIs and malignancies by effectively suppressing plasma HIV RNA levels and simultaneously increasing CD4 cell counts (Masur et al. 2014).
Common OIs that develop under these conditions include disseminated Mycobacterium avium complex illness, TB, CMV retinitis, Pneumocystis pneumonia, and Kaposi sarcoma. Furthermore, it has been

observed that certain individuals who commence ART with low CD4 cell counts may experience a counterintuitive exacerbation of an OI subsequent to the initiation of ART. (Novak et al. 2012).
Furthermore, despite the significant decrease in the occurrence of OIs and AIDS-defining malignancies among patients who have successfully suppressed HIV replication for extended periods of time, enhanced immune function does not completely eliminate the risk of new OIs, even when CD4 cell counts are above 200 cells/µL (Buchacz et al. 2010). There exist extensively documented reports that indicate the persistence of infection risks, particularly for TB, herpes zoster, pneumococcal disease, and Kaposi sarcoma, even at elevated CD4 counts (Van Rie et al. 2011).
Therefore, while the sustained and successful suppression of viral activity over an extended period of time diminishes the likelihood of HIV-associated infectious complications in these individuals, it does not eradicate the risk entirely. Healthcare providers must possess a comprehensive understanding of identifying and effectively addressing OIs. Additionally, they should approach the diagnosis of OIs as a potential indication of late-stage HIV infection, immune reconstitution inflammatory syndrome (IRIS), and illnesses in individuals with elevated CD4 cell counts (Masur et al. 2014).

28. CONCLUSION

Antiretroviral therapy can prove to be a great weapon against a disease like AIDS. It may have some side effects but these are not meant for everyone, in most cases, managing them is more straightforward and has less impact on the quality of life of the patients. Overall, ARV improves patients' quality of life and makes them confident in their daily routines. People at risk may need to adhere correctly to the preventive treatment, but it can be fixed by proper counselling and awareness. Appropriate measures should be taken to limit the spread of this disease and save other people from it before it is too late, as this virus is a matter to be taken seriously.

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Foot and Mouth Disease (FMD): A Zoonotic Threat to Animal and Humans

50

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ABSTRACT

Foot and Mouth Disease (FMD) is a highly contagious ailment caused by a single-stranded RNA virus, belonging to the picornaviridae family. The virus exhibits seven distinct serotypes with multiple subtypes, affecting a wide range of animals, including cattle, buffalo, sheep, goats, pigs, and various wild ruminants. While FMD is endemic in several countries, it remains a concern for global livestock due to its economic impact and rapid transmission. This comprehensive review explores the historical context, etiology, epidemiology, geographical distribution, and transmission modes of FMD. The disease's impact extends beyond animals, affecting humans through zoonotic transmission. The primary site of infection is the pharynx mucosa, with subsequent spread through the lymphatic system, causing vesicles in the mouth, feet, muzzle, and teat. Various factors contribute to the swift global dissemination of FMD, including its contagious nature, genetic adaptability, diverse transmission pathways, and host range. The study delves into the specific characteristics of different FMDV serotypes, highlighting the prevalence of serotype O and its significant role in outbreaks. It also discusses the pathogenesis of FMD, emphasizing the viral replication process and host interactions. The zoonotic potential of FMD is acknowledged, with historical instances of human cases linked to close contact with infected animals. Geographically, FMD plagues numerous nations in Africa, southern Asia, and the Middle East, impacting the livestock environment. The disease's economic repercussions are staggering, with global losses estimated between 10-20 billion US dollars in endemic regions. The review provides a detailed analysis of the economic impact in various regions, emphasizing both direct and indirect losses. Diagnostic methods for FMD, including clinical diagnosis, laboratory procedures, and serological testing, are elucidated. The paper concludes with insights into the challenges of controlling FMD and the ongoing efforts to manage and prevent its outbreaks. Understanding the complexities of FMD is crucial for implementing effective control measures and safeguarding animal and human health on a global scale.

Keywords: animal, human. FMD, zoonosis, Epidemiology

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1. INTRODUCTION

Foot and mouth disease (FMD) is a swiftly spreading ailment with substantial economic consequences. The causative agent is a single-stranded RNA virus with a positive sense, classified within the picornaviridae family. This virus comprises seven distinct serotypes, each composed of multiple subtypes that exhibit unique antigenic and epidemiological characteristics. The spectrum of affected animals encompasses cattle, buffalo, sheep, goats, pigs, and wild ruminants (Alexandersen et al. 2005).

FMD is endemic in various countries; however, few countries remain FMD-free (Kohler et al. 2000). Tremendous economic damage to commercial cattle and buffalo farms suppresses the growth of livestock and its yielding (USDA et al. 2007). It is considered endemic in South Asian countries, inculcating serotypes O, A, and Asia 1 (Zahur et al. 2006; Tosh et al. 2002), and these serotypes are a consistent threat to these areas (Kesy et al. 2007).

Hand, foot, and mouth are other names for diseases that affect humans, and hoof-and-mouth disease is another name for the disease that affects animals with cloven hooves (Coetzer et al. 1994). FMD is a disease-causing concern for production losses worldwide because of its extensive host range and rapid aerosol transmission. The infection spreads through direct animal-to-animal contact, grub, lifeless things, and transport vehicles (Prempeh et al. 2001).

The primary site of infection is the pharynx mucosa, but the virus can also enter the body through wounds and the GIT. The virus then spreads through the lymphatic system, forming vesicles that burst within 48 hours in the mouth, feet, muzzle, and teat. Because it sheds in milk, FMDV can spread from one cow to another via raw milk. The Foot-and-Mouth Disease Virus (FMDV) can cause infection in sheep lasting around nine months, in goats lasting about four months, in cattle lasting approximately six months, and in individual African buffalo, the infection can endure for at least five years. This infection can persist within a herd for at least 24 years (Calkins et al. 2020). Morbidity may touch 100% in non-endemic regions. After recovery, animals grow immunity to the infectious strain. Young animals can die much more quickly than adults; adult mortality is typically less than one percent (Gibbens et al. 2001).

2. HISTORY OF FMD

Hieronymus Fracastorius was the first person to describe FMD in cattle in 1514. He had observed vesicles on the animals' feet and mouths and that the infected animals would not eat. In any case, Loeffler and Frosch's historical show that FMD was brought about by a filterable agent (virus) was the most vital move toward understanding the illness' pathogenesis. In 1898, FMD became the first disease that animals were infected with (Arzt Jonathan et al. 2011). However, the majority of advanced nations have eradicated this disease. Beginning in 1870 and culminating in 1914, the United States experienced nine significant outbreaks, the most devastating of which harmed 170,000 animals and cost approximately 4.5 million dollars in mitigation efforts. 442,000 animals were slaughtered in the UK in 1967 as a result of an outbreak of FMD. In 1997, FMD infected 100% of the pig population in Taiwan, killing 3.8 million pigs and causing 6.9 million dollars of damage. In 2001, the skillet Asia strain of FMD brought about approximately 2,000 cases to the UK (Paton et al. 2005).

In 2005, China and the Assembled Realm were infected with Asia-1, bringing about critical financial misfortunes. In 2011, Japan and Korea were tainted with serotype A in January and serotype O in April, with 3 million animals deceased, including cows and pigs. In Pakistan, FMD is a pervasive sickness with regular flare-ups. Type O is the most widely recognized serotype in Pakistan, with roughly 70% of cases; Asia-1 is about 25%, and type A is about 4% (Abubakar et al. 2012).

3. ETIOLOGY

The FMDV is categorized as a member of the Aphthovirus genus and is part of the Picornaviridae family. This viral species comprises seven well-defined serotypes: Asia 1, Asia O, Asia A, Asia C, SAT 1, SAT 2, and SAT 3. Notably, Serotype O is the most widely acknowledged on a global scale. It's worth noting that since 2004, there has been limited documentation of Serotype C isolation, rendering it uncommon. Although some FMDV serotypes are more diverse than others, there are 70 subtypes. The level of antigenic likeness between strains in a serotype impacts its protection from different strains (Abubakar et al. 2012).

4. EPIDEMIOLOGY AND TRANSMISSION OF FMD

According to the World Organization for Animal Health (WOAH), FMD is rapidly and extensively advancing across countries and can create significant societal and economic repercussions (Sansamuret et al. 2020). In FMD outbreaks, the most common control measures, including animal culling or vaccination and shipment restrictions, are implemented following the control policy and the infected area's landscape and population (Tsao et al. 2020).

Immunizations don’t safeguard among serotypes. FMD-free Countries either illegalize importing unvaccinated animal products against FMD or only allow it if additional risk-mitigating measures are taken. As a result, there are fewer opportunities for international trade (Kijazi Ahmed et al. 2021). Zoosanitary measures, often accompanied by vaccination campaigns, have successfully eliminated the disease from North America, Australia, Europe, and a significant part of South America (Paton et al. 2021).

5. GEOGRAPHICAL DISTRIBUTION OF FMD

FMD plagues numerous nations in Africa, southern Asia, and the Middle East. Infected animals make spreading the virus easy (Belsham et al. 2020). The disease has affected virtually every aspect of the environment where domesticated animals are kept. More than 100 countries are currently affected by FMD, and the spread of the disease typically reflects economic conditions (Dabasa et al. 2021).

Due primarily to the seven recognized serotypes, FMD weighs seven immunologically distinct diseases from an epidemiological and disease control perspective. Consequently, the immunity developed by animals against a specific FMDV serotype does not confer protection against other serotypes. Additionally, the level of immunity animals have against distinct strains within a serotype is contingent upon the similarity of their antigens. The rapid global dissemination of FMD can be attributed to its exceptional contagiousness, swift genetic adaptability, diverse transmission pathways (including direct contact, airborne transmission, and fomite transmission), and a broad spectrum of host affinities (Wubshet and Ashenafi, 2019).

The disease is anticipated to cause annual losses of between 10-20 billion US dollars in nations where it is prevalent (Belsham et al. 2020). As the new examination reports indicate, six FMD infection serotypes (O, A, Asia-1, SAT-1, -2, and 3) flow universally.

Serotype O is the most pervasive and answerable for roughly 70% of worldwide flare-ups (Samuel et al. 2001). Even though SAT 2 FMDV persisted long enough in Egypt, the SAT (Southern African Territories) serotypes are typically only found in sub-Saharan Africa. Most of the time, the scope of some of the serotypes is limited (Brito et al. 2017).

5.1. FMDV Type O

The most widely studied and prevalent FMD serotype worldwide. It contains eight topotypes.

5.2. FMDV Type A

The serological FMD virus subtype A is often acknowledged as the most varied antigens among the Eurasian serotypes. Recently, it has given rise to new antigenic variants, particularly in the western Asian region, where no cross-protection is observed between these variants.

5.3. FMDV Type SATs

The genetic diversity of FMDV Types SAT1 and SAT-2 differs markedly. SAT1 is characterized by eight distinct topotypes tightly confined to specific geographic regions. On the other hand, SAT-2 showcases a more extensive genetic diversity, encompassing 14 topotypes. Notably, South African variants exhibit significantly higher sequence diversity than those of serotype O. In contrast, SAT-3 displays a comparatively lower epidemiological presence on the continent and is infrequently identified in African bison populations (Wubshet et al. 2019).

5.4. TRANSMISSION

Infected animals can quickly and directly transmit FMDV to susceptible animals. Another critical method is indirect transmission through contaminated objects, animal products, or vapor (Gao et al. 2021). FMD can spread directly between animals or indirectly through fomites, and both can occur frequently over shorter distances (Tsao et al. 2020). However, aberrant strategies for transmission, for example, employing the airborne course, have been displayed to assume a significant part in the spread of the sickness. Because a particular set of factors needs to pave the way for airborne proliferation, airborne dissemination of FMD is considered a low-probability event with high consequences (Brown et al. 2022). Although most FMD outbreak transmission events occur locally, larger-scale transmission, such as animal shipments, has been crucial in spreading the infection to new locations and launching new local transmission chains. Catching different transmission sizes is a significant part of FMD reenactments (Tsao et al. 2020).
A prolonged, asymptomatic infection in ruminants and the virus's presence may occur in all infected animals' body secretions. The shedding of the virus is an essential factor in the transmission of FMD (Nawaz et al. 2019). Due to airborne spread, the virus poses a particular challenge for transmission from infected pigs, which exhale large quantities of the virus in their breath, to cattle, which are highly susceptible to infection by airborne virus but highly resistant to this route (Belshamet al. 2020).

6. MODES OF TRANSMISSION TO HUMANS AND ANIMALS

It is inevitable for living things to interact with one another. Even though it is necessary to give a typical advantage in interspecies connection for the progression of life, when the equilibrium is weakened, life is risked correspondingly (Bhabhor et al. 2020). Air, spit, milk, pee, dung, and the sperm of intensely contaminated creatures all contain FMDV (Calkins et al. 2020). Cows, bison, camels, goats, sheep, pigs, and deer all contain it. Abraded skin becomes infected when it comes into close contact with infected animals or their droppings. Animal hides may have been a source of viruses for some time. Blisters on the finger, the palm, the underside of the foot, or oral depression are symptoms of this mild illness in humans(Pal et al. 2013).

7. ANIMAL RESERVOIR AND HOST

Over 70 cloven-hoofed creatures, such as pigs, cattle, sheep, goats, and African buffaloes, can fall victim to the Foot-and-Mouth Disease Virus (FMDV), as it exhibits a wide range of hosts. The symptomatic

effects of FMD encompass fever, lameness, and vesicular lesions on the hooves, tongue, and teats. The livestock sector bears a significant brunt from FMD, as it restricts the international trade of animals and their byproducts. FMD virus can endure in sheep herds for up to nine months, goat herds for four months, cattle herds for six months, and individual African buffaloes for a minimum of five years, given that the infection persists within the group for at least 24 years (Calkins et al. 2020).

