

REVERSE ZOOONOSIS AND ANIMAL HEALTH

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INTRODUCTION

When pathogens are capable of transmission from human to non-human hosts, such phenomenon is referred as reverse zoonosis. It is also known as anthroponosis or zooanthroponosis (Hubálek 2003). Whereby, Anthroponosis is a term used to describe human to non-human animal transmission, as well as human transmission, zooanthroponosis is exclusively used to explain human to animal pathogenic transmission (Joint and Organization 1967; Hubálek 2003). Humans transmit the pathogenic agents to the animals, where they sometimes mutate and spread through different species of animals. Depending upon the nature of pathogens, reverse zoonosis is categorized as reverse zoonosis by bacteria, viruses, protozoa/parasites and fungi. Infection potential of a pathogen in a population, either humans or animals, depends upon the mode of its transmission. Direct human to human, animal to human or human to animal via aerosol or feco-oral route is easy and quicker than the involvement of any other vector. This is because in a geographical distribution, presence and survival capabilities of different vectors are different. If a vector is abundantly present in an environment, then disease spreading rate will be higher and arthropod vectors are the most notorious in this field. Attempts have been made to compile the incidence of reverse zoonosis occurred around the world. Most of the focus is on the bacterial and viral pathogens, as they are mainly involved in interspecies transmission. Since transmission of pathogens is either direct or vector involved, both of these aspects are considered in discussion. Human pathogens can affect variety of species of domesticated animals, as well as wildlife. Evidence of reverse zoonosis can be found in domestic animals or captive wildlife, but it is difficult to ascertain in the free-range wild animals (Fig. 1). It is also observed that drug resistant pathogens are also involved in interspecies transmission, which is alarming. Mutation is also one of the factors in the reverse zoonosis that is discussed in this chapter.

Reverse Zoonosis by the Bacterial Pathogens

Bacterial zooanthroponosis has been documented since long, affecting wide range of animals including farm animals, companion animals and the wild life. The mechanisms involved in the transmission vary among various species of animals. However, generally the

mechanisms involved include the direct contact, feco-oral route, fomites, direct inoculation and aerosol route (Hackendahl et al. 2004; Messenger et al. 2014; Barasona et al. 2017). There are certain bacteria which are involved in the reverse zoonosis, causing the outbreak of diseases of human origin in animals with possible outcome of severe ailment, drug resistance and mortalities.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Staphylococcus aureus (*S. aureus*) is considered as a bacterium of substantial importance in human medicine. It is also proclaimed as a serious public health concern. *S. aureus* imparts adverse effects and conditions in human beings, ranging from minor skin and soft tissue infection to serious ailments including meningitis, bacteremia and pneumonia (Tong et al. 2015). The non-human hosts (mostly livestock) are focused as the reservoirs of infections and antibiotic resistance related to humans. Now, the interest has been shifted to investigate the role of humans as the source of infection for animals (zooanthroponosis) (Fluit 2012; Price et al. 2012).

Anthrozoponosis is more common than the zooanthroponosis by the *S. aureus*. However, it is now obvious from the studies determining the potential of *S. aureus* to shift the host species, with resultant adaptation in new host and further transmission in newly adopted host species (Shepherd et al. 2013).

This phenomena of adapting in the new host after switching and interspecies transmission is now very well known to occur between humans and animals. Therefore, *S. aureus* associated with the human origin causes rapid colonization and infection in the host as compared to non-human primates (animals), either domesticated or in the wild (Schaumburg et al. 2012).

The premiere driver of host adaptation following the inter-host transmission is addition or deletion of the genes directly associated with mobile genetics of the bacterium (Spoor et al. 2013). Therefore, non-human host provides suitable environment to the bacterium to acquire the novel virulence and antimicrobial resistance (Sung et al. 2008). The antimicrobial resistance and acquisition of unusual virulence have been observed in the clones of MRSA from humans that have been reported in livestock and vice versa (Sung et al. 2008; Köck et al. 2013). Reverse zoonotic potential of the *S. aureus* is adversely affecting many livestock species. One such example is from the equines, where 11 horses from

