An Overview of the Selected Zoonotic Diseases in Pakistan

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ABSTRACT

Zoonosis is a class of diseases that specifically originates in the animals. Pakistan is particularly susceptible to zoonotic illnesses because of its varied environment, large-scale cattle husbandry, and intimate relationships between humans and animals. This chapter looks at the epidemiology, clinical presentation, and public health consequences of various zoonotic diseases that are of high priority in Pakistan: anthrax, Avian Influenza, brucellosis, rabies, Salmonella infections, tuberculosis, Crimean-Congo hemorrhagic fever (CCHF) and Leishmaniasis. The complex interactions between humans, animals, and the environment that contribute to the appearance, spread, and transmission of various illnesses sign and symptoms, economic importance and possible remedies of the aforesaid diseases and infections. The text draws attention to the difficulties Pakistan has in managing zoonotic illnesses, which include inadequate resources, insufficient knowledge, and subpar surveillance systems. Additionally, the chapter offers a number of intervention techniques, highlighting the necessity of multi-sectoral cooperation and the advancement of One Health programs. Improved public awareness campaigns, immunization campaigns, better animal husbandry techniques, better veterinarian services, and better disease tracking and reporting are some of these tactics. In Pakistan a significant number of human and animal population are susceptible to these diseases. As these diseases have the competency to spread from the infected animals through skin contact and body fluids which is most of the time lethal, Pakistan may guarantee the health and safety of its populace while considerably lowering the burden of zoonotic illnesses by tackling these issues and putting into practice efficient treatments. However, some common traits include the capacity to spread by contact with sick animals or their products, the capacity to produce a range of symptoms in both humans and animals, and the capacity to be lethal. It's crucial to be informed about the zoonotic diseases that are common in Pakistan and to take precautions against them.

Key words: Anthrax, brucellosis, CCHF, influenza, rabies, Salmonella

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1. INTRODUCTION

Zoonotic diseases are the class of diseases that are either wildly or domestically originated in animals. As it has two points of origin however policymakers and researchers pay much attention to the wild origin of zoonotic diseases as the wild source of origin has a great impact on global health and biodiversity conservation. The invasion of SARS-CoV-2 from an unidentified origin led to the COVID-19 pandemic situation globally. The wild and unidentified origin requires much attention due to (A) the incorrect use and broad use of terms such as the field researcher coined a term with any evidence or proof that “bat is the reservoir of MERS-COV and/or SARS-COV-2 (Balkrishna et al 2021). Unstable usage (B) unstable usage of terms such as Bats were both called endemic and vector leading to public confusion. (C) Incorrect explanation of biological mechanisms or their products publicly such as “spillover /Novel” and (D) incorrect decoding of the proof or evidence of a biological process (serological evidence, Phylogenetic evidence) due to the lack of knowledge among the audience. An overview of various zoonotic diseases has been enlisted in Fig. 1. Hence at the start of the chapter, we are going to define some of the terminologies related to zoonotic diseases as follows.

1.1. PATHOGEN

A Pathogen is a microbe that causes or has the capability to induce a disease in a susceptible host. Such as a virus, bacteria fungus, or a eukaryotic entity all this class of microbes have the potential to induce a specific disease in a host body.

1.2. PATHOGENICITY

A microbe's capacity to transmit disease or harm to the host Definition of zoonotic diseases. The Greek term that gave rise to the phrase zoonoisis is nosos, which denotes sickness and zoon, which refers to animals (Balkrishna et al. 2021). If we look at the broader definition of the term zoonosis we priorly said an infection that originates from animals According to the WHO 1951, any disease transmitted between vertebrate animals and humans through any possible way is referred to as zoonosis However, a definition is required since it will enable accurate categorization of pertinent infections, direct comprehension of their connections and larger, non-medical characteristics Through public health Initiatives and modifications to social, medical, and veterinary policies that influence the effect of zoonoses a correct definition would also enable the functional targeting of the elements that support the persistence of zoonotic illness. The word sapronoses describes illnesses with an abiotic substrate as their source, whereas the term "anthroponoses” describes illnesses that have an infectious human source Anthropozoonoses and zooanthroponoses are additional terms used to describe zoonoses when they are made from people to animals, respectively. In rare instances, zoonotic illnesses that are spread in either direction have been referred to as amphixenoses following that WHO expert committees dropped all of the subterms. The word zoonoses often refers to diseases that can be transmitted from animals to people because of our art anthropocentric perspective on nature, whilst the opposite remains a topic that is only of interest to environmental specialists (Abdullah et al. 2019).

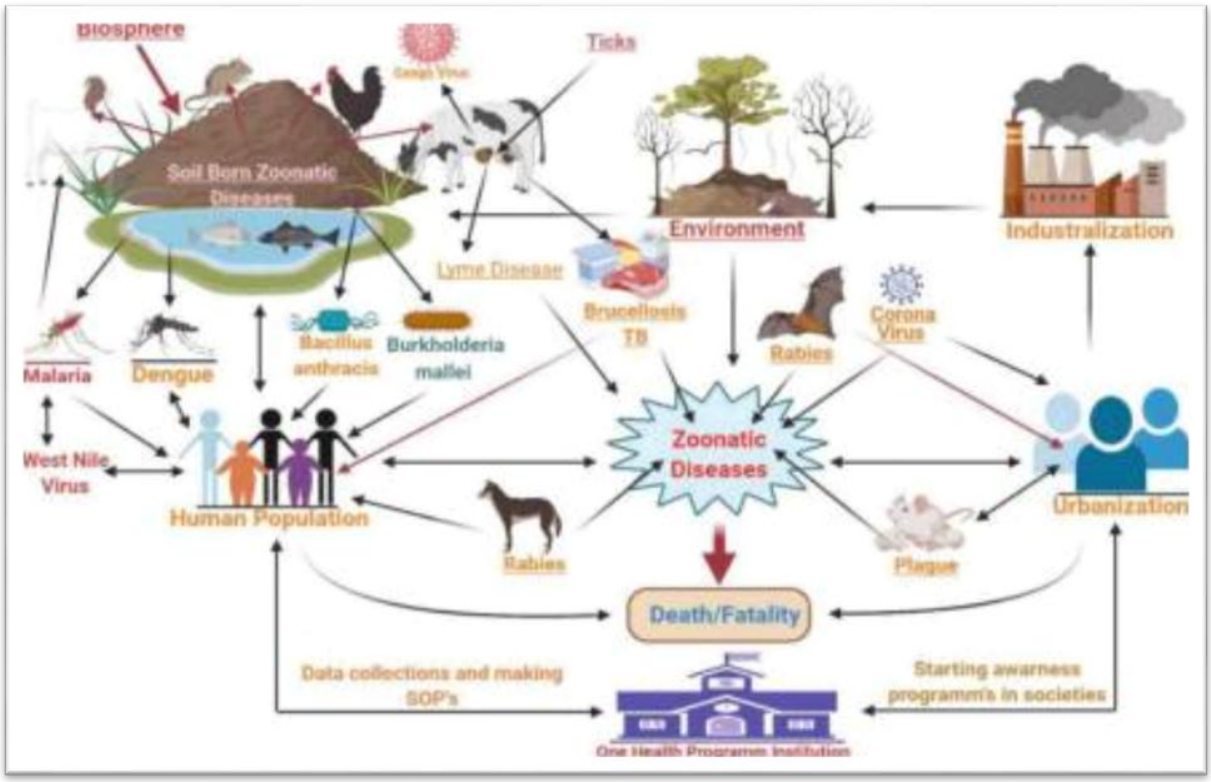

Fig. 1: Overview of different zoonotic diseases (Yasmeen et al. 2021).