8. FMD PATHOGENESIS

Each virion particle is made up of a single strand of RNA that is about 8.5 kilobytes long. This is transformed into a solitary polypeptide and then separated into the underlying and non-primary infection proteins (Grubman et al. 2004). The infectious proteins are formed from the open reading frame (ORF), surrounded by the 5' and 3' untranslated regions. The ORF undergoes post-translational cleavage to yield ten non-structural proteins (Lpro, 2A, 2B, 2C, 3A, 3B1–3, and 3Dpol) and four structural proteins (VP1, VP2, VP3, and VP4). These proteins are produced as a single polyprotein and then divided. Interestingly, FMDV's 5'UTR is notably more extended than other Picornaviridae members. It contains various optional RNA sequences of different lengths and is covalently linked to the 5' end of the short peptide VPg (a structure found among the three VPg forms). At the 5'end, the S piece, running someplace in the scope of 350 and 380 nucleotides, occurs as an extended stem circle construction that contains essentially 4.5% of the whole FMDV genome and is fundamental for multiplication of the viral RNA is proposed (Kloc et al. 2017).
A series of interactions between the virus and the host constitutes the pathogenic mechanism of the virus. Depending on the virus and the host, different actions may be required. Notwithstanding, a general model that applies to most cases can be utilized to make sense of how the infection causes disease:

1. Access to a vulnerable host
2. Multiplication to increase the viral load
3. Spreading from the passage site to the tissues and target organs, promoting contamination and causing damage to cells and organs
4. Dumping, polluting, and spreading to the environment
5. The persistence of the environment
6. Starting a new cycle and spreading to new hosts (Finlay et al. 2006)

9. ENTRANCE AND REPLICATION OF VIRUS IN HOST CELL

The respiratory system is the main pathway through which the FMDV generally disseminates among animals. The virus gains access to the body through airborne particles discharged when animals cough or sneeze. This transmission is frequently observed in infected pigs, cattle, and sheep. Additionally, the virus has been detected in high concentrations in milk and fecal matter sprays, indicating their potential role in spreading the infection. In many species, the disease typically starts with few viral particles, except for pigs, which are more impervious to respiratory contamination than cows or sheep. Still, it is much more likely to get an infection in the mouth. Therefore, five to ten viral particles can infect cattle, sheep by fifteen to twenty, and swine by respiratory route require significantly more (Rodríguez-Habibe et al. 2020).
By binding to specific cell surface receptors, viruses enter host cells. The FMDV receptors that have been reported are the integrin receptor, the heparan sulfate (HS) receptor (Xin et al. 2015; Xin 2018), and the unidentified third receptor (Bai et al. 2019; Bao 2019). The chemical stripping and release of the virus's genome, which translocates through the endosome membrane to the cytosol, is initiated by the low pH of an endosome—6.0 to 5.5 pH for the late endosome and 6.5 to 6.0 pH for the early endosome. This translocation is cap-independent (Gutiérrez M et al. 2010; Torres et al. 2009). Infectious is the positive polarity of genomic RNA (gRNA), the messenger RNA (mRNA). The cytidine-rich poly(C) 5′ UTR region,

which is approximately 834 nucleotides long and contains the internal ribosome entry site (IRES), which binds directly to the ribosomes, follows the genome-associated viral protein (gVP) at the 5′ extreme. The ORF comes next (Rodríguez-Habibe et al. 2020).

While handling viral polyproteins, protein precursors are delivered through proteolytic cleavage: L proteinase (Lpro), the polypeptides P1, P2, and P3 (Gullberg M et al. 2017). While P1 is in charge of assembling the structural proteins VP1, VP2, VP3, and VP4 into the viral capsid, P2 is in charge of the three non-structural proteins 2A, 2B, and 2C, and P3 is in charge of the four non-structural proteins: 3A, 3B, 3C, and 3D (Xie et al. 2016).

After characteristic contamination, the infection begins to reproduce, generally in oropharyngeal cells. Primary ulcer sores, some of the vesicles that result from this, usually go unobserved (Alexandersen S et al. 2003). Following the initial replication, the virus infiltrates the bloodstream. Elevated body temperature and the animal's discomfort indicate the resultant viremia phase. Throughout this period, the Foot-and-Mouth Disease Virus (FMDV) undergoes further replication within reticuloendothelial cells and the parenchyma of specific target organs, such as the liver, spleen, bone marrow, and striated muscle. Subsequently, the viral presence returns to the epithelial cells within the nose, hooves, and mammary organs, culminating in the characteristic vesicles that define the disease's symptoms. The mechanism for transporting viral particles from the bloodstream to less vascularized epithelial regions remains undisclosed. It is plausible that this process is linked to the quantity of infectious particles introduced into the host or facilitated by the migration to infected macrophage tissue (Arzt et al. 2014).

10. ZOONOTIC POTENTIAL OF FMD IN THE WORLD

The World Organization for Animal Health (WOAH) has designated Foot-and-Mouth Disease (FMD) as a "notifiable condition." This disease is estimated to impact approximately 77% of the global livestock population, leading to substantial economic repercussions within the livestock sector. Recently, novel strains of the Foot-and-Mouth Disease Virus (FMDV) have consistently surfaced, giving rise to a persistent epidemic. The dynamic emergence of these new strains presents a formidable challenge in managing the causative pathogen, as it spreads rapidly and poses significant risks to global health, particularly in regions that have remained free from the disease (Santos et al. 2018; Mahapatra et al. 2018).

FMD rarely affects humans when it crosses species boundaries owing to the disease's high prevalence in animals, both in the past and in more recent global outbreaks, limiting human exposure. The last human case of foot and mouth disease reported in Britain was in 1966, during the final outbreak. However, all of the cases that have been reported involved close contact with infected animals; it is unclear when humans contract the disease (Prempeh et al. 2001).

10.1. ASIA

Among seven serotypes, only the O serotype poses a threat worldwide; perhaps, more than 80% of outbursts about the O serotype seem to occur in Southeast and East Asia. Chronologically, three strains of FMDV serotype O**:** O/CATHAY, O/SEA/Mya-98, and O/ME-SA/PanAsia remain. Southeast and East Asia have seen a rise in these lineages in recent years. An additional variant, O/MESA/Ind-2001, was initially detected and contained within the Indian subcontinent, leading to extensive outbreaks of foot-and-mouth disease (FMD). Epidemiology has been more difficult (Hemadri et al. 2002).

Since its discovery in 2013, this lineage has spread throughout the Middle East and North Africa. In 2015, O/ME-SA/Ind-2001 emerged in Myanmar, Vietnam, and the Lao People's Democratic Republic (Qiu et al. 2018). 2019 Cambodia, Pakistan, and Malaysia reported O/ME-SA/Ind-2001e (Jamal et al. 2021).

China possesses the most livestock of any Asian nation. However, the prevalence of FMD impedes economic growth significantly in several regions owing to the enormous animal population and frequent animal transport. China's national FMD reference laboratory was the first to identify the appearance of O/ME-SA/Ind-2001 in 2017. In China, cases of FMD have been reported since 1958. The advent of new subtypes makes FMDV epidemiology and control parameters more challenging. Between 2005 and 2021, China reported 175 FMD epidemics to the WOAH (Zhang et al. 2023).

10.2. AFRICA

Among seven known FMDV serotypes, five (O, A, SAT 1, SAT 2, and SAT 3) are available in Africa. Nonetheless, serotype C has only been reported a handful of times in the past 15 years, with the most recent confirmed outbursts appearing in Kenya and Brazil in 2004 (Rweyemamu et al. 2008). FMDV's genome is highly adaptable and rapidly evolves due to replication-related errors. By sequencing these viruses, we can precisely describe novel FMDV isolates and follow their origins and movements across international borders. Variants and serotypes vary widely worldwide (Samuel and Knowles 2001).
The intrusion of FMDV strains into other regions rather than their endemic pool is cause for grave concern due to the possibility of disease unfolding in previously unaffected areas (Vosloo et al. 2010). For instance, livestock mortality rates of up to 20% were reported following a recent incursion of SAT 2 into Egypt, which demonstrated the host's vulnerability to new strains (Ahmed et al. 2012).

11. FMD ACROSS THE BORDERS

FMD is known to be the most contagious virus, twenty times more virulent than Variola. Consequently, a single vaccine does not progress in controlling disease. Approximately 15 different FMD vaccines are produced worldwide, and the production and utility of whole live viruses are required. A brand-new molecular FMD vaccine that can be administered to cattle was recently granted a conditional license by the USDA.
The last outbreak of FMD in the United States occurred in 1929; Russia, the European Union, Australia, North and Central America, and New Zealand represent FMD-free countries. However, the rest of the world experiences it regularly. Despite being FMD-free countries, importing live animals and animal products that might contain the virus remains illegal. A world-leading, highly productive agribusiness built on these animal herds generates a significant portion of our GDP and exports abroad (Morse et al. 2017).

12. ECONOMIC IMPACTS

The global dairy industry produced more than 655 million tons of milk in 2014. This number is expected to rise by 23% between 2014 and 2025. However, numerous potentially perilous diseases, particularly FMD, prevent adequate milk yield (FAO 2017; Rushton 2009).
The FMD impact on the economy results in both direct and indirect losses. A loss due to death, vigor loss, milk production, and the value of livestock products are all examples of direct losses. The increased costs for vaccination, movement control, diagnostic and surveillance, and treatment of secondary bacterial infections in diseased herds are the causes of the indirect losses. Smallholder farmer's earnings deescalate with FMD's influence on productivity and food security, making its economic impact particularly significant (Alhaji et al. 2020). Table 1 shows the economic impact of FMD throughout the world.

13. DIAGNOSIS

The World Organization for Animal Health (OIE) Terrestrial Animal Health Code states that FMD requires a 14-day incubation period. It is said to take anywhere from one to twelve days for sheep to get sick, with

Table 1: FMD Economic Impact Worldwide.

Region	Economic impact per year (US$)	Reference
Endemic regions	11 B (90% range of6.5-21 B)	(Alhaji et al. 2020)
USA	1.5B	(Alhaji et al. 2020)
Africa	830M (17% global annual cost)	(Kerfua et al. 2023)
Bangladesh	1.5 M	(Giasuddin et al. 2020)
Pakistan	629 M	(Abubakar et al. 2022)
Indonesia	6.6 B	(FAO 2023)

the majority of infections showing up within two to eight days; two to fourteen days for cattle; also, typically for at least two days in pigs (with some trials reporting clinical signs within 18-24 hours). There have been reports of incubation times of four days for wild boars, two days for feral pigs, two to three days for elk, and two to fourteen days for Bactrian camels.

13.1. CLINICAL DIAGNOSIS

The extent of clinical symptoms is influenced by various factors, including the type of virus strain, the degree of exposure, the age and genetic makeup of the animal, the species of the host, and the host's immune response. Although fatalities are infrequent, they can occur among young animals due to causes like starvation or multifocal myocarditis. Secondary infections can slow recovery, but most adults recover in two to three weeks. Morbidity can reach 100%. Young calves, lambs, and piglets have higher mortality rates than adult animals, with a 1 to 5% mortality rate. Recovery typically takes about two weeks in straightforward cases.

13.2. CATTLE

- The severe clinical manifestations are commonly observed in highly productive dairy breeds in developed countries. These symptoms include shivering, anorexia, pyrexia, and a notable decline in milk production lasting for two to three days. Additional signs of the ailment include lip smacking, teeth clenching, drooling, impaired movement, or even kicking or stamping of the foot. These behaviors result from the development of vesicles (aphthae) on the mucous membranes within the oral and nasal regions, as well as between the claws of the animals. Furthermore, vesicles can also manifest on the mammary organs. As the condition progresses, approximately 24 hours later, the vesicles rupture, leading to the formation of erosions. Recovery from these symptoms typically takes place within 8 to 15 days.
- Complications associated with this ailment include erosions on the tongue, secondary infections of the lesions, deformities in the hooves, mastitis, and lasting impairment in milk production. These tongue erosions can also result in infertility, abortion, persistent weight loss, and a loss of thermoregulation, often referred to as "panters."Another consequence of this ailment is myocarditis, which can lead to the fatalities of young animals.

13.3. GOAT AND SHEEP

- Many infected animals can be asymptomatic or only have lesions at one location. Fever and mild to severe leg numbness are common symptoms.
- Vesicles are found in the coronary band and interdigital spaces on the feet, but they can rupture and be obscured by other foot lesions.
- Mouth lesions typically appear as shallow erosions and are rarely severe or noticeable.
- Pyrexia

- A characteristic of milking sheep and goats is agalactia. In some outbreaks, a significant number of ewes give birth.
- Young stock can die without showing any clinical signs.

13.4. PIG

- It may foster extreme foot injuries and weakness with the separation of the hook horn, mainly when housed on concrete.
- Vesicles frequently form along the carpus, the "knuckle," and other pressure points on the limbs.
- Dry tongue lesions and snout vesicular lesions are possible.
- Heart failure can cause sudden death in young pigs as young as 14 weeks; Piglets younger than eight weeks are especially vulnerable.

13.5. LESION

- Blisters or vesicles can manifest on various oral and facial areas, including the tongue, dental pad, gums, cheeks, hard and soft palate, lips, nostrils, muzzle, coronary bands, pig snout, udder, dewclaw corium, and interdigital regions.
- After death, erosions may appear on rumen pillars with gray or yellow streaks in the heart, stemming from myocardial degeneration and necrosis in young animals of all species; this condition is commonly referred to as "tiger heart."

14. DIFFERENTIAL DIAGNOSIS

- Vesicular stomatitis
- Swine vesicular disease
- Vesicular exanthema of swine
- The infection was caused by Seneca virus A, also known as Seneca Valley virus.

14.1. LABORATORY DIAGNOSIS

14.1.1. SAMPLES

- Fluid extracted from vesicles or epithelial tissue of unruptured or recently ruptured cysts.
- Epithelial specimens should be placed in a transport solution with a pH ranging from 7.2 to 7.6 and kept stable.
- In cases where epithelial samples are not attainable, ruminant blood and esophageal-pharyngeal fluid collected using a probang cup or swabs from the pig's throat can be utilized as an alternative viral source.
- Following collection, probang samples should be promptly refrigerated or frozen.
- For fatal cases, myocardial tissue or blood can be submitted; nevertheless, vesicle samples are once again the preferred choice if available.

15. METHODS

15.1. AGENT IDENTIFICATION

To establish a diagnosis, it is imperative to detect the presence of the live Foot-and-Mouth Disease (FMD) virus, FMD viral antigen, or FMDV nucleic acid.

A comprehensive bio-risk assessment should determine the appropriate containment level for laboratory procedures involving live FMD viral cultures or potentially contaminated materials, such as blood and tissue samples.

The reverse-transcription polymerase chain reaction (RT-PCR) is the initial diagnostic test to identify FMDV-specific nucleic acids in various sample types like epithelium, milk, and serum. Different RT-PCR formats include:

- Agarose gel-based RT-PCR
- Real-time RT-PCR
- Lineage-specific RT-PCR methods
- RT-PCR amplification for nucleotide sequencing

15.2. VIRUS INOCULATION

- Inoculation can be performed using primary pig, calf, lamb kidney cells, or primary bovine (calf) thyroid cells. Alternatively, susceptible cell lines such as BHK-21, LFBK-V6, and IB-RS 2 can be utilized.
- After reducing cytopathic effects, culture fluids can be subjected to complement fixation (CF), antigen ELISA, or RT-PCR tests.

Antigen Detection via ELISA:

- ELISA assays that rely on monoclonal antibodies or polyclonal antisera can effectively detect and classify FMD viral antigens.
- The complement fixation test, which is less sensitive and specific compared to ELISA, is influenced by multiple factors.

15.3. SEROLOGICAL TESTING

Serological tests for FMD serve several vital purposes:

1. Verification of individual animals before import/export (for trade)
2. Confirmation of suspected FMD cases
3. Estimation of infection prevalence or verification of absence
4. Demonstration of vaccine efficacy

- Virus Neutralization Test:

A quantitative VN micro-test for FMD antibodies uses IB-RS-2, BHK-21, lamb, or pig kidney cells in flat-bottomed tissue-culture grade microtitre plates.

- Solid-Phase Competition ELISA:

This method can identify antibodies against each of the seven FMDV serotypes. Peroxidase-conjugated monoclonal antibodies can be substituted for rabbit or guinea pig antisera to directly or indirectly detect antigens coated onto ELISA plates.