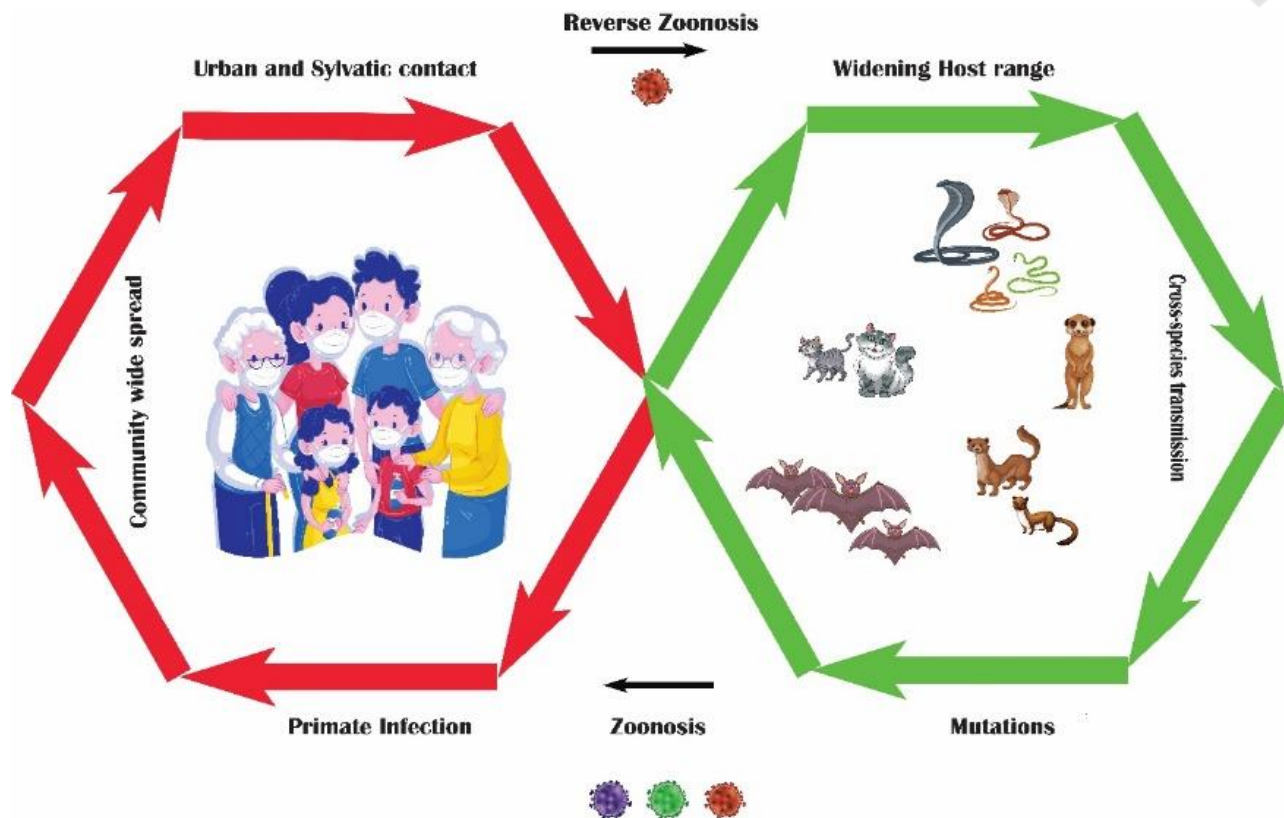


Fig. 1: Showing transmission possibility of pathogens between human and animals, mutation and its spread through community

different farms exhibited MRSA infections. As the MRSA is extremely rare in horses, the outbreak was acquired at the hospital, which is known as nosocomial infection (Seguin et al. 1999). However, potential of the *S. aureus* to affect non-human primates is not restricted to equines, as it also affects other species like cows, turkeys, and pigs (Hasman et al. 2010; Price et al. 2012). Although, mutation is continuously reducing the zoonotic threat for humans, but it augments the *S. aureus* resistance capabilities, which will ultimately enhance the occurrence of MRSA infections (Price et al. 2012). Human to livestock transmission of MRSA has also been documented in advanced countries of the world, including USA (Smith 2015), UK (Graveland et al. 2011), Canada (Armand-Lefevre et al. 2005), China (Zhou et al. 2018), Germany (Köck et al. 2009) and France (Price et al. 2012).