2. ZOONOTIC DISEASES IN PAKISTAN

Since zoonoses make up about 60% of all infectious illnesses and are the source of 75% of newly developing transmissible pathogens, they represent serious risks to public health. The most prevalent zoonotic illnesses in Pakistan include tuberculosis, Q fever, Lyme disease, Crimean-Congo hemorrhagic fever (CCHF), brucellosis, leishmania, Chagas diseases/trypanosomiasis, balantadiasis, avian influenza, Giardia, foot and mouth disease, and anthrax. Infections caused by soil-borne zoonotic pathogens including *Burkholderia mallei* and *Bacillus anthracis* have been reported in the Punjab province in both humans and animals. Furthermore, DNA-based research has shown that Pakistan has a significant incidence of B. anthracis (Yasmeen et al. 2022). Mycobacterium bovis and drinking raw cow milk were major contributors to human tuberculosis infections during the 19th and 20th centuries. The enormous population of cattle in Pakistan is well suited to the regional environmental conditions and provides 1.63 million tons of meat yearly. Bovine tuberculosis infections are lethal to calves and can be passed to humans by aerosols (through cough, and sneezes) or consuming unpasteurized cow's milk. When it comes to countries where the seroprevalence of TB is comparatively Elevated, Pakistan comes in fifth. Out of which 510000 new TB cases are reported per year. For instance, M. bovis was discovered with an overall prevalence of 10.18 and 11.53%, in 4 cattle and 17 buffaloes respectively. A study was conducted in three major slaughterhouses of Peshawar, that included lung and liver tissue samples from 124 buffaloes and 28 cattle (Muqaddas et al. 2023). The high prevalence of bovine tuberculosis has been associated with not doing proper medication and unhygienic conditions at slaughterhouses indicating a lack of veterinary inspection and monitoring for the prevention and management of animal TB. Inspection and monitoring procedures should be followed

to improve the quality of animal meat and prevent the spread of TB from infected animals to humans. A single-stranded RNA virus that not only infects humans but also warm-blooded animals is among the worst. The rabies virus is a member of the *Rhabdoviridae* family and is one of the deadliest viruses. The three species that transmit the virus to people are dogs, bats, and raccoons, which are the most affected. Dog bites are responsible for 50,000 fatalities per year and 5 million documented cases (Jafar et al. 2014). In many rural areas of Pakistan, rabies remains a severe hazard, according to the National Rabies Control Programme of Pakistan (NRCP), and 54.7% of dogs that have bitten people have not received rabies vaccines. Additionally, according to another estimate, around 70 dog bite victims receive daily medical care in both public and private facilities. So, it is more possible that there are up to 9 million cases of rabies worldwide. Several dengue outbreaks have recently been reported in different parts of Pakistan since the first outbreak was reported in 1994. Most specifically the Lahore outbreak (in 2011) resulted in cases exceeding 21000 out of which 350 died, in 2019 44,415 cases were reported 66 died and the Karachi outbreak resulted in more than 6000 incidences and up to 55 deaths. Although the number of cases is elevated annually however the death ratio has shown to decline (Abdullah et al. 2019).

3. MORPHOLOGICAL CHARACTERISTICS OF ZOONOTIC DISEASES

3.1. BRUCELLOSIS

Brucellosis is one of the Zoonotic contagious infections that is generally present in both wild and domesticated animals. Sir David Bruce, Hughes, and Zammit helped to completely understand the disease while they were conducting their study in Malta. Bang recognized brucellosis (brucellosis, also known as undulant fever)-causing bacteria B. abortus, which causes abortion in cattle and brucellosis in humans. With more than 500,000 new cases each year and a prevalence rate that surpasses ten cases per 100,000 individuals in some countries, the illness continues to be the most widespread bacterial zoonosis in the globe, with organized agricultural workers having a higher incidence rate Christopher (2010).

Brucellosis is not well diagnosed and documented, even though it is widespread in many underdeveloped nations. In humans, it greatly affects public health and causes substantial economic losses, and in livestock, it has causes caused about a 20-25% reduction in productivity, less milk production, miscarriages, and weak offspring. Moreover, it greatly affects general livestock trading. It also causes temporary or permanent infertility in the livestock. Despite being widespread, this disease has a significant impact on the general populace and livestock in underdeveloped nations where it is prevalent due to inadequate monitoring of public health, domestic animal health programs, and diagnostic facilities. Brucella is a gram-negative, species-specific, non-motile, anaerobic bacterium. Different Brucella strains, including two marine and six terrestrial species, are the primary cause of brucellosis. Fetal fluid, uterine exudates, semen, and aborted fetuses are the major sources of Brucella transmission. It causes epididymitis, seminal vesiculitis, orchitis, and lifelong infertility in men, whereas fetal membrane damage, retained placental contents, and severe metritis that can lead to death occur in women (Jamil et al. 2021). The physiology of the disease is still controversial. To date, numerous research studies have described that the Brucella arrives inside the body through GIT, mucosal layers, and respiratory tract, and spreads throughout the body. Similar to other intracellular infections, Brucella spp. are facultative intracellular bacteria with the capacity to escape the killing mechanism and grow inside macrophages. Brucella must successfully undergo four processes in order to be an effective infectious agent: linkage, incursion, establishment, and dissemination within the host. Following ingestion, Brucella moves within the cell while being swallowed by a phagosome. In order to prevent the Brucella-containing vacuole (BCV) from fusing with a lysosome, a number of virulence factors help

Brucella evade the phagocytic pathway (Ouahrani-Bettache et al. 2019). These elements consist of the type-4 secretion system, launched by the *vir*B operon, the two-constituents system BvrR/BvrS, the cyclic beta-1,2-glucan, which most likely functions via cholesterol release, SepA, which prevents the development of active lysosome by excluding the LAMP1 lysosomal protein, RicA, which controls vesicle transportation and other potential proteins. According to in vitro experiments, the utilization of macrophage cell lines, the T4 Secretion System is mandatory for the BCV to develop into an ER-like compartment (Guo et al. 2023).

There are three stages of brucellosis in animals: the development or incubation phase, when the bacteria proliferate vigorously and the infection is often undetected or the first pathological indications emerge; the incubation period, during which *Brucella* enters the host without generating any clinical symptoms; In the chronic stage, upon bacterial loads peak before dropping and occasional clinical signs emerge. Animals that are sexually mature are generally affected by the virus. The third trimester of pregnancy, when women are more susceptible to infection, enhances this vulnerability. Except for *Brucella suis* infection in pigs, Mortality is quite rare, and there is no pyrexia like in people. Instead, as long as there are no other systemic abnormalities, infection is frequently self-limiting. Lameness, tissue abscesses, arthritis, lumbar and sacral spondylitis, and limb paralysis are some of the clinical symptoms of the latter illness. The continual discharge of *Brucella* from reproductive organs or mammary glands secretion over a prolonged period is what determines chronicity, in any case. Therefore, *Brucella's* persistence in the environment and ability for propagation are ensured by infertility, numerous abortions, and early stillbirth (Rivas et al. 2022).