- Liquid-Phase Blocking ELISA:

Antigens are produced from specific FMDV strains cultured on BHK-21 cell monolayers.

- Non-Structural Protein Antibody Tests:

Enzyme-linked immunoelectrotransfer blot assay (EITB) formats, both indirect and competitive, are utilized for this purpose.

16. PREVENTION AND CONTROL

16.1. SANITARY PROPHYLAXIS

- Border surveillance and animal and product movement control for the protection of free zones

- Implementing the OIE-recommended methods for FMDV inactivation in animal-derived products
- Quarantine measures
- The killing of infected recovered and contact animals that are susceptible to FMD.
- Disinfection and cleaning of the premises as well as all infected objects like tools, automobiles, and clothing
- Removal of tainted creature items, bedding, and cadavers in the contaminated region

17. MEDICAL PROPHYLAXIS

17.1. INACTIVATED VACCINES

One or more chemically inactivated cell-culture-derived preparations of a seed virus strain are mixed with the appropriate adjuvants and excipients in traditional FMD vaccines. The potency of FMD vaccines can be categorized as either "standard" or "higher."

- Commercial vaccines of standard potency: formulated with enough antigen and the suitable adjuvant to have a minimum PD50 [50 percent protective dose] of 3

1. Provide immunity for six months following two one-month-apart initial vaccinations.
2. The antigenic relationship between vaccine and circulating strains is the basis for selection.
3. Many are multivalent to protect against prevalent circulating strains and provide extensive antigenic coverage.

- Vaccines with greater potency (emergency vaccines): formulated with enough antigen and the suitable adjuvant to have a minimum PD50 [50 percent protective dose] of 6

❖ Higher-potency vaccines are recommended in adolescent populations due to their rapid onset of protection and a more comprehensive range of immunity (Brown et al. 2008; WOAH 2018; WOAH 2019).

18. CONCLUSION

This article discusses the zoonotic effects of foot and mouth disease (FMD) on animals and humans and its economic and production repercussions. The illness predominantly targets cloven-hoofed creatures like cattle, pigs, sheep, goats, and wildlife. The livestock sector experiences substantial setbacks in production and finances due to FMD. Although the disease rarely leads to severe illness or fatalities in humans, there exists a potential for transmission to occur via direct interaction with infected animals or materials carrying the virus.

Preventing and controlling FMD requires stringent biosecurity measures, including vaccination, quarantine, and movement restrictions. Rapid detection and response are crucial to containing outbreaks and minimizing the risk of transmission to humans. Surveillance systems and international cooperation are vital in monitoring and managing the disease, as FMD can easily spread across borders through trade and animal movement. By implementing comprehensive control strategies, the risk of FMD transmission to animals and humans can be significantly reduced, safeguarding animal health, livelihoods, and public health.

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Role of Vitamins and Minerals as Immuno-boosters in COVID-19

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ABSTRACT

Vitamins and minerals are receiving a lot of attention for their potential to boost the immune system, particularly in relation to the COVID-19 pandemic. Although these nutrients do not act as a cure or preventative measure for the virus, their role in boosting the immune system is essential for fighting infections such as respiratory illnesses, including COVID-19. Vitamin C is recognized for its ability to act as an antioxidant, stimulating the development of white blood cells and antibodies, which strengthens the body's ability to defend itself. Likewise, vitamin D is crucial for the functioning of the immune system, and a lack of it has been associated with a higher risk of getting sick. Vitamin A helps maintain the health of skin and mucous membrane cells, acting as a protective shield against harmful pathogens. Zinc and selenium are necessary for the proper operation of immune cells, while vitamin E serves as an antioxidant, shielding cells from harm. Although it is ideal to have a well-rounded diet that is high in these nutrients, it is important to recognize that excessive supplementing may not provide any extra advantages and may even be harmful. The focus should be on getting a variety of nutrients from a wide range of foods such as fruits, vegetables, nuts, seeds, and lean meats. Amid the COVID-19 pandemic, it is crucial to prioritize compliance with public health precautions including vaccination, hygiene protocols, and maintaining physical distance. It is recommended to seek guidance from medical professionals before making any dietary changes or starting on any supplements, especially for those with pre-existing health issues. Recognizing the importance of vitamins and minerals in supporting the immune system contributes to a comprehensive approach to staying healthy during difficult times.

Keyword: COVID-19 pandemic; Vitamins and minerals; Immuno-boosters; antioxidant; immune system

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1. INTRODUCTION

The World Health Organization (WHO) declared COVID-19 a global pandemic due to its potential to endanger public health worldwide. The focus has switched to techniques that might boost the immune system against COVID-19 due to the lack of expedient therapeutics in the developing countries. Pharmaceutical firms are striving to manufacture-cum-launch anti-COVID-19 vaccines and therapeutic agents because of significant viral influence on the immune system in the form of cytokines storm. A well-balanced diet rich in essential vitamins (A, B, C, D, E, and K) and minerals (sodium, potassium, phosphorus, calcium, magnesium, zinc, selenium, sulfur, etc.) has been shown to be highly beneficial in enhancing immune function and in the prevention and management of COVID-19 (Silver 2020).

Coronavirus is responsible for the spread of COVID-19. Previous outbreaks such as; the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) modeled serious health-threats to the entire world (Rothan et al. 2020). Both of these illnesses were zoonotic and originated from bats to the whole mankind (Derbyshire and Delange 2020). It is believed that COVID-19 was disseminated to the exposed persons from routinely traded animals of the Wuhan (China) market. Still, a search for reservoir/intermediate host remained a big mystery and challenge. However, aside from mammals and birds, there hasn't been any conclusive proof of the existence of its additional reservoirs (Bassetti et al. 2020). In December 2019, the first instance of COVID-19 was recorded (Du Toit 2020) that primarily affects the human respiratory system (Lu et al. 2020).

A cluster of epidemiologically connected individuals from Wuhan (Hubei Province, China) were identified with an early symptom of idiopathic pneumonia. Along with respiratory symptoms, vomiting, diarrhea, dry cough, dyspnea, sore throat, headaches and disorientation were also noted (Shakoor et al. 2021). The outbreak incidence was typically higher in people > 60 or with diabetes, heart or lung co-morbidities. Males exceeded females despite the absence of a clearly defined dominant gender because of their inclination for drinking and smoking (Yuki et al. 2020). Since the COVID-19 epidemic started, fear and despair have spread around the globe. The immune system of an individual is compromised by this virus (Michienzi and Badowski 2020). Although the immune system is continuously monitoring itself, it becomes more active when a person is in a diseased state. Increased activity leads to a faster metabolism, requiring the consumption of energy sources, biosynthetic substrates, and regulatory molecules, all of which are derived from food. Many essential vitamins and trace minerals (such as zinc, copper, selenium, and iron) play a vital role in enhancing the body's immune response and lowering the likelihood of infection (Calder 2020). Alternatively, inadequate nutrition hindered the immune system's ability to work properly. Poor nutrition results in decreased natural and acquired immunity, increasing the likelihood of infections (Calder 2020). By rectifying the shortage, it is possible to enhance both immune function and resistance to infection, demonstrating a direct correlation between the presence of certain nutrients and the body's ability to fight off pathogens. This chapter specifically delves into how different vitamins and minerals can boost immunity against COVID-19.

2. NUTRITION, IMMUNITY, AND COVID-19

The European Food Safety Authority has authorized vitamins A, B6, B12, C, D, and folate (vitamin B9) as well as the trace elements zinc, iron, selenium, and copper to make claims related to the maintenance of

the immune system functions." (Calder 2020). Upon admission to the hospital, it is important to assess the nutritional status of all patients with COVID-19. Those at risk of malnutrition should be prioritized for nutritional support, including increased protein intake through oral supplements (Jin et al. 2020). Pattern recognition receptors (PRRs) like the retinoic acid-inducible gene I-like receptors play a role in the innate immune system by identifying the viral genetic material when it enters the host cell (Li et al. 2020; Yi et al. 2020). The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2's) attachment to macrophages triggers the inflammatory cascade by presenting its antigens to the CD4 T cells, which then activated and differentiated into Th17 cells. Production of MCP-1, TNFα and IL (1, 6, 8, and 21) cytokines mobilize the adaptive IR. According to Li et al. (2020), these mediators cause T cells to activate NK and CD8 T cells. By activating B cells, TCD4 cells are in charge of causing specific antibodies to be produced against SARS-CoV-2 (Li et al. 2020; Yi et al. 2020). SARS-CoV-2 spike glycoprotein (S-protein) bound to the DPP4 receptor and encouraged protein-receptor adhesion that instigated the release of viral DNA. The key responder protein MyD88 is essential for the production of pro-inflammatory cytokines (IFN-1, TNFα, NF-kB activation, IL-1, and IL-6) and was dependent on S-protein (Li et al. 2020). Viral RNA binding to the TLR-3 receptor stimulated interferon regulatory factors (IRF) to activate inflammatory pathways. As a result, it causes the synthesis of TNFα, IL-1, IL-6, and IFN-1. The activation of IRF and NF-kB by the viral RNA's binding to TLR-7 and/or TLR-9 was also demonstrated as these cytokines caused lymphocytes and leukocytes to migrate to the infected cell to cope the infection (Li et al. 2020). It is important to underline IFN-1's role in preventing viral transmission. IFN-1 also triggered dendritic and NK cells and in response enhancing macrophages' phagocytosis of viral antigens (Li et al. 2020; Yi et al. 2020). Vitamins and minerals are necessary for the entire procedure. SARS is especially dangerous to the cardiovascular system, kidneys, stomach, lungs, brain, and other organs that express the angiotensin-converting enzyme 2 (ACE 2) (Guo et al. 2020; Shi et al. 2020). This is particularly true if the immune system was struggling and the virus was allowed to propagate unconstrained. Recent studies have shown that the respiratory epithelium must display ACE 2 for the virus to enter and start replicating (Cheng et al. 2020). Then the virus was introduced to lymphocytes, triggering the inflammatory cascade that caused the injured cells to produce pro-inflammatory cytokines. The primary symptom of COVID-19's most severe stage was respiratory which are brought on by IR and pro-inflammatory granulocytes and macrophages (Shi et al. 2020; Xu et al. 2020). High levels of pro-inflammatory cytokines, including IL-1, IL-6, and TNFα are present in the lungs of the infected patient which may serve as a catalyst for the creation of pulmonary mucus and the stimulation of the immune system (Guo et al. 2020). Because of this, medications that allowed for the inhibition or limitation of those pro-inflammatory cytokines' actions might be expedient for advanced stage COVID-19 patients (Shi et al. 2020).

3. VITAMINS AS IMMUNITY BOOSTERS IN COVID-19

It is commonly recognized that when a person was exposed to diseases due to dietary deficiencies, their immune system could become weakened. Recent studies have underlined the importance of feed additives, and they might be helpful in lowering viral loads and therapy rates for COVID-19 patients if taken in more than the prescribed daily doses. Vitamins were crucial nutritional components because of their capacity to regulate the immune system and function as defenders. There wasn't yet an approved COVID-19 drug or vaccination. To maintain a healthy body and a strong immune system until they were available, one must eat a well-balanced, nutrient-rich diet. Micronutrients like vitamin C and vitamin D have drawn a lot of interest because of their capacity to lower inflammation and strengthen the immune system. Vitamin D and C deficiencies weakened and degraded the immune system, causing pancytopenia and bleeding disorders. There was evidence that people with COVID-19 who have low vitamin D concentrations die more frequently. Additionally, giving vitamin C to COVID-19 patients increased their

oxygenation level (Shakoor et al. 2021). Vitamin B was important because it was required for optimal immune system function, energy metabolism, and cell function. In a manner similar to this, a vitamin B shortage could lead to hyper-homocysteinemia, which in turn could lead to poor immunological and cell function as well as inflammation (Mikkelsen and Apostolopoulos 2019). Vitamin B facilitated the appropriate induction of innate and adaptive immune responses. Hospitalizations were reduced, respiratory function was improved, endothelium integrity was protected, pro-inflammatory cytokine levels were reduced and vascular consistency was upgraded (Zhang and Liu 2020).

Table 1.1: Impact analysis of minerals and vitamins supplementation on COVID-19 patients (Nimer et al. 2022).

Supplement taken before COVID-19	Total number of users	Severity			Hospitalization		
		P	OR	95%CI	P	OR	95%CI
Vitamin C	651	0.18	0.81	0.59-1.11	0.08	0.73	0.51-1.04
Vitamin A	144	0.36	0.77	0.43-1.36	0.40	0.77	0.42-1.41
Vitamin D	796	0.01	0.68	0.50-0.92	0.001	0.64	0.45-0.89
Omega 3	356	0.43	1.15	0.81-1.65	0.30	1.23	0.83-1.80
Folic acid	213	0.16	0.69	0.40-1.17	0.23	0.70	0.39-1.26
Vitamin B complex	190	0.69	1.10	0.70-1.74	0.40	1.23	0.76-2.00
Vitamin B12	395	0.06	0.70	0.48-1.02	0.15	0.74	0.49-1.11
Zinc	326	0.46	1.15	0.79-168	0.21	1.29	0.86-1.93
Calcium	245	0.76	0.94	0.61-1.43	0.40	1.21	0.78-1.88
Magnesium	143	0.73	1.09	0.66-1.81	0.24	1.36	0.81-2.29
Iron	371	0.83	1.04	0.70-1.55	0.37	1.22	0.79-1.88
Selenium	57	0.80	1.10	0.54-2.26	0.48	1.30	0.62-2.71
Aspirin	427	0.28	1.20	0.86-1.66	0.08	0.96	0.67-1.37

Age, gender, BMI, status as a smoker, and the number of comorbidities were all taken into account while adjusting each independent variable. **p<0.01; *p<0.05.

4. ROLE OF VARIOUS VITAMINS AS IMMUNITY BOOSTERS

To combat COVID-19 and SARS-CoV-2, pharmaceutical companies are developing specific drugs and vaccines since COVID-19 infection has a serious adverse effect on the immune system by causing a variety of allergic reactions. To maintain overall health and avoid serious viral diseases, a balanced, healthy diet may be required. All fat- and water-soluble vitamins should be included in a balanced diet (Kumar et al. 2021). Some of them control immune cells' genetic makeup and promote their proliferation and differentiation. The antioxidant powers of vitamins C and E help fight free radicals. The body depletes these nutrients, vitamins, and minerals when combating infections because of the energy requirements for immune activation, a hectic lifestyle, viral infection, diabetes, and obesity all of which have a direct impact on nutrient status (Gombart et al. 2020).

4.1. ROLE OF VITAMIN A

The process by which vitamin A imposes its effects is through the conversion of vitamin A into retinoic acid, which binds to nuclear receptors in target cells, especially the retinoic acid receptors (RARs) and retinoid X receptors (RXRs). To control the transcription of particular genes involved in cellular differentiation, proliferation, and death, these receptors attach to retinoic acid response elements (RAREs) on DNA. Following ligand interaction, the RARs and RXRs heterodimerize, and the resultant complex attract coactivator or corepressor proteins to the gene promoter region, therefore either activating or suppressing gene expression. In the end, this process results in the preservation of sound immunological, bone, and eyesight development.

According to Raverdeau and Mills (2014), RA, also known as vitamin A and made from retinyl esters, controls a number of genes involved in both innate and adaptive immune responses. Numerous studies (Angulo et al. 1998; Trottier et al. 2008; Lee and Han 2018; Li et al. 2018) have demonstrated the protective effects of synthetic as well as natural retinoids against a variety of viruses, including viruses such as hepatitis B (HBV), influenza, norovirus, MeV, and cytomegalovirus (CMV). It affects MERS-CoV and SARS-CoV by blocking SREBP-controlled lipogenic pathways (Yuan et al. 2019).

4.2. ROLE OF VITAMIN B

The B vitamins, which are soluble in water, support a number of cellular and metabolic functions. Although each B vitamin has a different mode of action, they all serve as cofactors or coenzymes in activities that are catalyzed by enzymes. In the metabolism of carbohydrates, vitamin B_1 (thiamin) functions as a coenzyme, whereas vitamin B_6 (pyridoxine) is required for the metabolism of amino acids. Cobalamin, a form of vitamin B_{12}, is necessary for the synthesis of DNA and the production of red blood cells. It works with folate to help the body maintain homocysteine levels. Deficits in B vitamins, which are often obtained through diet, can cause a variety of health issues. Red blood cell (RBC) synthesis is known to be aided by the naturally occurring chemical vitamin B. For organisms to operate normally, all of the B complex vitamins are required (Zhang et al. 2018). The human body utilizes nutrients such as proteins, lipids, and carbohydrates to sustain the functional integrity of skin, brain cells, and other bodily tissues by furnishing energy. The inclusion of Vitamin B facilitates and contributes to the aforementioned process. Thiamine (vitamin B_1), riboflavin (vitamin B_2), niacin (vitamin B_3), pantothenic acid (vitamin B_5), pyridoxine (vitamin B_6), biotin (vitamin B_7), folate (folic acid), and cyanocobalamin (vitamin B_{12}) are the eight vitamins that make up the vitamin B complex. It is essential for maintaining the integrity of the intestinal barrier and managing the immune system of the colon (Lindschinger et al. 2019).

4.2.1. ROLE OF VITAMIN B_1

Vitamin B1 (Thiamine) functions as a vital coenzyme in facilitating the energy production process within the human body, regulates body temperature, is involved in fat formation, and is required for the proper operation of the nervous and immunological systems (Kraft and Angert 2017). Thiamine deficiency exerts a notable influence on the immune system through various pathogenic mechanisms, including heightened inflammatory response and augmented oxidative stress and other factors. Additionally, aberrant antibodies are produced as a result of metabolic abnormalities (Mikkelsen and Apostolopoulos 2019). Thiamine has been shown to significantly help with SARS-CoV-2 virus eradication by inducing humoral and cell-mediated immunity. The development of immunity against SARS-CoV-2 patients is thus supported by proper thiamine levels (Shakoor et al. 2021).

4.2.2. ROLE OF VITAMIN B_2

A lack of vitamin B_2, a neuroactive chemical with immune-modulating properties, causes the expression of genes that promote inflammation. Riboflavin demonstrated a conspicuous protective effect in experimental animal models when exposed to carbon tetrachloride (CCL4)-induced liver damage. The subsequent mitigation by TNF further indicates its potential use as a medication for hepatoprotection (Yoshii et al. 2019). Nucleic acids are permanently damaged when riboflavin is exposed to UV radiation,

which stops bacteria from multiplying. It can be used to lower infections in COVID-19 patient blood plasma in order to lessen the chance of COVID-19 transmission by transfusion.

4.2.3. ROLE OF VITAMIN B_3

Niacin affects inflammatory mediator synthesis as well as immune cell migration in a variety of ways. Therefore, it has an anti-inflammatory impact even if its whole spectrum of actions is unclear. Targeting IL-6 in COVID-19 patients, according to recent studies, may assist to lessen inflammation (Liu et al. 2020). Niacin's anti-inflammatory properties help patients with ventilator-induced lung damage by reducing neutrophil infiltration (Jones et al. 2015). According to the most recent scientific research, nicotinamide reduced viral infection and strengthened defensive mechanisms. Niacin may be added to other medications for COVID-19 patients because of its therapeutic advantages (Mehmel et al. 2020).

4.2.4. ROLE OF VITAMIN B_6

Vitamin B_6 affects immune cell activity, proliferation, and innate/adaptive immunity (Ueland et al. 2017). The suppression of cytokine/chemokine release was used to identify individuals with vitamin B_6 deficiencies. According to studies, vitamin B_6 activates IFNɣ, which mediates the cellular immunological response (Parra et al. 2018). A recent study revealed that pyridoxine supplementation has an impact on vascular, pro-inflammatory cytokine, and immunological responses. Integrity, hypercoagulability, and other factors all help to lessen COVID-19 symptoms.

4.2.5. ROLE OF VITAMIN B_9

The vitamin folate is essential for the adaptive immune system and is required for the synthesis of DNA and proteins. A recent study found that folic acid inhibits the binding of the SARS-CoV-2 spike protein as well as the furin enzyme, which promotes bacterial and viral infections. Folic acid might thus aid in the early treatment of respiratory illnesses linked to COVID-19 (Sheybani et al. 2020). Tetrahydrofolate and its derivatives, 5-methyl tetrahydrofolate and folic acid, exhibit a significant affinity for SARS-CoV-2, according to a recent study (Kumar et al. 2021).

4.2.6. ROLE OF VITAMIN B_{12}

The generation of chemokines and cytokines as well as the interaction of immune cells in pathogenic pathways may be regulated by vitamin B. It is therefore suggested that it may provide defense against a number of bacterial and viral illnesses. Probiotics like bifidobacteria and lactic acids may be essential for defense against the COVID-19 pathogen and revealed a significant role in colonic immune regulation (Calder et al. 2020). These probiotics have been shown in studies to be able to modulate immune responses and protect against infections such as respiratory tract infections. This is the process by which dendritic cells (DCs) transform vitamin A from the diet into retinoic acid (RA). The molecules CCR9 and 47 integrins are expressed by dendritic cells, which then activate B and T cells in the presence of retinoic acid. Moreover, RA encourages the development of regulatory T (Treg) cells from inexperienced T cells. Upon transformation into Treg cells, T-cells begin to display the folate receptor 4 (FR4), a receptor for vitamin B9. The interaction between vitamin B9 and FR4 is crucial for T cell survival. Vitamin D stimulates the production of antimicrobial peptides (AMPs) in macrophages and epithelial cells, promoting their ability to fight off pathogens. Additionally, it prevents DCs from maturing and promotes the migration of the IEL population within the epithelium (Kumar et al. 2021).

4.3. ROLE OF VITAMIN C

In general, the mode of action of vitamin C is critical for preserving the health and functionality of different body tissues and preventing oxidative damage. In terms of its metabolic pathway, vitamin C is absorbed in the small intestine and then transferred to tissues throughout the body. Once ingested, it can undergo enzymatic and non-enzymatic processes that will either cause it to oxidoxidizeo dehydroascorbic acid (DHA) or reduce it back to ascorbic acid. Through the action of certain transporters, DHA can also be converted back into ascorbic acid. When the body has more vitamin C than it requires, it is expelled in the urine**.** Vitamin C possesses antiviral attributes that encompass the amelioration of endothelial dysfunction, elevation of interferon-alpha production, regulation of cytokines, mitigation of inflammation, and restoration of mitochondrial function (Carr and Maggini 2017; Dey and Bishayi 2018). Numerous investigations have shown that vitamin C has viricidal effects (Furuya et al. 2008). Vitamin C facilitates the enhancement of the immune system's ability to combat bacterial and viral infections. The process of eliminating dead cells and introducing new cells offers advantageous outcomes. Vitamin C's antioxidant properties protect against the damaging consequences of oxidative stress (Carr and Maggini 2017; Ekert and Vaux 1997). Numerous studies have shown that taking vitamin C supplements lowers the chance of developing upper respiratory tract infections (Carr and Maggini 2017). Children and adults experienced fewer common cold symptoms (Hemilä and Chalker 2013). The use of intravenous vitamin C has been shown to significantly decrease the risk of developing severe infections like sepsis and acute respiratory distress syndrome (ARDS) (Kashiouris et al. 2020). Several pieces of indirect and direct evidence support the utilization of vitamin C for the management of COVID-19 patients. According to a systematic review conducted by Cochrane and a randomized controlled trial, the administration of 0. 2 g/day of oral vitamin C demonstrated a significant reduction in both clinical manifestations and subjective symptoms of the common cold. In a controlled experiment, adult patients were subjected to the administration of two varying doses of vitamin C. The outcomes of this trial revealed a direct correlation between the dosage of vitamin C and the duration of pneumonia, as a reduction in the length of the illness was observed in a manner corresponding to the administered dose (Baladia et al. 2020). Therefore, it is crucial to conduct research on the function of vitamin C (Carr 2020).

4.4. ROLE OF VITAMIN D

The body can synthesize Vitamin D through sun exposure or by consuming it in food. The body undergoes two stages of hydroxylation. The main type of vitamin D found in the body is 25-hydroxyvitamin D [25(OH) D], which is produced through initial hydroxylation in the liver. The kidneys are responsible for the majority of the second hydroxylation process that creates 1, 25-dihydroxy vitamin D [1, 25(OH)2D]. This dynamic form engages with the vitamin D receptor (VDR) in specific body tissues such as the intestines, bones, and immune cells, to kickstart a sequence of biochemical reactions that control calcium and phosphate levels, bone formation, and immune system performance. A secosteroid with antioxidant and anti-inflammatory effects is vitamin D. It supports the metabolism of calcium and phosphorus. Additionally, it influences how the immune system reacts to autoimmune and viral disorders. The skin absorbs ultraviolet B light from the sun, which changes 7-dehydrocholesterol into cholecalciferol (Sajadi et al. 2020).

Because food sources did not supply enough vitamin D. As a result, oral supplementation is frequently in need of fortification. According to the latest research, COVID-19-affected cities have similar latitudes and temperatures to the worst-affected regions. This is crucial since people in high-latitude nations have low vitamin D concentrations (Cannell et al. 2006). Patients residing in regions categorized as high-alert areas

have previously been subject to suspicion regarding their potential vitamin D deficiency. Moreover, the prevalence of vitamin D deficiency exhibits substantial variation among distinct geographical areas within each nation, thus rendering the task of summarizing findings considerably challenging. Respiratory tract infections can be brought on by vitamin D insufficiency, according to published research (Lemire 1992). Extensive research has been conducted to explore the therapeutic efficacy of vitamin D in the treatment of acute respiratory tract infections (ARTIs). Calcitriol, a vitamin D agonist, has been found to play a role as a pathogenic factor in COVID-19. It exerts its effect by modulating the expression of angiotensin-converting enzyme 2 (ACE2) in lung tissue, thereby mitigating the risk of acute lung injury (Xu et al. 2017). Observed substantial findings from studies using large doses of vitamin D between 250,000 and 500,000 IU, including shorter hospital stays, higher hemoglobin levels, and better blood oxygenation (Han et al. 2016). Vitamin D supplementation lowered the likelihood of getting acute respiratory tract infections in comparison to individuals with low baseline vitamin D levels (25 nmol/L) (Martineau et al. 2017). Based on empirical evidence, scholarly studies indicate that the administration of vitamin D exerts a multi-faceted impact on microbial infections and mortality, yielding notable decreases in both. The assessment divided the effectiveness of vitamin D in fighting the common cold into three specific areas: physical defenses, natural cellular immunity, and adaptive immunity (Rondanelli et al. 2018). Vitamin D improves the body's natural ability to fight off infections by helping to produce antimicrobial peptides such as cathelicidin and defensins (Laaksi 2012). Due to its ability to increase glutathione production and enhance cellular immunity, vitamin D has been suggested as a potential preventive and therapeutic measure for COVID-19 (Wimalawansa 2020).

4.5. ROLE OF VITAMIN E

By giving its electrons to free radicals, unstable chemicals that can harm cells, vitamin E functions as an antioxidant. This procedure aids in scavenging free radicals and stopping their ability to harm cells. In addition, vitamin E interacts with proteins and enzymes that are important in cellular signaling and gene expression, which may have health advantages. Vitamin E has also been demonstrated to block the action of some enzymes linked to inflammation, which may aid in reducing inflammation in the body**.** As a strong antioxidant, vitamin E is essential for controlling and sustaining immune system activity (Jayawardena et al. 2020). Vitamin E reduces oxidative stress, prevents unshared electron free radicals, highly energetic damaged cells, and all of the above, in addition to acting as a free radical scavenger. Oxygen and unused electrons readily combine to generate reactive oxygen species (ROS) (Di Credico et al. 2015). In addition to its involvement in immunity, vitamin E has anti-inflammatory and antioxidant properties. Alpha-tocopherol prevents smooth muscle cells, monocytes, and platelets from proliferating, differentiating, and activating protein kinase C. By preventing the metabolism of arachidonic acid, which dilates blood arteries and prevents platelet aggregation, vitamin E raises prostacyclin levels (vitamin E-Health Professional Fact Sheet). According to one study, maintaining immunological function benefits older people more than younger people when vitamin E intake is higher (Meydani et al. 2018).

4.6. ROLE OF VITAMIN K

A vitamin K-dependent enzyme called glutamyl carboxylase converts glutamyl residues in these proteins into carboxy glutamyl (Gla) residues, which is the basic mechanism of action of vitamin K. To create vitamin K epoxide, which is then transformed back into vitamin K hydroquinone by the enzyme vitamin K reductase, vitamin K hydroquinone, the reduced form of vitamin K, is needed as a cofactor in this process. Because of carboxylation, clotting factors can bind calcium ions and participate in the

coagulation cascade. Along with aiding in blood clotting, vitamin K also supports bone health by regulating the activity of osteocalcin, a protein essential in bone development. Vitamin K is offered as a food additive in two different forms: K1 (phylloquinone) and K2 (which is made up of numerous MKs, or menaquinones) (Walther et al. 2013). Vitamin K plays a crucial role in facilitating the synthesis of proteins and other fundamental physiological processes. Additionally, it acts as a co-factor and co-enzyme during hemostasis (Janssen and Walk 2020). The pulmonary extracellular matrix is guarded against degeneration brought on by inflammation in SARS-CoV-2 patients by producing more matrix Gla protein (MGP) in the lungs. Utilizing vitamin K from extrahepatic stores is encouraged by the MGP. The occurrence of venous and arterial thromboembolic disease can be influenced by the severe inflammation, hypoxia, immobilization, and diffuse intravascular coagulation (DIC) associated with COVID-19.On top of that, blood clotting and lung elastic fiber degradation are potential side effects. By inducing hepatic coagulation factors in COVID-19 patients, vitamin K1 reduces thrombosis (Klok et al. 2020).