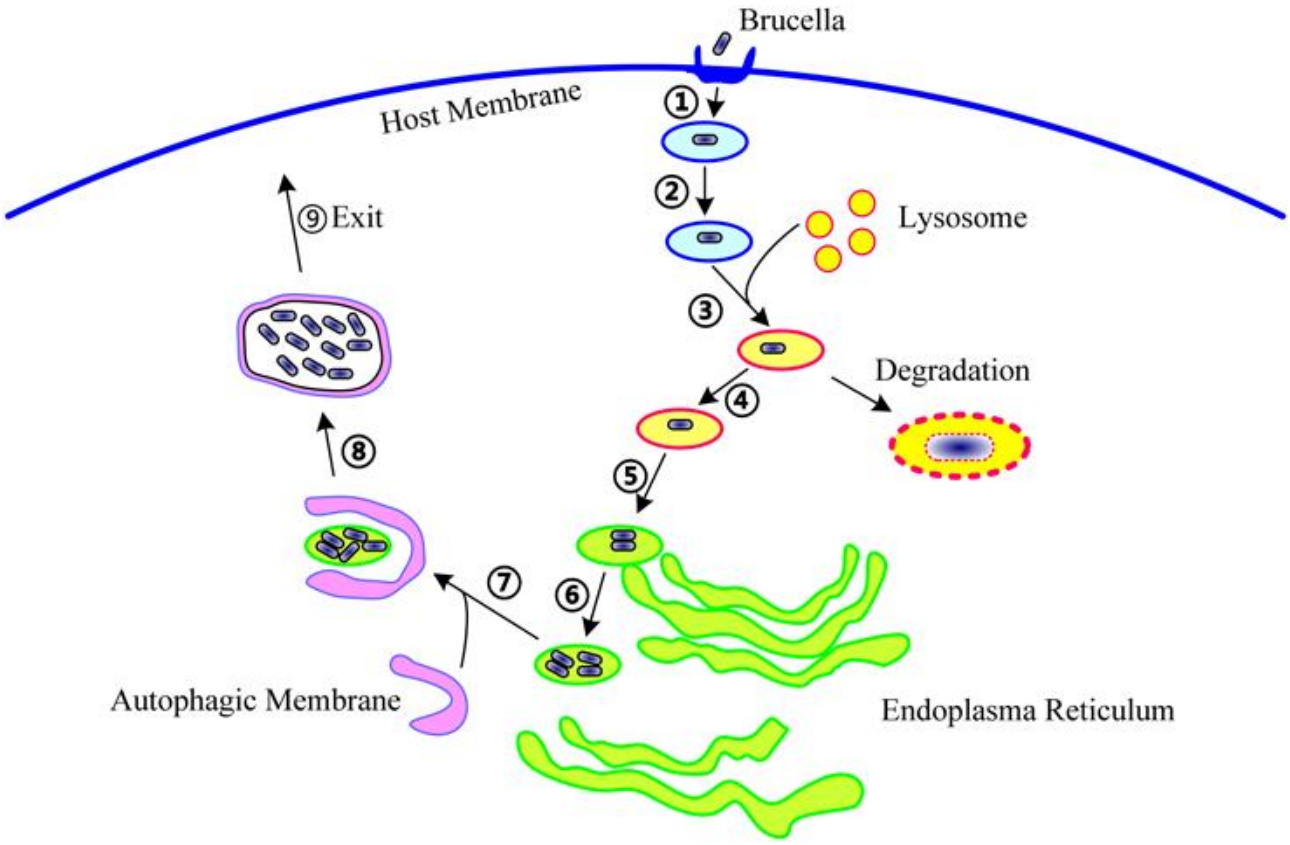

Fig. 2*:* Life cycle of Brucella; Source: (Ke et al. 2015).

3.2. TUBERCULOSIS

Food-borne zoonotic pathogens can infect both humans and animals, causing a variety of potentially lethal diseases (Alvi et al. 2021). Pakistan has the fifth-highest ratio of tuberculosis. Regular annual increase in the prevalence of is observed among which 20% of cases belong to extrapulmonary tuberculosis (EPTB). In underdeveloped nations all across the world, TB has been a major source of sickness and mortality (Tehseen et al. 2020). According to a survey conducted in 2019, there are around 10 million TB cases worldwide. Access to healthcare facilities, lack of diagnostic tools, and under-reporting of diagnosed people are the reasons blame to main reasons for the high prevalence. TB is still being spread by undiagnosed patients. Those who live in households with patients who have undiagnosed pulmonary TB are at an especially high risk of transmission. According to studies, household contacts of contagious people experience an infection rate of 25%–45%, with the incidence in children under 5 reaching 70%. 12% to 23% of persons with TB infection go on to acquire the illness throughout the course of their lifetimes, and this percentage rises even more for those with immunocompromised, such as those who also have HIV infection (Hussain et al. 2021).

3.2.1. MORPHOLOGY OF MYCOBACTERIUM TUBERCULOSIS AND M. BOVIS

The virus *Mycobacterium tuberculosis (Mtb*), which mostly infects the lungs, causes the infectious illness known as tuberculosis (TB), which is communicable and results in characteristic pulmonary TB symptoms. The extra pulmonary form of tuberculosis (TB) can also affect all other organs and tissues that includes lymph nodes, brain, kidneys, and spine. Mycobacterium tuberculosis (Mtb) is the globally prominent infectious killer, taking about 1.4 million lives annually is the causing agent of tuberculosis (TB). Since the MTB only resides with in the living organisms not having any ecological role (Ghodousi et al. 2019). The life cycle events of *M. tuberculosis* as shown in Fig. 3.

The life span starts by reaching the alveolar spaces of the lungs (distal part). It is embedded in the mucosal or epithelial layer. As a result of their constant exposure to airborne infections and particles, alveoli have alveolar macrophages, specialized innate immune cells that gather and interact with air-borne antigens. Beside alveolar macrophages, dendritic cells in the interstitial space counter the airborne particles. As a result, the first infection, MTB that penetrates the alveolus infects both alveolar macrophages and interstitial dendritic cells, which are present in the alveolar area. It can also enter the body through an alternate way which is infecting of type II alveolar epithelial cell by the Mtb. Both alveolar macrophages and dendritic cells fails to control the infection with high ratio of cell death. The enormous cell death of alveolar macrophages is the important mechanism through Mtb enters the mucosa. Alveolar macrophages infected with Mtb and dendritic cells both function to initiate an adaptive immune response and act as early repositories of infection. Alveolar macrophages that are infected move into the interstitial space from the alveolar sac (Jee 2020). These diseased cells act as infection reservoirs and initiate the immune response. The cells travel from the alveolar sac towards the interstitial spaces. Sometimes the infected cell permanently resides in the interstitium while sometimes the infected cells migrate into the draining lymph nodes in order to launch the B and T cell to limit the progress of infection. Here the cells engulf the bacteria and the infected cells are released. When extracellular bacteria escape phagocytosis or flee from dying cells, resident interstitial macrophages in the interstitium devour them. Alveolar and interstitial macrophages that have been infected as well as non-infected macrophages, inflammatory monocytes, neutrophils, and T cells that have been drawn in by the inflammation and tissue damage go on to create the distinctive TB granuloma. It is yet unknown whether the presence of this multicellular structure inhibits or promotes Mtb infection. But for many primary infections, the illness is managed either