5. ROLE OF VARIOUS MINERALS AS IMMUNITY BOOSTERS

The COVID-19 pandemic has increased our understanding of the immune system's significance. The immune system may be boosted by a healthy diet, vitamin and mineral consumption, and appropriate cleanliness habits. There are distinct anti-infection defensive mechanisms in the immune system. The COVID-19 pandemic, characterized by its rapid and extensive dissemination, has emerged as a worldwide health concern, eliciting severe respiratory tract infections in affected individuals. The defense mechanism and its influential determinants presently constitute the primary challenges associated with the COVID-19 pandemic. "Cow's milk is highly abundant in an array of micronutrients which possess the capacity to enhance and sustain the immune system as is widely recognized. Research has shown that these nutrients are particularly good for preventing COVID-19, and those who are lacking in any of them may be less able to fight the infection. These nutrients have demonstrated efficacy in mitigating COVID-19, with the absence of any of them diminishing the body's immune response against the virus. Given that cow's milk is readily available to the general population, individuals who possess a transient immunity against the SARS-CoV-2 virus may potentially benefit from consuming colostrum, raw milk, or micro-filtered milk obtained from vaccinated cows. The COVID-19 pandemic has emerged as a significant global health crisis due to its exponential rate of transmission and consequential manifestation of severe respiratory tract infections among individuals. The primary challenges associated with COVID-19 involve the defense system and the various influential factors affecting its functioning. The nutritional composition of cow's milk includes a plethora of micronutrients which are known to enhance and sustain the functionality of the immune system, a widely acknowledged assertion within the academic community (Dhok et al. 2020).

5.1. ROLE OF MACRO-MINERALS

A robust immune system constitutes a formidable defense mechanism against the adverse consequences of COVID-19 infection, particularly in the absence of suitable therapeutic interventions. According to research by Jayawardena et al. (2020), mineral supplements have also been proven to boost resistance to viral infections. Inorganic substances called minerals are needed by the body to support biological function. Minerals have an impact on a variety of physiological functions, including bone growth, blood synthesis, hormone production, and cardiac modulation (Rondanelli et al. 2018). Numerous epidemiological studies have shown that dietary deficiencies in essential minerals are essential for

avoiding and minimizing CVS and CSF problems, which may speed the onset of corona infections (Zabetakis et al. 2020).

5.1.1. ROLE OF SODIUM

In SARS-CoV-2, salt has a substantial effect on both the change in electrolytic balance and the expression of ACE2 (Luo et al. 2020). Furthermore, a study discovered that when disease severity grows, salt levels decrease (Lippi et al. 2020). A meta-analysis revealed that COVID-19 patients' sodium concentration considerably drops (Habib et al. 2020). Hyponatremia of this type could be a biomarker for COVID-19 infection and be linked to the virus.

5.1.2. ROLE OF POTASSIUM

The most frequent side effects of COVID-19 are thought to be ARDS and acute cardiac damage, both of which are considerably increased by hypokalemia. Angiotensin-II levels rise as a result of COVID-19 binding to ACE2 and inhibiting its synthesis, which ultimately results in hypokalemia (Alwaqfi et al. 2020). Potassium content was found to be significantly lower in COVID-19 patients with severe disease compared to non-severe patients and to be less variable than salt (Lippi et al. 2020). According to SARS-CoV animal models, higher plasma angiotensin-II concentrations in COVID-19 patients may be the cause of acute lung damage (Zemlin et al. 2020).

5.1.3. ROLE OF PHOSPHOROUS

Phosphorus plays a crucial role in the stimulation of protein synthesis, which is essential for the growth, maintenance, and repair of cells and tissues (Vance 2011). Monitoring the blood phosphorus level in COVID-19 patients who are severely or seriously ill has been shown to be helpful for prognosis. According to research, hypophosphatemia and the severity of the illness are directly associated (Xue et al. 2020). The innate immune system works overtime to combat infection when a virus enters the body through ACE-2 receptors. However, due to the dearth of accessible minerals, phosphorus has a substantial impact on immunological responses, impairing their ability to repair damaged cells and tissues and fostering the development of illness. This clarifies how phosphorus could play a part in the transmission of illness (Ni et al. 2020).

5.1.4. ROLE OF CALCIUM

In addition to helping to strengthen our bones, calcium also helps to fight against viruses by flushing them out of the cells. Thus, calcium ions offer protection against the common cold. The severity of the disease is negatively correlated with the calcium level in the patient's serum, with critical COVID-19 patients having lower calcium concentrations than patients with less severe disease (Rodriguez-Morales et al. 2020), according to a combined analysis. Hypocalcaemia, low salt and potassium levels, and SARS-CoV-2 infection severity are all indicators.

5.1.5. ROLE OF MAGNESIUM

Magnesium is frequently underestimated. The stress brought on by the pandemic and the resulting PTSD that would affect COVID-19 survivors, medical personnel, and the general public may both be greatly reduced by magnesium supplementation. Moreover, it plays a crucial part in enhancing the

immune system by controlling a range of functions, such as immune cell adhesion, production of immunoglobulins, attachment of IgM lymphocytes, antibody-dependent cell breakdown, and adjustment of macrophage reaction to lymphokines (Ni et al. 2020). Research conducted both in laboratory settings and in living organisms has shown that magnesium is essential for the immune system to effectively combat viral infections (Jayawardena et al. 2020). A study in Singapore showed that older individuals with COVID-19 experienced a slower progression of the disease when they took a combination of vitamin D, magnesium, and vitamin B12 (DMB). Taking 150 mg of magnesium and 1000 IU of vitamin B12 can reduce inflammation and protect against respiratory infections. We suggest conducting a double-blind experiment using random selection (Tan et al. 2020).

5.2. ROLE OF MICRO-MINERALS

In general, medical experts and scientists advised preventive measures during this COVID-19 pandemic emphasize the significance of immunity as a potential COVID-19 defense (Calder 2020). Since there is now know WHO-approved treatment for the illness, the only line of defense against this viral infection is a strong, functioning immune system (Cascella et al. 2022). In fact, trace elements are important micronutrients that have a big impact on immunity. Trace elements including Cu, Zn, Se, and others exhibit antiviral activity in addition to their immunomodulatory effects by preventing the replication of viruses in host cells. Small elements' antioxidant properties have an impact on the viral DNA and alter the immune response. Through a variety of immunomodulatory routes, trace elements strengthen the body's immune system (Calder 2020).

5.2.1. ROLE OF ZINC

Zinc (Zn) is a vital component of dietary immunity and has several functions in the biological system. This mineral is considered to be in charge of the circulatory, reproductive, and neurological systems in addition to its active participation in lipid metabolism and glucose management (Collins 2016). The immune system's fight against H1N1 is said to depend heavily on zinc (Sandstead and Prasad 2010). The etiology of COVID-19 (SARS-CoV-2) centers around the angiotensin-converting enzyme 2 (ACE2), through which the virus gains entry into the host cell, akin to COVID-19 (SARS-CoV). Therefore, angiotensin-converting enzyme 2 (ACE2) emerges as the most optimal candidate for therapeutical intervention in the management of this pandemic (Zhang et al. 2020). The findings from in vitro experiments revealed that the Zn2+ cation effectively impeded the replication process of the virus RNA polymerase, thereby inhibiting its activity (Te Velthuis et al. 2010). The idea that using zinc in a complement treatment regimen might help treat COVID-19 is substantially supported by each of these justifications and pieces of evidence (Zhang et al. 2018).

5.2.2. ROLE OF SELENIUM

Considering its antiviral and anti-inflammatory qualities, she is regarded as the most trustworthy trace element. Several sets of seleno-proteins generally regulate the immune system, which is made up of seleno-cysteine. Selenium deficiency dramatically raises the risk of viral infections (Guillin et al. 2019). Basal selenium levels in the body are associated with COVID-19 patient cure rates, according to data from China (Zhang and Liu 2020). The cytosolic selenoenzyme that Se activates and is in charge of the enzyme's antiviral activity is glutathione peroxidase 1 (GPX1). The severity of oxidative stress induced-inflammation brought on by SARS-CoV-2 has been balanced by sialoproteins (GPX1) (Seale et al. 2020). Hence, a substantial intake of selenium with high nutritional value may potentially exert a notable

influence on the infection caused by SARS-CoV-2. This information proposed that selenium-based mechanisms are crucial for SARS-CoV-2. Fig. 1 shows the proposed technique by which SARS-COV-2's life cycle and mutation towards virulence may be inhibited.

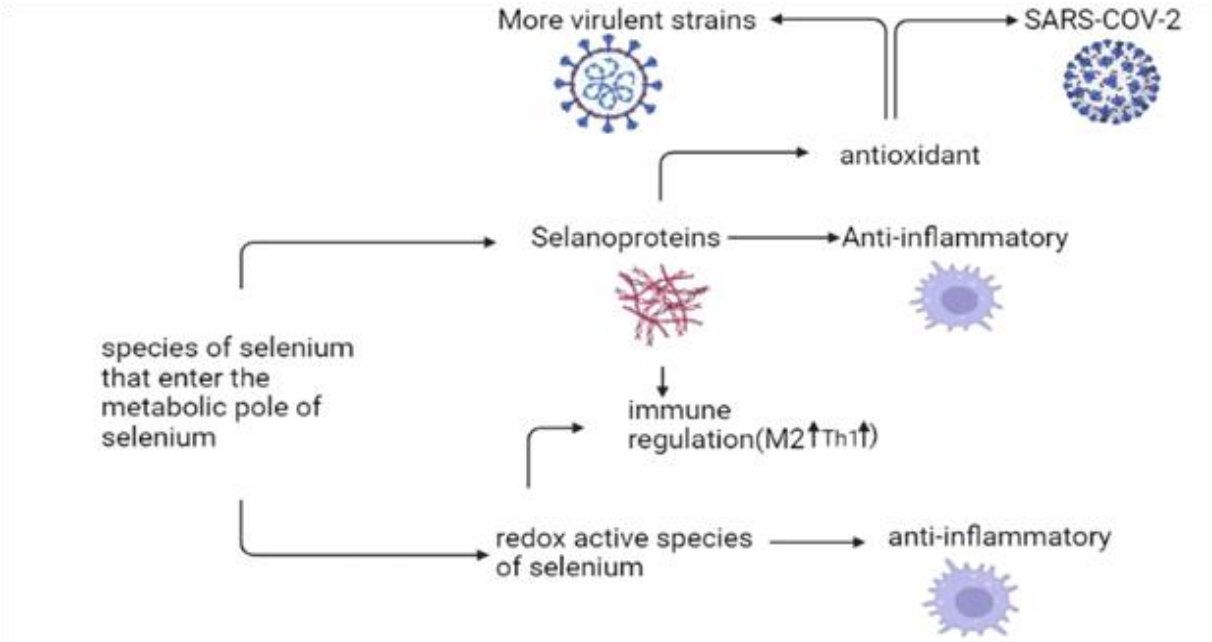

Fig. 1: Proposed technique by which SARS-COV-2's life cycle and mutation towards virulence may be inhibited while the virus's effects on organ damage, oxidative stress, and cytokine storm were reduced.

5.2.3. ROLE OF SULFUR

In addition to other physiological activities including transport across cell membranes, immunological responses, and blood coagulation, cysteine, and methionine- two significant amino acids produced by sulfur- are essential for bio-catalytic reactions (Dutta et al. 2009). According to studies on COVID-19, sodium is a sulfate-based molecule that has therapeutic potential for the lungs and respiratory illnesses. Additionally, clinical evidence shows that sodium thiosulfate ($Na_2S_2O_3$) is a successful therapy for pneumonia and lung damage in both adults and children. Sulfur may be protective against COVID-19 because of its numerous medicinal uses and connection to the respiratory system (Evgen'ev and Frenkel 2020).

6. CONCLUSION

Numerous successful vaccinations have been created in response to the current situation and work is being done on pharmaceutical therapies that are particularly customized; nevertheless, they are very expensive and challenging procedures with a limited range of focused activity. On the other hand, when supported by strong clinical trials, supplementing with vitamins and minerals is a relatively simple and cost-effective method that may have broad-spectrum of activity and long-term health effects. It is probably reasonable with very little risk to eat vitamins and minerals when assessing the risk-to-benefit ratio. On the other hand, certain new medications and vaccinations come with some risks. As a result, nutritional supplementation appears to be an effective way to treat SARS-CoV illness.

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Management, Control and Treatment of Monkeypox Disease

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ABSTRACT

Monkeypox is an uncommon virus that is mostly found in Central and West Africa and can be transmitted to humans from animals. The treatment of monkeypox requires the prompt isolation of potential cases, strict infection prevention protocols for healthcare workers, and placing close contacts under quarantine. It is essential to have surveillance systems in place to monitor the spread, while public health education is crucial in order to increase awareness and encourage the adoption of preventative measures. While there is no targeted antiviral treatment, smallpox vaccination has proven to be effective in preventing the disease, and scientists are currently working on developing vaccines specifically for monkeypox. Control tactics concentrate on identifying and controlling animal reservoirs, imposing travel limitations, and managing possible vectors. It is crucial to make efforts to minimize the interaction between humans and animals in areas where diseases are prevalent. Supportive care is the main component of treatment, focused on easing symptoms, addressing secondary bacterial infections with antibiotics, managing pain, and maintaining fluid levels. It is crucial for local health authorities to work together with international organizations in order to effectively implement control measures and prevent outbreaks. As our understanding of monkeypox grows ongoing research and monitoring play a key role in improving methods for managing, controlling, and treating the disease. This highlights the necessity of a comprehensive and well-coordinated approach to addressing this public health issue.

Keywords: Monkeypox; Zoonotic virus; Surveillance; Vaccination; Supportive care

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INTRODUCTION

Monkeypox (MPX) is an emerging zoonotic viral infection. The causative agent of this disease is a DNA virus of the genus Orthopoxvirus. MPXV is a member of the Poxviridae family and subfamily of Chordopoxvirinae. It is a double-stranded DNA virus that multiplies in the cytoplasm of infected cells. It is wrapped and lump-shaped (Karagoz et al. 2023).

The first case of MPXV infection was reported in 1958 in Denmark (A small Scandinavian country), where the monkeys were kept for study purposes (Brown and Leggat 2016). The term "Monkeypox virus" is used for the pathogen that was first discovered in monkeys in 1958. However, the name is misrepresentative because monkeys are incidental hosts, not natural hosts, of viruses. This viral disease was found to be prevalent in animals other than monkeys, like rodents, squirrels, rats, and mice. The disease is endemic to Africa and caused by MPXV. The virus exists naturally in the woody regions of central and West Africa (Chomel 2016).

Evolution of monkeypox The origin, evolutionary history, genetic diversity, and phenotypic traits of the accessible MPXV genomes must be determined in order to inform diagnosis, prevention, and research. OPVs typically change their gene composition to adapt in the hosts. Furthermore, whereas pathogenicity and genome-sequence length are inversely correlated, they pragmatically correlate with a wide spectrum of hosts (Isidro et al. 2022). Larger genomes and content in the WA clade of MPXV than in the CB clade (196,850-196,959 bp) may be a factor in the WA clade's decreased pathogenicity. Additionally, a phylogenetic study of the MPXV viral classifications linked to multicounty outburst in 2022 showed that the virus belongs to a third recently formed clade: (Within the earlier named "WA" clade, which also includes Clade two). The hMPXV-1A clade and the 4 recently identified lineages A.1, A.1.1, A.2, and B.1, with heredity B.1 having all MPXV genomes from the 2022 epidemic, However Clade 3 has a reduced disease-fatality rate. The three clades' principal distinctions are connected to coding areas. In comparison to the related viruses, the 2022 MPXV differs from 50 single-nucleotide polymorphisms (SNPs) by an average. This divergent branch, which separates the current epidemic virus from the sequence, might point to faster evolution (Luna et al. 2022).

2. MPXV STRUCTURE GENOME AND MORPHOLOGY

According to morphological studies, MPXV is an ovoid or brick-shaped particle covered in an outer lipoprotein membrane with geometric corrugations. Its virions are physically identical to those of other orthopoxviruses. MPXV is expected to be between 200 and 250 nm in size. (Khattak et al. 2023). The DNA genome, enzymes, and transcription factors of viruses are all shielded by the outer membrane. Due to an anomaly in electron microscopy, the core is described as being biconcave and having an adjacent body on either side (Manoj et al. 2020). A linear double-stranded DNA molecule with a length of 197 kb makes up the structure of the MPXV genome and contains a lot of open-reading frames (ORF). The structure of viruses contains palindromic hairpins with inverted terminal repeats (TTRs), simultaneous repeats, and hairpin looping, which are inextricably linked at both ends (Ghosh et al. 2023). DNA viruses, including MPXV, Complete their full life cycle inside the infected cells. All of the proteins required for viral DNA replication and transcription are encoded by the MPXV genome. Orthopoxvirus (OPV) species share a set of constitutive genes in the genome's central region. Genes that regulate virus-host communication are found in the terminal region and are less conserved (Senkevich et al. 2021). MPXV produces two different types of infectious virions: EEV (extracellular-enveloped virus) and IVM (intracellular mature virus). In contrast to IMV, when cell lysis starts, IMV is released. EEV is formed when actin tails come into contact with cells, allowing the virus to easily spread in the host body (Khattak et al. 2023).

Inner encapsulated viruses (IEVs) that reach the cell's edge and fuse with the plasma membrane form cell-associated virions (CEVs). CEVs are fundamentally in control of cell-to-cell communication. IEV is formed when IMV is encircled by a double membrane produced by the trans-Golgi network (TGN) (Khatif 2017). Orthopoxvirus (OPV) species share a set of housekeeping function genes in the genome's central region. Through the plasma membrane is another method for EEV synthesis in addition to IEV exocytosis. A-type inclusions (ATIs) include neither ATIs nor IMVs because MPXV truncates the gene for the A-type inclusion body protein (Khattak et al. 2023).

3. IMMUNITY TO MONKEYPOX VIRUS

There is a scarcity of knowledge about human immunity to MPXV infection. However, the virus has been recognized and known for years. The research studies related to members orthopoxviruses group are often considered to suppose how MPXV interacts with the immune system of the host.

4. INNATE IMMUNE RESPONSES TO MPXV

Innate immune cells of the body are usually considered as the first line of defense, When a virus attacks the individual with active viral infection, though some viruses also consider these immune cells as their targets. Among these cells, monocytes are the first cells that target poxviruses. According to several *in-vitro* and *in-vivo* studies, it has been proposed that early identification of poxvirus antigens in neutrophils and monocytes is a powerful aspect to predict against MPXV. Monocytes causing monkeypox are aggressively drawn to infection sites, and viral pneumonia is caused by MPXV infection. It causes a substantial increase of CD14+ monocytes in the lungs of cynomolgus macaques. Inflammatory monocytes have been revealed to be permissive to replication of VACV and may be possible carriers of the virus. Moreover, it was revealed that M2 human primary macrophages promoted VACV replication and spread (Davies et al. 2017). These primary macrophages developed actin tails, cell connections, and branching structures linked with the VACV virions after becoming infected, suggesting that these cells may help in the transmission of the virus. It was also noted that phagocytic cell depletion did not completely stop the spread of VACV72, indicating that other immune cells are also capable of promoting virus spread. Ly6G+ innate immune cells, were in charge of invading and regulating virus-infected cells, hence reducing viral tissue damage. These findings were indirectly supported by a study that discovered a link between sickness in MPXV-infected animals and low blood neutrophil extents. It is highly essential to consider that immune cells reach to the infection site to stop fleshy tissue pathology. However, immune cells don’t play any role in stopping the transmission of the virus. Systemic immune response is required for recovery from widespread infection. Natural killer cells are an essential part of innate immunity and may involve directing the course of the response of adaptive immunity.

5. EPIDEMIOLOGY

MPX infection was identified when a smallpox-like disease broke out in colonies of monkeys in a research institution in 1958. The virus-causing MPX infection was isolated and characterized for the first time in 1958 when monkeys with vesicular illness were brought from Singapore to Denmark. However, the first case of MPX disease in humans was detected in a 9-month-old child in the year 1970 in the Democratic Republic of Congo.The Democratic Republic of the Congo recorded 485 MPX cases, of which 25 were deaths, from 2001 to 2002 (Iqbal and Jaffri 2022). From the years 2017 to 2018, in Nigeria, 122 cases of MPX infection were reported, in which seven people died due to the

disease. However, the outbreak of MPX disease outside of Central and West Africa was considered to be rare (Yinka-Ogunleye et al. 2019). By May 23, 2022, Pakistan had challenged two sporadic occurrences of the zoonotic MPX disease, which had already spread to 12 other nations. According to the medical staff of Lahore Services Hospital (LSH), two cases of MPX were found in Lahore Jinnah Hospital, Pakistan. The patients were isolated and given good care in different isolated wards. After the detection of these cases, the National Institutes of Health (NIH) advised the nation's healthcare facilities to treat the illness with caution. 8 Moreover, the MPX disease outbreak was declared a Global Health Emergency on July 23, 2022, and 18597 cases of MPX were reported worldwide. According to the latest WHO data (January 3, 2023), a total of 25,736 MPX cases have been detected in 45 countries and regions in the European Region. The CDC's most recent data show that there are 84,471 cases overall in the world as of January 10, 2023. 1,200 of them are from areas where MPX cases have previously been found; the remaining are from areas where MPX has never been reported historically (Doganay and Aydin 2023).

6. TRANSMISSION

It was stated that the transmission began when rats were imported from Ghana to the United States. These rodents are thought to be responsible for causing MPX infection among prairie dog species that were being sold as pets (Simpson et al. 2020). The disease may also be caused by close physical contact, lesion exposure, and direct and indirect contact with infected animals. However, it is still under inquiry whether the virus is spread via rodent invasions or by eating wild animal meat. Exposure to animal excrement can be a serious risk factor in common regions of Africa due to insufficient resources and basic structure (Kaler et al. 2022). Many people live near or travel to forests where infected animals are more prevalent, sleep outside, or sleep on the ground. Hunting is the only option available in places where there are not enough resources or necessities like food, which raises the danger of exposure to MPX. It was also observed that the rate of animal transmission to animals is higher than that of human transmission to humans in the case of this disease. The transmission of viral infection may involve respiratory droplet exposure and face-to-face or lesion contact between infected individuals (Anwar et al. 2023).

6.1. TRANSMISSION BETWEEN ANIMALS AND HUMAN

The MPX virus has a variety of host species, so there are chances for better transmission modes to humans. Squirrels, Gambian pouched rats, dormice, and non-human primates are the natural reservoirs of MPXV (Cohen 2022). Exposure to the stools, saliva, and meat of infected prairie dogs In 200, 47 cases were documented in the United States because the infected people were in contact with these prairie dogs (Siegrist and Sassine 2023). An epidemiologic study shows that prairie dogs and imported rodents from Ghana have a long history of close interaction. Likewise, five cases were confirmed by patients who had contact with infected wild animals and reported. Transmission from people to pets has also been noted. Animal lovers are in danger of spreading the MPX infection to their pets (Seang et al. 2022). Fig. 1 shows the potential sources of infection transmission from animals to humans.

6.2. TRANSMISSION BETWEEN HUMAN AND HUMAN

Previously, it was thought that outbreaks were caused by human-to-human transmission; however, long-term transmission between humans was thought to be limited. Currently, it is thought that a significant factor in MPXV transmission is sexual transmission. For example, according to a report, four

individuals had insecure sex. MPXV was detected in their seminal fluids (Antinori et al. 2022). In addition, 86 cases of MPX were reported, all of which involved sexual activities like bisexual, homosexual, or (men sex with men) MSM (Vivancos et al. 2022). MSM was the cause of all 54 occurrences at one UK health Centre (Girometti et al. 2022). Evidence shows that close physical contact is also a major cause of the transmission of MPX. According to the information that is available today, males having sex with other males (MSM) account for increasing the cases of MPX (Russo et al. 2021).

6.3. TRANSMISSION BETWEEN HUMANS AND ENVIRONMENT

Direct contact with items such as sheets, clothing, or towels that have been used by an infected person's body fluids, lesion fluid, or scab may serve as a transmission medium. In general, OPXVs have a high level of environmental stability and are more resistant to environmental stress. Depending on the parameters of the room. However, information on environmental transmission is currently scarce. There is no information available right now about MPXV contamination of wastewater.

7. MANAGEMENT OF MPXV

7.1. CLINICAL EFFECTS AND SYMPTOMS

MPXV infections have two stages. First, the invasion phase, which lasts 2 to 13 days. The second rash phase, which lasts 7 to 24 days. After an MPXV infection, symptoms may take 6–10 days to manifest. Monkeypox is a self-limiting illness with symptoms that last between two and four weeks. Severe headache (27%), Fever (62%), myalgia (31%), and lymphadenopathy (56%) (WHO 2022). During a fever, the patient will develop skin lesions that primarily affect the face (95%), as well as the palms, feet, oral mucosa, genitals, and conjunctiva (20%) (Thornhill et al. 2022).

8. HOSPITAL MANAGEMENT AND PRECAUTION

Patients who are exposed to the primary infection of monkeypox may be at risk of secondary infection at the lesion stage of MPX. The patient should be encouraged to wear fully covered clothing and a full-sleeve shirt to prevent secondary infection. A disposal sheet should be used to cover the lesions. So that exposure will be reduced. Medical staff should inform the patients of the importance of surgical masks, which play a vital role in the prevention of spreading respiratory droplets. Moreover, after every 8 hours, the temperature, pulse rate, blood pressure, and respiratory rate should be monitored (Bryer et al. 2022). Patients with primary infections should be treated with medications including analgesics, antipyretics, anti-allergics and a wide range of antibodies. The lesions of the patients should be managed with analgesic ointment, saline compresses, and soft paraffin massages. All the isolation ward common rooms and washrooms should be washed with hypochlorite solution. Additionally, all healthcare workers have to design the proper duty schedule. They must use personal protective equipment, including a cover nail, N95 mask, face shield, and double gloves, for patient care activities (Relhan et al. 2023).

9. DIAGNOSTIC TECHNIQUES

9.1. LABORATORY TEST

Currently available diagnostic methods for MPXV detection include enzyme-linked immunosorbent assay (ELISA). Polymerase chain reaction (PCR), immunohistochemistry, electron microscopy cell culture,

Fig. 1: Potential sources of infection transmission from animals to humans.

Western blot examination, or sequencing, with PCR being utilized for conclusive diagnosis. Laboratory diagnosis calls for the collection of lesion roof, scab, tonsillar tissue, nasopharyngeal parts swabs, punch biopsy kits, and whole blood. The lesion sections must be kept in a dry, cool, and disinfected tube. Typical contact and droplet precautions must be used when collecting specimens, and any sections that may be contaminated with the MPXV must be handled.

10. REAL-TIME PCR

After 5 and 8 days of infection, immunosorbent assays (ELISA) are used to identify specific IgG and IgM antibodies in individuals' serum who had monkeypox. For serological testing. Both the acute and

convalescent stages of MPX infection can be identified using a four-fold increase in blood antibodies. The technique, which is often used in epidemiologic studies, is ineffective at identifying monkeypox virions. Because virions cannot be discriminated morphologically (Sterlin et al. 2021). Monkeypox can be found using the real-time polymer chain reaction (RT-PCR) genomic test. When a brick-shaped particle is discernible after negative staining in viral cultures, scab material, vesicular fluid, or biopsy specimens. The virus can be visually identified by using electron microscopy to find the viral particles. A main laboratory with trained staff and an electron microscope is required to conduct the test (Anwar et al. 2023).

11. SEROLOGIC TEST

Orthopoxvirus antibodies can be measured by immunofluorescence in serology tests (anti-orthopoxvirus IgG and IgM). WHO does not advise using antibody testing alone to diagnose MPXV (Altindis et al. 2022).

12. ELECTRON MICROSCOPE

Viral cultures, vesicular fluid, blood samples, and biopsy samples from lymph nodes can all be examined using electron microscopy with negative staining. Under an electron microscope, 24 MPXV is seen as an intracytoplasmic brick-shaped particle with lateral bodies and a central core that are 200-300 nm in size. Because OPXV species cannot be identified morphologically, this approach does not offer a conclusive diagnosis; however, it does show that the virus is a member of the Poxviridae family, which helps to identify it from Herpes and Parapox viruses (Petersen et al. 2019; Alakunle et al. 2020).

13. TREATMENT

13.1. SUPPORTIVE CARE

The majority of MPX patients heal without any medical assistance. Those who experience gastrointestinal symptoms (such as vomiting or diarrhea) will need oral or intravenous rehydration (Reynolds et al. 2017).

14. ANTIVIRALS

MPX infections may be successfully treated with several antivirals. The animal models were used to support the approval of these medications for the treatment of smallpox. Human dose studies for these medications have been carried out, although their effectiveness has not been fully investigated.

15. VACCINATION

Vaccination has traditionally been a powerful tool for preventing or dissipating viruses. There isn't yet a specialized vaccine to prevent MPXV infection. Vaccination against smallpox offers 85% protection against MPXV (Nasir et al. 2018) (Petersen et al. 2019). The older smallpox vaccine generations are no longer used in normal immunization programs. Modified smallpox vaccinations have undergone several advancements in recent years, including second-generation vaccines like ACAM200025, which was advised for post-exposure prophylaxis (PEP). Seven guidelines recommended the third-generation vaccination, also known as Imvanex or Jynneos, for PEP. Only two guiding lines offered suggestions for when PEP should be administered.

The PEP recommendations for various at-risk populations were scarce. A smallpox vaccination may be contraindicated by pregnancy, age, and a history of eczema in the pre-event setting, but it can be given with caution in the event of exposure, according to one of the two guidelines published on PEP in children and pregnant women.47

A different recommendation urged against immunizing newborns and expectant mothers.45 Two recommendations particularly advise against administering the smallpox vaccine to immunosuppressed individuals (i.e., those with HIV and CD4 counts below 200 or those receiving chemotherapy).

The instructions for using VIG were unclear. Three recommendations suggested taking into account VIG in people with weakened immune systems47. While the two guidelines did not make any recommendations about its use, they did state that there is a dearth of information regarding its efficacy for PEP and therapy. Six guidelines advised immunizing those who might be exposed to MPX, such as healthcare professionals.