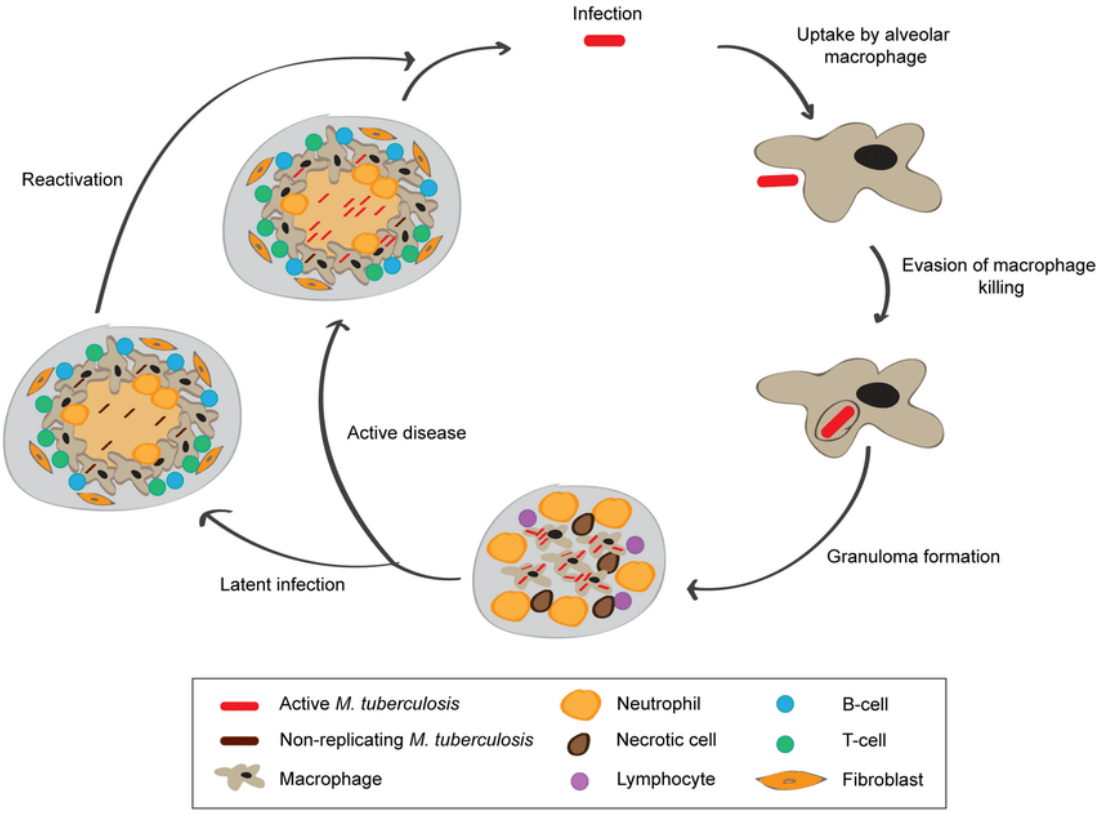

Fig. 2*:* Life cycle of M. tuberculosis shown schematically. By inhaling aerosolized droplets produced by a person with active illness, person-to-person transmission takes place. Alveolar macrophages in the lungs absorb bacteria that have traveled there. The reactive oxygen (ROS) and nitrogen (NOS) species that macrophages produce inside the alveolar macrophages expose bacteria to these substances.

by total eradication of the bacteria, leaving just an immunologic memory of the contact, or by the development of a permanent granuloma (Ernst 2012).

3.3. AVIAN INFLUENZA

3.3.1. MORPHOLOGY OF INFLUENZA A VIRUSES

AIVs are negative sense, single-stranded RNA viruses that typically infect wild ducks and other water-dwelling birds from the order *Anseriformes* and *Charadriiformes*. The genomes of AIVs consist of eight genomic RNA sections that encode twelve viral proteins minimum. The two surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) are joined to form the nomenclature for viruses. Wild aquatic birds have sixteen HA (H1-H16) and nine NA (N1-N9) subtypes known to date, whereas bats have two novel HA (H17 and H18) and two new NA (N10 and N11) subtypes. Due to sporadic AIV transfer from waterfowl to domestic bird species, there are multiple stable AIV lineages in domestic poultry. However, some subtypes (namely A/H5 and A/H7) are able to mutate into highly infectious (HPAIV) variants that are able to cause elevated death ratio in domestic avian species. These domestic lineages generally circulate in poultry flocks that carry low pathogenic (LPAIV) variants, triggering negligible illness. The subsequent

dissemination of these HPAIV lineages to wild bird species accelerated the disease's international expansion (Annika Suttie et al. 2019).

Several labs have investigated the mouse model to study the pathogenicity of the avian H5N1 virus in mammals. The H5N1 viruses powerfully multiplied in the respiratory tracts of BALB/c mice without the prior adaptation, frequently required for human influenza A virus to proliferate in this host. The human H5N1 viruses were responsible for the two distinct H5N1 phenotypes that were found in inbred mice. Animals were only able to reproduce low pathogenicity viruses in the respiratory system and often without dying after cleaning the virus up to 9 days post-infection (p.i). On the other hand, high pathogenicity viruses proliferated not just in the respiratory tract but additionally in other systemic organs, depleted the animals' lymphocytes, and ultimately caused their death 6 to 9 days after infection. The congenital mouse model led to several clinical features of human disease, and pathogenicity in mice is frequently associated with the severity of the disease in humans, so it was crucial to conclude whether the pathogenicity of the H5N1 viruses look like those in other, outbred mammalian hosts. The life cycle events of H5N1 virus has been enlisted in Fig. 4.

The deterioration of the alveoli is frequently extensive in the lungs. The most frequent symptoms in cases with a short illness duration (10 to 12 days) include edema, fibrous exudates, and hyaline membranes. Interstitial fibrosis and changes related to the fibrous proliferative phase (organizing diffuse alveolar damage) have been observed when the sickness has been present for a prolonged period of time (Korteweg et al. 2008). In most cases involving autopsies, type II pneumocyte hyperplasia has been shown. Pneumocytes have not been shown to exhibit viral inclusions or other cytopathic alterations. Within the alveoli, macrophages seemed to predominate, whereas T lymphocytes, whether they include neutrophils or not, can be seen in the interstitium. In some instances' lungs were found to have sporadic histiocytes that were hemophagocytic in activity. Other histological abnormalities that have been reported include bronchiolitis, cystically dilated air spaces, haemorrhage, symptoms of interstitial pneumonitis that resemble pleuritis, and apoptosis in alveolar epithelial cells and leukocytes Imai et al (2012). There have been two reports of fungi-related potential superinfections. Hence above-mentioned histopathological traits are not unique to H5N1 influenza, it may be tough to differentiate between diffuse alveolar

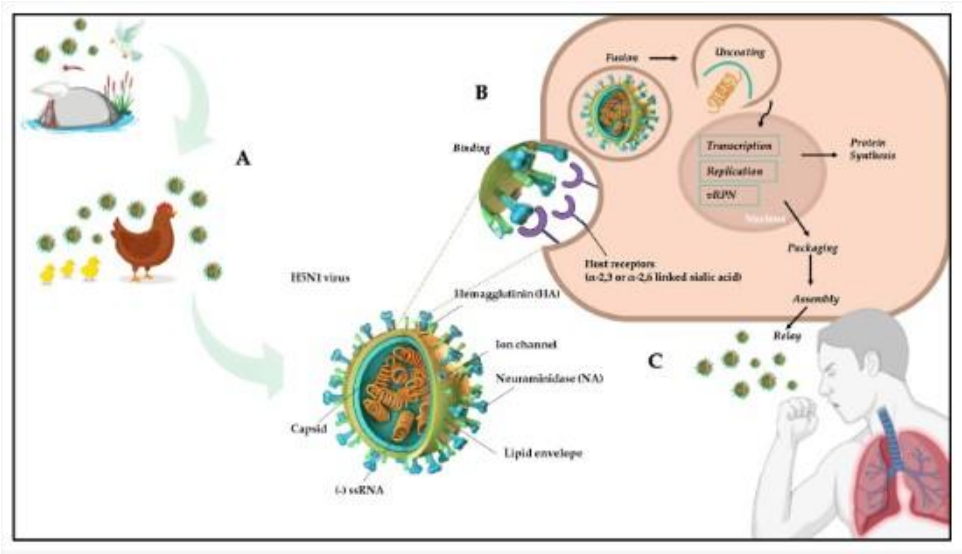

Fig. 3: Lifecycle of the H5N1 virus. (A) The spread of AVI among aquatic birds and domestic fowl. (B) Local replication of the virus' pathogenic mechanism. (C) Clinical symptoms and environmental spread.

impairment initiated by H5N1 virus infections and diffuse alveolar damage caused by other microorganisms like the SARS coronavirus (SARS CoV) or by other factors like aspiration or oxygen toxicity.