16. PREVENTION MEASURES AND CONTROL

Epidemiology studies in high-risk areas strengthened laboratory-based surveillance capabilities, laboratory diagnostics, the development of regional capacities to put effective local solutions into action, and increased research activities Animal outbreaks can be prevented by control techniques such as routine screening and isolation of newly affected animals. By keeping in mind the following, people can prevent the spread of MPX. A patient with a suspected or confirmed infection should stay at home and minimize contact with others; an immunocompetent person who has mild MPX symptoms should avoid contact with others for three to four weeks; and clinical and other healthcare workers face greater challenges in preventing MPX infection because they come into contact with patients who are sick. Follow-up advice like avoiding direct contact with skin lesions or items used by MPX patients can help reduce the risk of infection. An individual should avoid intimate contact, including sexual contact, with someone infected with or exposed to the MPX virus. The individual should maintain good hand hygiene and respiratory etiquette, such as wearing a fitted mask and covering coughs and sneezes with a bent arm, piece of tissue, or cloth. After having visitors at home, proper cleaning and disinfection of high-touch areas are recommended. Any interaction with diseased people or animals should be avoided. It's crucial to observe sick people and to practice self-quarantine. Healthcare professionals should use protective clothes, eye protection, gloves, and protective cloth during the treatment of infected patients (Marshall et al. 2022). They should provide hand sanitizer and masks to travelers during travel. People should take the necessary safety measures to minimize the danger of infection (Sotomayor-Castillo et al. 2021). Maintaining healthy sexual performance is crucial, particularly for MSM people. By supplying fundamental knowledge, it is essential to increase public awareness of viral infection and MPVX transmission. Additionally, global efforts should be promoted. Monkeypox is a complicated infection that is caused by MPXV. The disease can be transmitted from animals to humans or from humans to humans. The disease can also be transmitted through physical contact, such as taking a bite from, through lesion exposure, the saliva of infected animals and humans, and also from cockroaches and unlocking food from infected animals. Due to large outbreaks all over the world, a global health emergency was declared on July 23, 2022. MPX disease spreads all over the world, even in those countries in which MPXV is not endemic. In Pakistan, some cases were reported. Some specific parameters have been measured to prevent the disease. All over the world, medical staff were trying to treat the infection. Proper management is necessary for the cure of patients. Treatment like antivirals, vaccination, and some supportive parameters used. At first, patients are treated with supportive measures, and then antivirals are given to patients to treat the infection. Vaccination is also a good way

to prevent the disease. Hospital management plays an important role in the prevention of disease. For the prevention of disease, proper treatment is necessary, and patients have to stay in isolated wards. The use of masks must increase. Wear full-sleeved dresses and contact lenses. Visitors must be at a minimum. People should be aware of all of the prevention measures that can help reduce diseases.

17. CONCLUSION

Monkeypox is a complicated infection that is caused by the MPXV. The MPX disease was first recognized in 1958 during the monkeys' research study in humans. The disease is endemic to the central and West Africa. The disease can be transferred from animals to humans or also from man to men. The disease also can be transmitted through the physical contact, taking a bite from, lesion exposure, saliva, of infected animals and humans, and also from cock and unlock food from infected animals. Due to large outbreaks in all over the world, Global health emergency was declared on 23 July,2022. MPX disease spread all over the world even in those countries in which the MPXV is not endemic. In Pakistan some cases were seen. Due to some specific parameters have been measured to prevent the disease. all over the world medical staff were trying to treat the infection. Proper management is necessary to for the cure of patients Treatments like Antiviral, vaccination, and some supportive parameters used. At the start, patients are treated with supportive measures then Antiviral are given to patients to treat the infection. Vaccination is also a good parameter to prevent the disease. Hospital management plays a vital role in the prevention of disease. For the prevention of disease, proper treatment is necessary, patients have to stay in the isolated wards. The use of mask must be increased. Wear full-sleeved dresses and contact. With visitors must be minimum. People should be aware of all of the prevention measures that can help to reduce the diseases.

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Genetic Diversity of Zoonotic Viruses and their Ability to Jump the Species Barrier

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ABSTRACT

This chapter goes into detail about the complicated world of infectious viruses, focusing on their wide range of genetic variations and the things that allow them to infect different species. Living things on Earth are all linked, and these germs, which have caused pandemics in the past, show how connected everything is. Zoonotic diseases, which include many different pathogens, are a problem for everyone around the world because they hurt people's health, crops, and budgets. This chapter talks about different types of zoonotic viruses, how they spread, and why a "One Health" method is essential for effective prevention. A look at the past shows how terrible viral animal diseases have been, from the Spanish pandemic to more recent epidemics like SARS and MERS, along with COVID-19. Recent progress in genetics, epidemiology, and surveillance of illnesses is a big part of solving these problems. This shows how important it is for people, animals, and the world to work together. Zoonotic viruses are essential for more than just health care; they also affect the economy, the environment, and society. Outbreaks have a significant effect on the economy because they affect manufacturing, foreign trade, and consumer spending. Healthcare systems are essential for managing diseases, so money needs to be spent on infrastructure, studies, and ways to keep diseases from happening. Zoonotic viruses have an ecological impact on environments and animal populations, which makes conservation efforts even more critical. Five primary examples are used to show how genetic variation in zoonotic viruses can be used to show how adaptable they are and what this means for diagnosis, treatment, vaccine creation, and healthcare preparedness. It is talked about with examples of how immune evasion, interferon-gamma blocking, genetic recombination, cross-species contact, and reservoir hosts can allow species to jump barriers. The chapter stresses how complicated zoonotic viruses are and how important it is to have a complete knowledge of inherent, ecological, and host-related factors. Experts in people, animals, and the environment must work together as part of the One Health plan to lessen the effects of these viruses on people and animals around the world. Animal-to-human viruses are studied because they are harmful to humans and because they show how different parts of life on Earth are linked.

Key words: Zoonotic viruses, Genetic diversity, Pandemics, Disease transmission, Cross-species interaction, Interconnected nature, Viral spillover, Public health, Genetic recombination.

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1. INTRODUCTION

Infectious illnesses have fascinated and challenged scientists and public health officials with animal origins that may spread to people. These mysterious diseases can cross species barriers and penetrate human society because of this. The zoonotic viruses at the center of these enigmas are microscopic infectious organisms that can hop from animals to humans. This chapter explores zoonotic viruses and why they can cross species barriers (Tomes 2023). The existence of zoonotic viruses serves as a continual reminder of the interconnected nature of all life on Earth. Diseases from other species serve as a sobering reminder that we all inhabit the same planet. From past terrible pandemics to current difficulties, the development of zoonotic viruses has impacted human history. Protecting global health requires more than just an intellectual interest in the genetic variety of these viruses and the mechanisms behind their capacity to leap species borders. To better understand these deadly foes, we shall delve into the complexities of zoonotic viruses in the next sections (Tomori and Oluwayelu 2023).

Zoonosis, often known as zoonotic illnesses or infections, represents the complex relationship between animal and human health. It includes viruses, bacteria, parasites, fungi, and prions that can cause illness. Zoonotic illnesses can cause pandemics in humans, a dangerous consequence of our relationship with animals. These diseases spread in several ways. They can spread by direct contact with diseased animals, polluted food or water, animal excreta, or arthropod vectors like ticks and mosquitoes. Animals often silently sustain viruses without showing symptoms and secretly transmit them to humans. Pathogens, whether viral (flu, HIV, Ebola), bacterial (Salmonella, Lyme disease), parasitic (malaria, toxoplasmosis), fungal (ringworm), or prionic (variant Creutzfeldt-Jakob disease), present unique challenges to containment and eradication (Haruna et al. 2023). Zoonotic illnesses affect public health, agriculture, and economies worldwide, causing illness, death, and economic turmoil. Their unrelenting development, highlighted by the SARS-CoV-2 virus-caused COVID-19 pandemic, reflects changing human-animal interactions, landscapes with deforestation and urbanisation, and agricultural practices. The "One Health" approach to zoonosis requires collaboration between human, animal, and environmental experts to address the complex relationship between them. Thus, zoonosis awareness and knowledge are essential for protecting public health and the fragile balance of life shared by many species (Toyoshima et al. 2020).

Zoonotic illnesses can impact biodiversity in multiple ways, one of which is by reducing or eradicating animal populations. Ebola virus epidemics in Africa have wiped out great ape populations, which are critical to forest ecosystems. Moreover, harming animal populations can have far-reaching consequences for ecosystems. It can disrupt food webs, change predator-prey dynamics, and alter species composition, leading to ecological imbalances. Human interference, such as illegal animal trade and habitat degradation, is often the reason behind the spread of zoonotic viruses. As people come into closer contact with animals due to loss of habitat and intrusion into wildlife territories, the risk of disease transmission

increases. To mitigate the ecological impact of zoonotic viruses, the conservation of species, preservation of habitat, and adoption of sustainable practices are all crucial.

2. A BRIEF HISTORY OF VIRAL ZOONOTIC DISEASES

Viral zoonotic illnesses have a long and convoluted history because of the many ways in which infectious organisms have jumped from one species to another. Scientists believe that animals have harbored viruses like influenza, smallpox, and measles for many years, leading to their evolution. Millions of people lost their lives in the devastating Spanish flu (H1N1) epidemic that hit the world in the twentieth century (Begeman et al. 2023).

Diseases such as severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), and the continuing COVID-19 pandemic put emerging coronaviruses in the spotlight as we entered the 21st century. The increasing contact between humans and animals, the loss of habitat due to deforestation, and the ease with which people and things may travel around the world all contribute to the dynamic character of zoonotic dangers in our interconnected world. Scientific progress in genetics, epidemiology, and disease surveillance has helped address these issues by illuminating the dynamics of viral changes. This information highlights the critical need for proactive monitoring, research, and a collaborative One Health approach, bringing together experts in human health, animal health, and environmental health to manage the dynamic nature of zoonotic diseases and lessen their global and societal impacts (Niemi et al. 2022).

2.1 SIGNIFICANCE OF ZOONOTIC VIRUSES

Zoonotic viruses are important beyond labs and clinics. These mysterious viruses, which may jump from animals to people, affect many aspects of our environment. They suffer economic disruptions that damage industry and trade. They demonstrate healthcare system resilience and the need for readiness and reaction. Zoonotic viruses cause fear, influence behaviour, and illuminate social dynamics. They threaten agricultural output and food supply. Additionally, these viruses create ecological shadows that might decimate wildlife populations and change ecosystems. They emphasize the need for global collaboration, improved research, and public health measures as disease indicators. Zoonotic viruses affect the economy, health, environment, and society, requiring a complex and cohesive strategy to reduce their impact (Parkhe and Verma 2021).

2.2. ECONOMIC

The effects of zoonotic viruses on international trade, manufacturing, and, ultimately, consumer spending are too widespread to ignore. Both affluent and poor countries might suffer significant economic losses as a result of these pathogenic pathogens. Healthcare expenditures associated with treating infected persons, increased demands on medical infrastructure, and the deployment of expensive containment measures like quarantines are all examples of the direct economic consequences that might result from a zoonotic outbreak (Rahman et al. 2020).

Further, they pose a threat to vital economic areas. For instance, when zoonotic infections break out in animals, it can lead to culling, trade restrictions and decreased productivity in the agriculture sector. Pandemics like avian flu or foot-and-mouth disease can lead to the killing of animals, jeopardizing food security. When a zoonotic disease breaks out, it can halt exports, limit travel, and lower customer trust in the safety of items from the affected region. Companies, employees, and international trade are all impacted by the resulting interruptions to supply networks. Further, zoonotic infections can have an

adverse effect on the local economy by discouraging tourists from visiting places where outbreaks have been recorded. To reduce the financial burden of zoonotic viruses and protect public health, it is crucial to invest in monitoring, research, and preventative measures (McNeely 2021).

2.3 HEALTHCARE

(Keesing and Ostfeld 2021) When it comes to managing diseases, particularly those brought on by zoonotic viruses, healthcare plays a key role in society. It covers a wide range of medical assistance, from routine checkups to more complex procedures, from diagnosis to preventative care. Zoonotic illnesses can represent major hazards to public health. Hence, it is crucial to have a reliable healthcare system in place for their early identification, diagnosis, and treatment.

When a zoonotic disease suddenly spreads, it may put a tremendous strain on the healthcare system and even overwhelm hospitals and doctors. Effective management of these situations requires ready access to adequate infrastructure, medical supplies, and qualified healthcare staff. Vaccination drives, public health education, and epidemic monitoring are all crucial parts of healthcare that are sometimes overlooked in favour of treating the sick. Healthcare systems also play an important role in R&D, which is necessary for the development of vaccines and therapies for zoonotic viruses. Healthcare infrastructure investment on a national and international scale is essential for dealing with these new dangers, protecting people and places, and decreasing the spread of zoonotic illnesses (Mohapatra et al. 2022).

2.4 ECOLOGICAL EFFECTS

Wildlife populations and ecosystem health are inextricably linked to the ecological consequences of zoonotic viruses. The spread of these viruses from animals to people has the potential to have devastating effects on ecosystems (Ribas et al. 2023). The reduction or extinction of animal populations is only one way that zoonotic illnesses can have an effect on biodiversity. Great ape populations, which are vital to forest ecosystems, have been wiped out by Ebola virus epidemics in Africa. Furthermore, if animal populations are harmed, it can have far-reaching consequences for ecosystems. Food webs can be thrown off kilter, and changes in predator-prey dynamics and species composition throw ecological processes off kilter. Many zoonotic viruses spread because of human interference, such as the illegal trade in animals or the degradation of natural habitats. As people come into more fantastic touch with animals due to habitat loss and intrusion on wildlife territories, this proximity raises the possibility of disease transmission. Conservation of species, preservation of habitat, and implementation of sustainable practices are all necessary to mitigate the ecological impact of zoonotic viruses. The probability of zoonotic spillover events can be reduced, and the ecological balance essential to sustain life on Earth can be preserved by protecting ecosystems and conserving the health of wildlife populations (Bezerra-Santos et al. 2021).

2.5 ZOONOTIC VIRUSES

Several viruses may spread from animals to people, and this has serious implications for public health. Here are a few prominent ones:

2.5.1. INFLUENZA VIRUSES

Depending on the type, the influenza virus can cause seasonal epidemics or even global pandemics, with consequences including moderate to severe respiratory symptoms and even pneumonia (Javanian et al. 2021).

2.5.2. CORONAVIRUSES

The SARS-CoV-2-induced COVID-19 pandemic has produced a wide range of symptoms, from simple respiratory problems to life-threatening pneumonia and multiple organ failure throughout the world (Abdel-Moneim 2020).

2.5.3. EBOLA VIRUS

High death rates are typically associated with epidemics of the Ebola virus, which causes severe hemorrhagic fever in humans (Jacob et al. 2020).

2.5.4. HIV (HUMAN IMMUNODEFICIENCY VIRUS)

HIV (Human Immunodeficiency Virus) targets the immune system, weakening it over time and, if untreated, leading to AIDS, which increases the risk of contracting opportunistic infections and malignancies (Wu et al. 2021).