More specialist tests, such in situ hybridization, reverse transcription-polymerase chain reaction (RT-PCR), and virus separation, must be used to approve H5N1 infection (Takadate et al. 2023).

The level of tissue damage and the length of the illness are likely determined by a combination of the several components that determine the pathogenesis of H5N1 influenza. A noteworthy amount of research has been done on the role of dysregulation of cytokines and chemokines in the pathogenesis of H5N1 influenza, which may be one of the key processes. Viral replication also causes damage, but this damage is not the only factor. Other factors, such as elevated levels of TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) and reduced cytotoxicity of CD8 cells, are also thought to be linked, though the specific nature of their role in the pathophysiology is now less clear. Below, we go over these elements and associated processes. The H5N1 virus is believed to reproduce similarly to human influenza infections, triggering cytolytic or apoptotic reactions that kill cells and organs. In the respiratory system, there are unmistakable signs of viral replication in progress. The virus has been identified in postmortem lung tissues, aspirates of the throat, and trachea (Offeddu et al. 2016).

Birds to humans transmission is the major way that the H5N1 virus infects people. Infected patients revealed a past history of contact with sick or dead chickens. The incubation phase can last up to 7 days, although it usually lasts between 2 and 5 days. According to recent statistics, human infections mostly affect the respiratory system but can also affect the digestive or central neurological systems. Rarely, respiratory symptoms may also go along with a headache, myalgia, sore throat, rhinorrhea, conjunctivitis, and/or bleeding gums. In extreme cases, multi-organ failure may also include renal dysfunction, lung hemorrhage, pneumothorax, and pancytopenia. Death due to respiratory failure may be accelerated by reactive fibroblasts, hyaline membrane development, lymphocyte infiltration into the interstitial area, and widespread alveolar destruction. The most frequent laboratory abnormalities are transaminitis (AST > ALT), increased lactate dehydrogenase, creatine kinase, and hypoalbuminemia (Jimenez et al. 2023). In order to decrease virulence and the likelihood of mutation accumulation, vaccines and medications are crucial. The key targets for medicines fighting the influenza virus are HA and NA since they are necessary for viral replication. The two most popular antiviral medications on the market now are amantadine and rimantadine. They interact with each other through the viral M2 protein's transmembrane area, which stops the disease causing viral nucleic acid from entering the host cell. They occasionally appear to prevent the replication of viruses from starting. With a particular focus on NA inhibition, researchers worldwide are looking for drugs that may be capable of targeting the NA and the M2 viral proteins. This is due to newly disclosed instances demonstrating an increased prevalence of resistance to this medication (Offeddu et al. 2016).

3.4. RABIES

Canine rabies is a deadly zoonotic illness that has been around for a very long time and affects both humans and animals fatally. The Sanskrit word "rabhas," which means "to do violence," is where the word "rabies" originates. Aristotle first articulated the importance of rabid dog bites in the spread of infection in the fourth century BC, over four thousand years after the Babylonian Code of Eshnunna (2300 BC), which mentions the disease's transmission by dogs. It is mentioned in the ancient Indian holy text Atharvaveda and has been recognized in India since the Vedic era (1500–500 BC) (Chaudhary et al. 2020). The first known fatal zoonotic viral disease, rabies, only affects warm-blooded species. Direct contact with saliva or brain/nervous system tissue from the animal that has the rabies virus (RABV), such as through injured skin or mucous membranes in the eyes, nose, or mouth (Fig. 5). In the end, RABV causes mortality and brain disease by primarily affecting neurons. The virus particle enters the cell by endosomal receptors and moves through the cell. After a few days or months, the virus's life cycle resumes, and it eventually

infects the peripheral nerves. As seen in the illustration, retrograde flow in the axons then transports it to the brain. (Khalafalla AI and Ali YH 2021).

In 1804, Zinke proved that saliva could spread the rabies virus. In the first century AD, Celsus blamed wild animals for the transmission of rabies. Pasteur established neurotropism of viruses in 1881. After Joseph Meister was attacked by a rabies-infected animal in 1885, Pasteur developed the rabies vaccine and gave it to him. The rabies virus was discovered by Remlinger and Riffat-Bay in 1903 (Kumar et al. 2023). Kissling was the first to successfully cultivate the rabies virus in tissue culture in 1958. During the 1940s, the Kaliningrad region saw the first red foxes (Vulpes vulpes) contract the rabies virus. Within a few decades, Central and Western Europe had also been infected. In 1978, Switzerland conducted the first round of oral rabies vaccinations for animals. Fox field testing began in Switzerland in 1978, and the oral rabies vaccine was developed for field use in the USA in 1971 Dietzschold (2005).

4. ECONOMIC IMPACT OF RABIES IN LIVESTOCK

The 8.6 billion USD estimated cost of canine rabies is mostly attributable to lost productivity as a result of early mortality, post-exposure prophylaxis (PEP) costs as well as revenue losses caused by PEP-related costs. The cost of livestock mortality was USD 512 million per year, mostly in Asia (China, India, Bangladesh, and Pakistan) and in parts of Africa that depended economically on cattle (such as Sudan, Ethiopia, and Tanzania). In Bhutan, the spread of rabies causes in the death of cattle and a reduction in their output, which directly harms farmers' livelihoods and costs the government money to contain outbreaks and provide widespread rabies PEP. In Asia and Africa, rabies claimed the lives of the most people. 55,000 estimated rabies-related human fatalities occur each year, with roughly 31,000 of those deaths occurring in Asia and 24,000 in Africa (John et al. 2021).

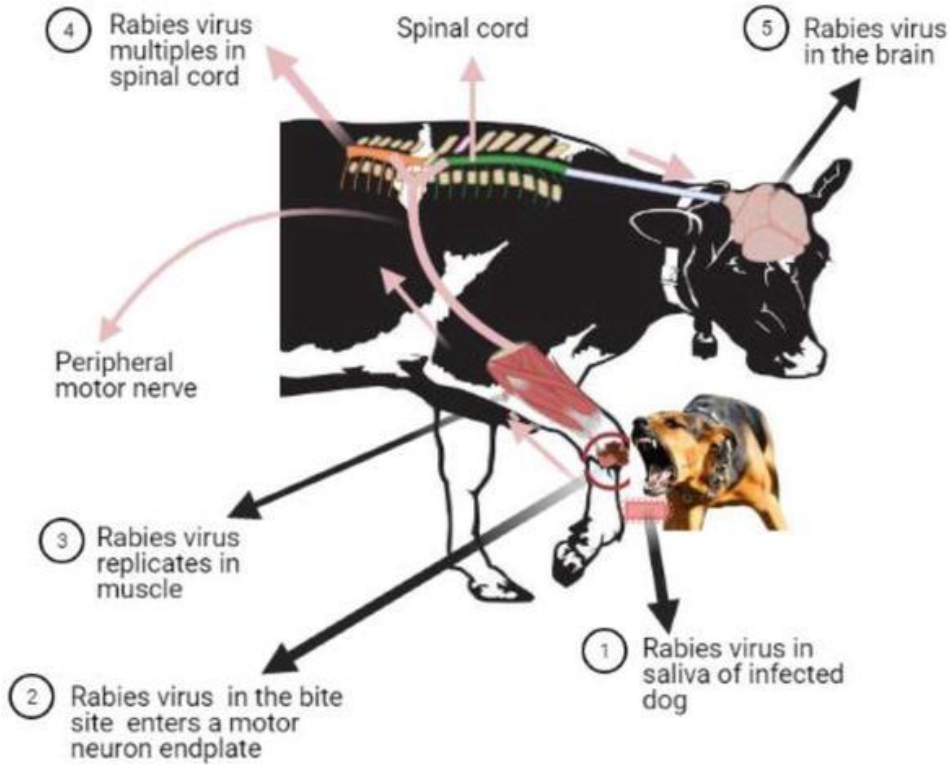

Fig. 4: Demonstration of how the rabies virus spreads in animals from the site of the bite to the central nervous system. (Khalafalla et al. 2021).

The primary methods for preventing rabies are immunizing sensitive animals, mostly dogs and cats, eradicating or controlling stray dogs, and immunizing susceptible people before and after exposure. Recombinant vaccines are used for wildlife, cats, and dogs, whereas live attenuated virus is used for wildlife and wild dogs. Inactivated viruses are used for companion animals and cattle. Cattle in affected areas began receiving vaccinations in 2012 in the USA, when a rabies epidemic was identified. To protect them against the disease that affects cattle, horses, goats, and sheep, more than 200 animals received two doses of the vaccination (Kumar et al. 2023).

5. SALMONELLOSIS

Young children, expectant mothers, immune-compromised people, and the elderly are the main populations that are affected by the gram-negative intracellular pathogenic bacteria known as salmonella (Villegas et al. 2021). Each year, the virus kills millions of people worldwide, and a sizable number of new infections are also reported each year. Approximately 97.9 million people have gastroenteritis each year throughout the globe, which results in roughly 155,000 fatalities, as opposed to the 21 million documented the occurrence of typhoid fever, which cause an estimated 200,000 deaths annually (Lublin A and Farnoushi Y 2023). Salmonella species can either exclusively infect a certain kind of host or infect a range of host types, resulting in a variety of disease pathologies. *Salmonella enterica*, and *Salmonella bongori*, have seven subspecies (I, II, IIIa, IIIb, IV, VI and VII) and one subspecies (V) respectively, are the two species of Salmonella, according to taxonomy (Pearce et al. 2021). Fig. 6 shows the virulence factors responsible for the spread of pathogen.

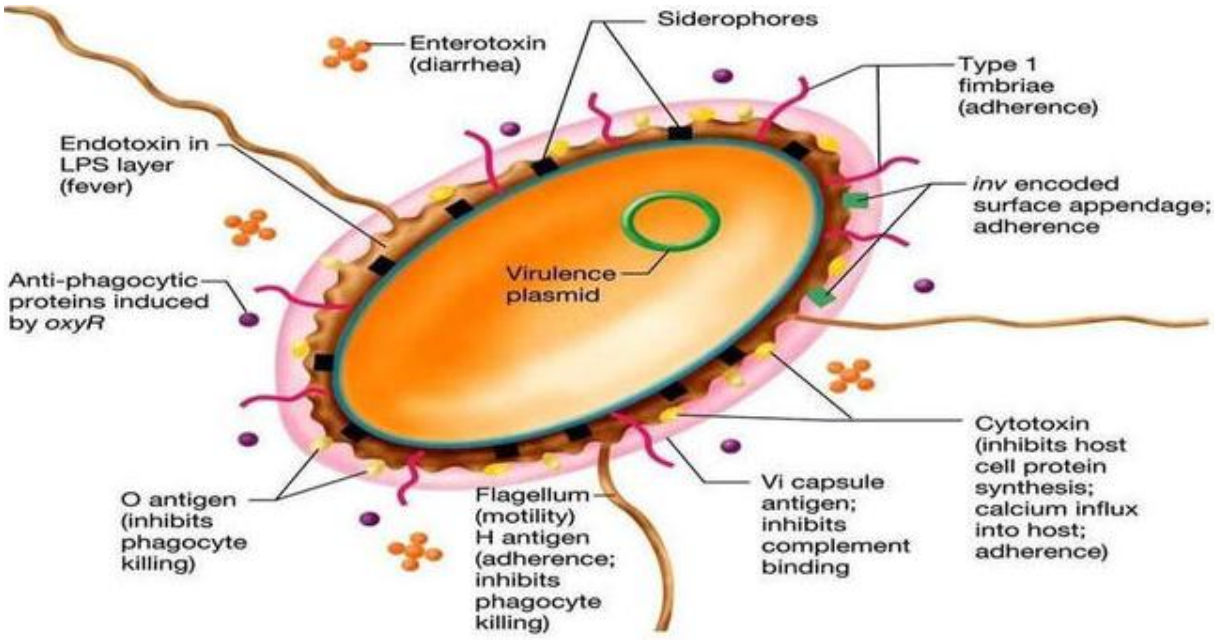

Fig. 5: The virulence factors of Salmonella typhi (Al-Khafaji et al. 2020).

The primary pathogenicity genes of the bacteria that have been produced by horizontally acquired pathogenicity islands (PAIs) include those that code for virulence genes including adhesion molecules, toxic substances, invasins, secretion of proteins systems, absorption of iron systems, etc. *Enterobacteriaceae* family member *Escherichia coli* (*E. coli*) is where PAI was initially identified. The

genomes of pathogenic organisms include PAIs, but those of nonpathogenic organisms or closely related species do not. The bulk of the virulent genes in Salmonella are found in islands of pathogenicity that have been acquired horizontally and are known as Salmonella pathogenicity islands (SPIs) (Saini et al. 2023). These islands are crucial for infection and intracellular survival, and Salmonella also has several regulatory mechanisms. Salmonella is one of the most effective infections due primarily to TTSS, its effector proteins, and horizontally inherited islands of pathogenicity (Kalafatis and Slauch 2021). The importance of HGT events as well as evolution in disease is demonstrated by the fact that Salmonella split from E. coli by acquiring many virulent genes through HGT during evolution. Approximately one-fourth of the Salmonella genome is obtained because of this process. Salmonella or any other organism that enters the human body runs across obstacles such intestinal mucosa, low stomach pH, and intestinal epithelial cell barriers (Kushwaha et al. 2020). It is widely recognised that Salmonella has the potential to overcome these barriers and successfully transmit infection. Salmonella's complex membrane structure enables it to survive until it reaches the lower intestine of the host and binds to the epithelial cell wall. Salmonella enters host cells via the Microfold (M) cells in the Peyer's patch, a collection of lymphoid tissue that is dispersed throughout the small intestine and which assesses and responds to the harmful bacteria in the gut (Richards AF 2021). About 10% of the cells in the patches of Peyer are M cells, which have an outer surface covered in numerous lymphoid cells including lymphocytes and phagocytes and an inner surface that faces the intestinal lumen. Salmonella may enter the host cell in two main methods. One method involves transcytosis, a passive process whereby M cells passively take in bacteria starting at the lumen till basolateral side. The second approach involves absorption brought on by bacteria secreting SPI-I TTSS effector proteins, which promote membrane disruption by rearranging the cytoskeletal structure of the epithelial cells. At the site of entry, immune cells such as neutrophils, T cells, B cells, dendritic cells, and macrophages among others infiltrate after the entry-related inflammation. Invading the nearby enterocytes from the M cells, these bacteria breach the intestinal epithelial barrier. Bacteria arrives at MLN via blood and lymphatic system, where they are further eaten by immune cells inside the lamina propria before going on to deeper organs like the spleen, liver, and even the bone marrow. As seen in the picture below, bacteria are located in the macrophages of all of these organs in Salmonella-containing vacuoles (SCV), which are specialist modified endosomal compartments (Al-Khafaji et al. 2021). Fig. 7 shows the basic steps in Salmonella pathogenesis.