2.5.5. RABIES VIRUS

Confusion, paralysis, and hallucinations are only some of the neurological signs of rabies, which can quickly progress to death if not treated quickly enough (Lian et al. 2022).

2.5.6. HANTAVIRUSES

Humans can contract deadly respiratory illnesses from hantaviruses, such as hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS) (D'Souza et al. 2020).
These examples underscore the importance of understanding and monitoring zoonotic viruses to mitigate the risk of outbreaks and protect global health.

2.6 CATEGORIES OF ZOONOTIC VIRUSES

Origin, mode of transmission, and illness manifestations are only a few of the factors that may be used to classify zoonotic viruses. Common types of zoonotic viruses include:

2.6.1. RESPIRATORY ZOONOTIC VIRUSES

Airborne droplets often spread these viruses and cause infections in the respiratory system. Certain coronaviruses, adenoviruses, and influenza viruses (including H1N1 and H5N1), as well as SARS-CoV-2 and MERS-CoV, are prime examples.

2.6.2. VECTOR-BORNE ZOONOTIC VIRUSES

Arthropods like mosquitoes and ticks act as vectors for the spread of these viruses to people. The Zika virus, West Nile virus, and other encephalitis viruses are only a few examples.

2.6.3. GASTROINTESTINAL ZOONOTIC VIRUSES

These viruses can infect the digestive tract and are commonly spread by tainted food or water or by coming into touch with infected animals. Viruses that cause stomach and intestinal illness are one example.

2.6.4. HEMORRHAGIC FEVER ZOONOTIC VIRUSES

Contact with infected animals or their body fluids is a common route of transmission for these viruses, which can cause life-threatening bleeding problems. The Ebola virus, the Marburg virus, and the Lassa virus are only a few examples.

2.6.5. VECTOR-BORNE FLAVIVIRUSES

A group of viruses spread mostly by Aedes mosquitoes; they include dengue, yellow fever, and chikungunya.

2.6.6. OTHERS

Many zoonotic viruses exist that cannot be simply classified. Nipah, Hendra, and other poxviruses are among them.
These groups show how many distinct kinds of zoonotic viruses there are and how many ways they may infect people. For the sake of public health and disease prevention, it is crucial to have a firm grasp of these classifications and the dangers they pose (Zhang et al. 2020).

3. GENETIC DIVERSITY IN ZOONOTIC VIRUSES

To fully grasp the versatility, transmission, and impact of zoonotic viruses on public health, an appreciation of their genetic diversity is essential. The genetic complexity of five well-known zoonotic viruses is discussed here: SARS-CoV-2 (Coronavirus), HIV-1 (a subtype found in the Democratic Republic of the Congo), Influenza A Virus, Ebola Virus, and Rabies Virus.

3.1 SARS-COV-2 (CORONAVIRUS)

As evidenced by the COVID-19 pandemic caused by SARS-CoV-2, genetic diversity among zoonotic viruses is critically important. The genome of this member of the family *Coronaviridae*, a coronavirus, is around 30,000 nucleotides long and consists entirely of single-stranded RNA. The virus apparently evolved genetic modifications that allowed it to spread efficiently from human to human once it emerged from an animal reservoir. Mutations in the spike protein, which interacts with the human ACE2 receptor, are the primary source of genetic variety in SARS-CoV-2. Transmission, immune evasion, and vaccination efficacy can all be influenced by the genetic fingerprints left by different strains of the same virus. Natural selection, immunological pressure, and host adaptability are all thought to be responsible for these alterations. The fact that new lineages are constantly forming demonstrates the virus's adaptability (Malik 2020).
Because certain mutations might modify a virus's sensitivity to therapy, diverse genetic lineages also provide difficulties for vaccine development and antiviral medicines. Tracking genetic variation and guiding public health efforts to battle a pandemic necessitates global monitoring and sequencing of virus genomes.

3.2 HIV-1 IN THE DEMOCRATIC REPUBLIC OF CONGO

HIV-1, the virus responsible for AIDS, has a lot of genetic variation, especially among its subtypes and recombinant forms. Subtype B is more abundant in North America and Western Europe, whereas Subtype C is more prevalent in Southern Africa. The HIV spectrum is on full display in the Democratic Republic of

the Congo (DRC) in Central Africa. Subtype D and recombinant variants are the most common types in the DRC. These recombinants are the product of gene exchange between different subtypes that occur when many subtypes infect the same host. The ramifications of this genetic variety for diagnosis, therapy, and vaccination development are significant. Vaccine candidates and antiretroviral medication regimens must take into account geographical differences in order to be effective. Studies conducted in the DRC provide insight into the complex dynamics between HIV subtypes and the difficulties posed by controlling viral populations with such a wide range of genetic diversity in the worldwide battle against AIDS (Rubio-Garrido et al. 2020).

3.3 INFLUENZA A VIRUS

The influenza A virus, like other members of the family *Orthomyxoviridae*, is very adaptable genetically. When two distinct influenzas A strains infect a host, the virus's eight RNA segments allow for genetic reassortment. This reassortment generates fresh strains with the potential to spread worldwide. Subtypes of influenza A viruses are defined by differences in their surface hemagglutinin (H) and neuraminidase (N) proteins. Seasonal flu epidemics and the infrequent appearance of pandemic viruses are both facilitated by the continual mutation and reassortment of these subtypes. The reassortment of genes from human, pig, and avian influenza viruses, for example, caused the 2009 H1N1 influenza pandemic. Point mutations in the H and N genes cause antigenic drift, necessitating regular revisions of flu vaccinations to keep up with circulating strains. The selection of vaccine strains, monitoring, and pandemic preparedness all rely on a thorough knowledge of the genetic variety of influenza A viruses. The worldwide health effect of these extremely adaptable viruses is a major concern, and current research seeks to forecast their development and lessen it (Liu et al. 2020).

3.4 EBOLA VIRUS

Recent Ebola virus outbreaks in Africa have highlighted the family's genetic diversity. Different species of Ebolavirus have somewhat different variations of the virus's single-stranded RNA genome. There are five different types of Ebolaviruses, but the one that causes the worst sickness in humans is the Zaire ebolavirus. The virulence and ease of transmission of Zaire ebolavirus are affected by genetic polymorphism within the virus itself. For instance, the Makona subtype of Zaire ebolavirus was responsible for the 2014 West African epidemic. Diagnostics, therapy, and vaccine development are all affected by the Ebola virus's genetic diversity. Diagnosing and treating diseases successfully requires targeting conserved areas of the genome. Vaccines against Ebola that are effective against several strains of the virus are still being developed (Woolsey and Geisbert 2021).

3.5 RABIES VIRUS

Lyssaviruses, like the one that causes rabies, consist of a single strand of RNA. In comparison to other RNA viruses, it is notable for its low levels of genetic variation and high genetic stability. The phylogenetic study, however, has shown genetic subgroups within lyssaviruses. There are public health consequences associated with the rabies virus's genetic diversity, particularly when considering variant-specific vaccinations. Rabies variations linked with distinct animal reservoirs may influence the choice of treatment and vaccination. In order to comprehend transmission patterns and locate high-risk locations, monitoring rabies virus genetic variation is essential. Data is useful for developing effective vaccine and control tactics, which will ultimately lead to the eradication of an ancient but still lethal zoonotic virus. In

conclusion, the genetic diversity of zoonotic viruses is a key factor in the way these pathogens have evolved, adapted, and affected human and animal populations. This variety provides a window into the ever-changing world of zoonotic viruses and their intricate genetic landscapes, which is essential for diagnostics, therapy, vaccine development, and public health preparation (Coertse et al. 2021).

4. FACTORS ENABLING SPECIES BARRIER JUMPING

Complex molecular and genetic processes are involved in the process by which zoonotic viruses are able to infect both animals and humans (Dhama et al. 2020). Some of the reasons and mechanisms at play, along with some relevant instances, are outlined below:

4.1 ESCAPING IMMUNE SYSTEM

Transmission of zoonotic viruses from animals to people relies heavily on the viruses' capacity to escape the immune system. These viruses are able to infect new host species because of a complex procedure involving many immune evasion mechanisms. Changing the surface proteins of the virus through genetic variants is an essential tactic for evading the host immune system. Because of this diminished recognition, the virus is able to establish itself within the host without being seen during the early stages of infection (Abdullah et al. 2021).

Some viruses produce targeted proteins to circumvent the immune system. To impede the host's immune response, HIV-1 creates proteins, including Vpu and Nef, which down-regulate critical cell surface receptors involved in immune detection. One typical strategy used by zoonotic viruses is antigenic variation. Because they may undergo fast genetic changes that modify the epitopes on their surface proteins, viruses might evade the host immune system's ability to generate an effective response because antibodies may no longer detect the mutated virus. More than that, certain viruses inhibit antiviral immune signalling pathways. Some viruses, for instance, are able to suppress the host's production of interferons, which are vital antiviral signalling molecules (Forni et al. 2021).

Dendritic cells and macrophages are two examples of host immune cells that may be manipulated by zoonotic viruses, leading to an immunosuppressive environment that prevents adaptive immune responses from being activated. Because of this, the virus is able to create long-lasting infections while remaining hidden from immune monitoring. There are instances where these viruses cause immunological tolerance in the host, thereby teaching the immune system to ignore the infection. Constant exposure to the virus, especially in endemic areas, can lead to this condition, which is typical of chronic viral infections (Blum et al. 2020).

4.2 COUNTERING INF GAMMA

To better infect new species, zoonotic viruses often develop strategies to neutralise interferon-gamma (IFN-), a vital part of the host immune response. IFN- is essential for antiviral defences because it sets off a chain reaction of immune responses to fight against viruses. However, when its activity levels are too high or undergo mutations, it can constitute a barrier to viral reproduction and spread. The IFN- responses of hosts can be modulated or suppressed by the methods that zoonotic viruses have evolved. These viruses are better able to infect new host species and thrive in their specific biological contexts if they are able to change their genetic makeup. This approach of immune evasion allows zoonotic viruses to overcome the robust host immune system, allowing for effective transmission across species and the possibility for long-term expansion into new host populations. To adapt and emerge, zoonotic viruses

must strike a delicate balance between being detected by the immune system and taking advantage of the host's resources (Liu et al. 2022).

4.3 GENETIC RECOMBINATION

An essential mechanism in virology, genetic recombination contributes significantly to the creation of new, potentially more dangerous zoonotic viruses. Hybridization is the process by which they exchange genetic material from two or more distinct viral strains or variations, giving rise to a new hybrid virus with a distinct genetic composition. Because it can help a virus adapt to infect new host species, this mechanism is of particular importance in the context of zoonotic illnesses. During the co-infection of a host cell, viral fragments of the genome (either RNA or DNA) can swap places, a process known as genetic recombination. This can happen if they infect the host with two separate but related viruses or two different strains of the same virus. These viruses' genetic material can mingle during replication, producing recombinant viruses containing features from both parental strains (Rockett et al. 2022).
Genetic recombination may drastically alter the capacity of a virus to identify and connect to host cell receptors, to elude the host immune system, and to multiply successfully in the new host. By rearranging their genes, zoonotic viruses may quickly adjust to the specific conditions of a new host species, which can boost viral dissemination and virulence. Therefore, genetic recombination is essential in the ever-changing process of zoonotic spillover and the formation of infectious illnesses with the potential to become pandemic. In order to forecast and reduce the hazards associated with zoonotic viruses, it is crucial to understand and monitor these recombination processes (Szpara and Van Doorslaer 2021).

4.4 CROSS-SPECIES INTERACTION

Pathogens such as viruses, bacteria, and parasites can be spread from one species to another through "cross-species contact," which is defined as contact between members of various animal species, including humans. The introduction of microorganisms that might cause zoonotic illnesses requires intimate interaction between animals and people. Wildlife trade, farming, hunting, and habitat intrusion are just a few of the places where species meet and mingle. These conditions allow infections to cross across from animals to humans or between species of animals. Factors enhanced the danger of zoonotic disease transmission, such as growing urbanization, deforestation, and changes in land use. For the early diagnosis and control of emerging infectious illnesses, it is essential to gain an understanding of the dynamics of cross-species interaction and the hazards associated with it. This is because it reveals how viruses may breach species barriers and potentially lead to outbreaks and pandemics (Warpeha et al. 2020).

4.5 RESERVOIR HOSTS

In order for zoonotic viruses to jump genetic species boundaries, reservoir hosts play a crucial role. These hosts act as natural reservoirs since they may carry the virus for long periods without showing any symptoms. The genetic adaptations and interactions that take place during this cohabitation have the potential to result in spillover events into other host species, including humans. Reservoir hosts may play many roles in the genetic development of zoonotic viruses. They maintain a constant supply of the virus, which boosts the potential for mutation and genetic diversity. It is recognised that genetic exchange and recombination are facilitated by the wide variety of related viruses seen in some reservoir hosts, such as bats for coronaviruses. These alterations to the viral genome may improve the virus's capacity to adapt

to new host species by allowing it to recognise and attach to receptors, avoid detection by the immune system, and multiply (Van Brussel and Holmes 2022).

Zoonotic viruses essentially employ reservoir hosts as "genetic melting pots," amassing mutations that might improve their adaptation to new hosts. Because of this genetic variation, zoonotic viruses are able to successfully spread to humans and other mammals, resulting in the formation of infectious illnesses. In order to forecast and prevent zoonotic disease outbreaks, an understanding of these genetic relationships is crucial (Holmes 2022).

5. CONCLUSION

In conclusion, the intricate interaction of genetic, ecological, and host-related variables underpinned the phenomena of zoonotic viruses. Because they can suddenly appear and spread throughout populations, zoonotic illnesses pose a serious risk to world health. Viruses are able to detect and exploit new host species thanks to genetic modifications generated by mutation and recombination. Genetic diversity is encouraged, and a source of potential spillover events is provided by the presence of natural reservoir hosts, which typically keep these viruses asymptomatically. Viruses' abilities to attach to host receptors and elude immune responses can be improved by changes in viral surface proteins, a consequence of the genetic variety that accumulates inside reservoir hosts.

Furthermore, possibilities for zoonotic viruses to overcome species barriers are facilitated by variables such as host range extension, cross-species interaction, and modifications in ecological landscapes. The spread of infectious diseases from wild animals to domesticated ones and then to people is called "zoonotic spillover," and it has become more of a concern as a result of increased human-animal interactions brought about by urbanization, deforestation, and shifts in agricultural techniques. Arthropods like mosquitoes can act as conduits for the spread of disease from animal reservoirs to human populations through vector-borne transmission.

Variables increased the likelihood of newly discovered viruses infecting vulnerable human hosts, such as behavioural and cultural patterns, international travel, and alterations in the global environment. Because of antibiotic resistance, zoonotic microorganisms can now spread between species despite attempts to contain them. Understanding the genetic, ecological, and immunological variables involved in zoonotic spillover is crucial in this age of increased human-animal interactions and global interconnection. It helps us spot potential danger zones so we can take preventative measures against the spread of zoonotic illnesses. To combat the persistent risk of zoonotic viruses and safeguard the health of human and animal populations throughout the world, a one Health strategy that prioritizes cooperation between human health, animal health, and environmental specialists is necessary.

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