6. ANTHRAX

Anthrax has been mentioned in conventional literature going back to Virgil's writings. It was the first sickness that could be definitively accredited to a microbe (Bacillus anthracis), discovered by Robert Kochin in 1877 Savransky (2020). Even though it is mostly a zoonotic disease spread by animals and contaminated soil, the Centres for Disease Control and Prevention (CDC) have designated it as a Class A potential agent for bioterrorism. In Soviet Union in 1979, Japan 1995, and the United States in 2001, B. anthracis has been considered responsible for mortality. In both the World Wars I and II, it most certainly served as a weapon. Anthrax disease is brought on by the rod-shaped, gram-positive, endospore-forming, facultatively aerobic bacterium B. anthracis. Large (1.0-1.5 mby3-8 m) and non-motile, the bacilli can be found alone or in short chains. The main factor in Bacillus anthracis' pathogenicity is the interaction between two plasmids, pXO1 and pXO2. They are in charge of generating anthrax toxins and creating poly-d-glutamic acid (PGA) capsules. The operon for the production of capsules is found on pXO2, whereas the genes for the anthrax toxin are found on pXO1 (Swick et al. 2016). Similar to how the PGA capsule safeguards the bacilli, the polysaccharide capsules of other harmful bacteria, like meningococci and pneumococci, also shelter bacilli from phagocytosis and immune response. Thus, the capsule

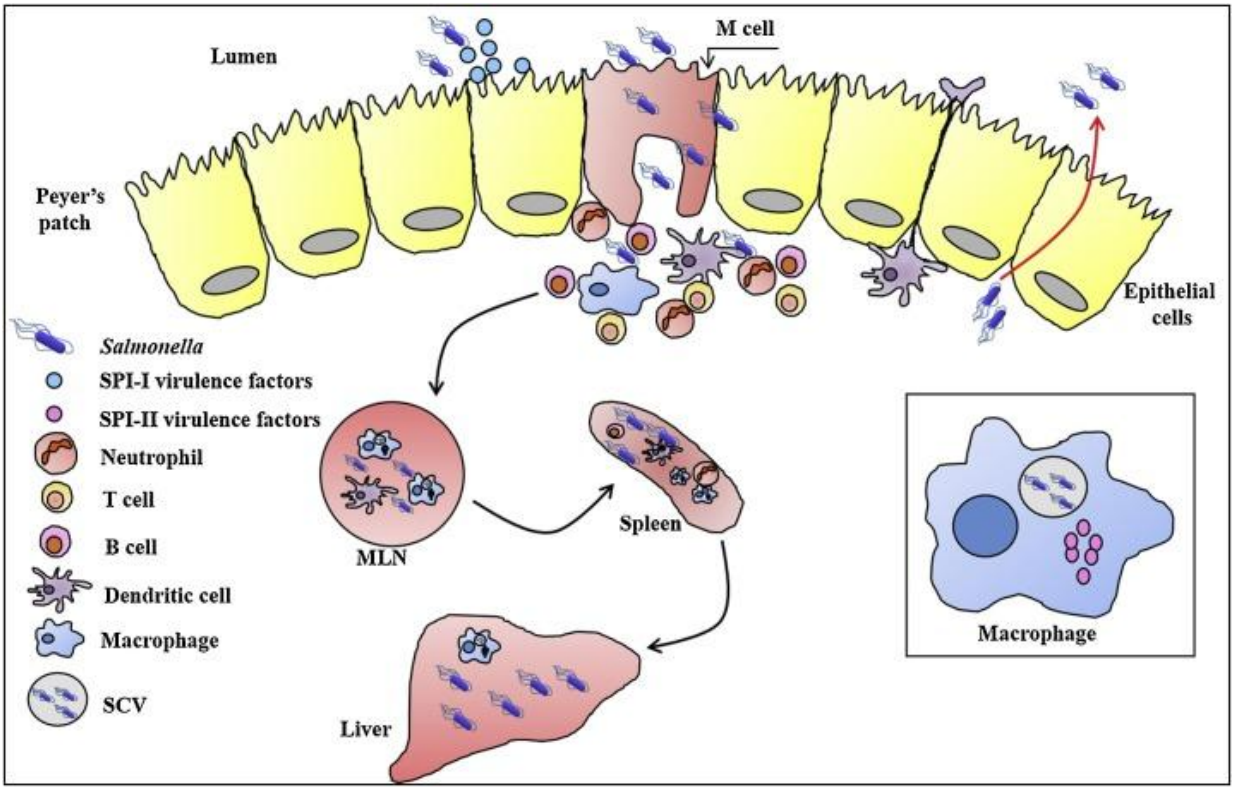

Fig. 6*:* Basic steps in Salmonella pathogenesis (Pradhan et al. 2019).

mediates the invasive phase of the infection. Protective antigen (PA), edoema factor (EF), and lethal factor (LF) are the three distinct polypeptide chains that make up the anthrax toxin. The pXO1 plasmid-encoded LF, EF, and PA combines to generate the lethal toxin (LT) and edoema toxin (ET). LF is a zinc-dependent metalloprotease that targets mitogen-activated kinase kinases (MAPKKs or MEKs) (Cote et al. 2015). LT also disrupts the signaling networks that regulate cell cycle, proliferation, and stress defense by severing the N-termini of these enzymes. The severe edoema linked to anthrax illness is brought on by a calmodulin-dependent adenylate cyclase EF. EF alters the host cell's signaling pathways by elevating cyclic adenosine monophosphate (cAMP) levels. By attaching to receptors (TEM8 and CMG2), PA causes a hole to develop in the membrane, allowing the toxin to pass through and enter the cytoplasm of the host cell. Anthrax toxin's method of action has been well investigated over the past few decades, and it is now understood.

7. CRIMEAN-CONGO HEMORRHAGIC FEVER (CCHF)

The most well-known illness spread by ticks is Crimean-Congo hemorrhagic fever (CCHF), which is brought on by the CCHFV virus. The Crimean-Congo hemorrhagic fever virus (CCHFV) is thought to be the most common tick-borne illness, producing CCHF. This zoonotic virus is widespread in around 50 countries across Africa, Asia, and Europe. As a result, there is a risk to human health due to acute and possibly deadly severe hemorrhagic syndrome as well as subclinical human infections. Additionally, both domestic and wild animals frequently get CCHFV through subclinical infections (Fanelli and Buonavoglia 2021). This zoonotic virus is widespread in around 50 countries across Africa, Asia, and Europe. As a result, there is a risk to human health due to acute and possibly deadly severe hemorrhagic syndrome as well as subclinical human infections. Additionally, both domestic and wild animals frequently get CCHFV

through subclinical infections. The length of the development period is influenced by the source of the contaminated blood or tissue, the disease's mode of transmission, and the viral load. Following a tick bite, the incubation period lasts 1 to 5 days, and it lasts 5-7 days after coming into touch with contaminated blood or tissues. When distributed by tick bite, it can last 3-6 days, with a extreme of 9 days, however when disseminated by contaminated blood or other infectious material, it can last 5-6 days, with a maximum of 13 days (Shahhosseini et al. 2021). The prehemorrhagic phase is distinguished by the abrupt development of a broad range of non-specific prodromal symptoms that remain for 4-5 days and are similar to those of other viral illnesses. The hemorrhagic phase typically lasts two weeks and has haemorrhage that progresses quickly. During this stage, symptoms might range from petechial to widespread ecchymosis (McEntire et al. 2021). Additionally, it can reveal bleeding from the gums, nose, internal organs, or digestive tract. Hepato-splenomegaly may also be seen in certain cases. In patients who make it through the first phases of the disease, the convalescent period often starts 10–20 days after the sickness first manifests. There has not been enough research done on the long-term impact of CCHFV infection in survivors to identify any specific issues. For patients to get treatment early and for the fast use of suitable precautions and infection control measures to stop the spread of CCHF, a quick and accurate diagnosis is crucial (Aftab et al. 2019). Laboratory testing, epidemiological considerations, and clinical signs are used to make the diagnosis. Due to the disease's random onset and vague first symptoms, clinical diagnosis is challenging to make until the hemorrhagic stage sets in. Therefore, a laboratory diagnosis is thought to be more certain and trustworthy. Its diagnosis is mostly accomplished using molecular, serological, and isolation approaches. Serum or plasma are the biomaterials that are sampled most frequently for their detection. Highest polymerase chain reaction (PCR) efficiency is ensured by blood taken in EDTA tubes (González et al. 2022).

8. LEISHMANIASIS

Infectious diseases, especially parasitic infestations, are major public health concerns in both animals and humans (Alvi et al. 2022; Alvi et al. 2023). Leishmania is a protozoan parasite of the Trypanosomatidae family that infects humans and other animals, triggering cutaneous, mucocutaneous, and visceral disease in both the Old and New Worlds. Around 91 nations in Asia, Africa, the Arab world, Central America, and South America are affected by leishmaniasis, a neglected tropical disease that mostly affects the world's poorest population. Current estimates of the prevalence of cutaneous leishmaniasis (CL), which are probably under-reported, vary from 700,000 to 1.2 million cases annually, with more than 95% of cases occurring in the Americas, the Mediterranean basin, the Middle East, and Central Asia. With more than 95% of cases reported to the World Health Organization (WHO) from Brazil, China, Ethiopia, India, Kenya, Nepal, Somalia, and Sudan, estimates of annual visceral leishmaniasis (VL) are presently fewer than 100,000, a considerable decline from earlier estimates of 400,000. Leishmaniasis risk factors include impoverishment, population movement, hunger, poor hygiene, and immunocompromised conditions. Among neglected tropical illnesses, leishmaniasis has the third-highest fatality rate, after only Chagas disease and sleeping sickness. However, the related morbidity of the condition is commonly misunderstood and overestimated by medical professionals and researchers. The real health cost of leishmaniasis is underestimated for a variety of reasons. First, only 32 of the 88 nations that are plagued by leishmaniasis are covered by the reporting requirements. Second, due to the disease's low mortality rates, it is well recognized that poverty is a major factor in its spread, and those who are afflicted, and their families often conceal it. When infected sand flies

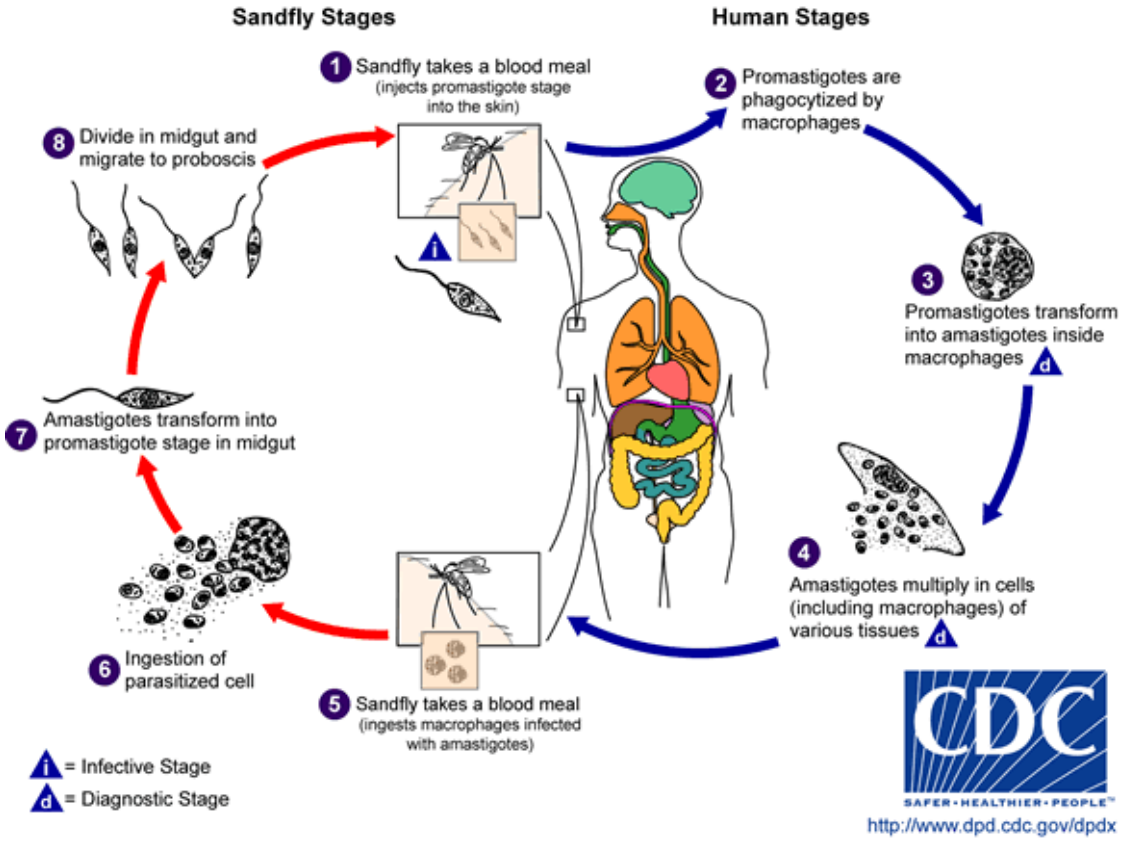

Fig. 7: The life cycle of leishmania (different phases of leishmaniasis) (DPDx 2020).

bite humans, they are exposed to Leishmania species (Roatt et al.2020). Metacyclic promastigotes in the sandfly's anterior midgut or foregut were regurgitated into the invertebrate's skin during the blood meal. As soon as possible, phagocytic cells like neutrophils and macrophages engulf the promastigotes. In the phagolysosome, the pro mastigotes form separate into dividing, aflagellated amastigotes. It's crucial to remember that the parasite that lives in sandflies originated in an infected host. Following the lysis of the host cells, the amastigotes transform into procyclic promastigotes. They utilise their flagella to link to the fly midgut via surface glyconconjugates in order to start the infection. Leishmaniasis therapy options are limited, and the drugs that are available have significant toxicity and unfavorable side effects. In addition, the emergence of drug-resistant strains, co-infections such as HIV/Leishmania spp., the constrained therapeutic toolbox, and the low investment needed for the discovery/development of new drugs force researchers and global health organizations to search for novel approaches to combat and control this serious neglected disease (Mann et al. 2021). In this situation, novel approaches with significant advancements in physical and local therapies, such as the use of CO2 lasers and thermotherapy, as well as topical pharmacological therapies using NO compounds and intralesional drug injection, have improved the outlook for patients with CL (Roatt et al. 2020).

9. CONCLUSION

In Pakistan, zoonotic diseases constitute a significant public health risk. Both humans and animals are susceptible to these diseases, which can result in significant illness and even death. Depending on the

particular disease, zoonotic diseases might have different physical and physiological properties. However, some common traits include the capacity to spread by contact with sick animals or their products, the capacity to produce a range of symptoms in both humans and animals, and the capacity to be lethal. It's crucial to be informed about the zoonotic diseases that are common in Pakistan and to take precautions against them.

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