Tuberculosis

Bovine tuberculosis (TB), caused by the *Mycobacterium (M.) bovis*, *M. tuberculosis*, or rarely by *M. caprae*, is an important and significant disease of public health concern due to its zoonotic potential and resultant considerable economic losses (Torgerson and Torgerson 2010, Bayraktar et al. 2011a, 2011b). In humans, majority of the TB cases happened either due to utilization of the contaminated milk or through aerosols from the infected animals (Moda et al. 1996). However, situation has become complex with the emergence of reverse zoonosis. Sharing of the micro environment and premises by the human and non-human primates has significantly

potentiated the disease (Shitaye et al. 2007). Previously, it has been reported that humans are preliminary the cradle of *M. tuberculosis* infection for animals (Bhanu Rekha et al. 2015). It is important to consider that *M. bovis* can infect urogenital system in humans and secretions from such patients can affect the animal health through reverse zoonosis (Ocepek et al. 2005). An extraordinary pervasiveness of zoonotic TB in humans is due to its significantly high occurrence in the cattle (Asiak et al. 2007). Nonetheless, transmission of the TB can occur mutually and previous studies have supported this phenomena of reverse zoonosis, where isolation of *M. tuberculosis* has been done from cattle and that of *M. bovis* from humans (Ocepek et al. 2005; Jenkins et al. 2011; Adesokan et al. 2012). The canvas of TB is expanding and many animal species other than the cattle have also been affected by the human infection. Lesions of TB have been reported in wild red deer and boars, where they had been confined under the intensive care management conditions such as large game fences and auxiliary feeding locations (Schöning et al. 2013). Spread of the same strains of TB found in humans to these wild deer and boars suggests that the possible spread was either through direct human contacts or their excretions (Barasona et al. 2017). The reverse zoonotic potential is also affecting the free range wild life species and in such an incidence the necroscopic findings of the African elephant revealed seriously damaged lungs due to the strain of the *M. tuberculosis*. This reverse zoonosis phenomenon was the culprit behind this infection that might be due to aerosolization of the agent either

through contaminations by the surrounding human community or tourists (Miller et al. 2019). There is significant evidence of direct or aerosol transmission of the *M. tuberculosis* from humans to companion animals (Hackendahl et al. 2004).

Escherichia coli

Multidrug resistant strains of pathogenic *Escherichia (E.) coli* are important in public health concern because of their speedy spread through the large population and also due to their supposedly perpetual evolution (Ewers et al. 2010). Transmission of the zoonotic pathogens has increased between the humans and animals due to sharing of the same habitat. There is strong evidence of transmission of *E. coli* from humans to livestock including mountain gorillas, which revealed that habitat sharing is affecting the human to animal transmission of this pathogen through the reverse zoonosis (Rwego et al. 2008). *Escherichia coli* DSM22664 is a human pathogen which showed the similarity index of >85% with six B2-O25b-ST131 CTX-M-15 strains detected in animals in five different countries of Europe. This is an indication of its potential of distant transmission (Nicolas-Chanoine et al. 2008). The possible spread of virulent serotypes of cephalosporin-resistant *E. coli* from human to companion animals, especially dogs, has been previously investigated in Germany (Ewers et al. 2010). These strains were previously considered exclusively for human population but emergence of the CTX-M-15-positive B2-O25:H4-ST131 strain in a dog infection is alarming (Coque et al. 2008; Nicolas-Chanoine et al. 2008; Pomba et al. 2009). Presence of the clonally related human pathogenic multi-resistant strains of *E.coli* in the pet animals across different European countries has pointed out its potential of inter-species transmission, humans to other animals and vice versa (Ewers et al. 2010).

Helicobacter pylori

Helicobacter pylori is an important pathogen of human gastrointestinal tract, causing serious and prolonged ailments. Animals in the captivity are also among those affected by this pathogen of human origin through reverse zoonosis phenomena. In such an example in Australia, the stripe faced marsupial suffered repeated and multiple outbreaks of the *H. pylori* while under captivity; the causative strain had 100% association with the strain of the human origin. Transmission of *H. pylori* to these animals was from the handlers of these animals, which further emphasizes the importance of the reverse zoonosis (Every et al. 2011).

Salmonella spp and *Shigella spp*

Salmonella and *Shigella* have significant potential to cause morbidity and mortality in captive gorillas (Stetter et al. 1995; Mundy et al. 1998). It has been found that free-running mountain wild gorillas are affected by these bacteria in human adjusted territories. Some of the

Shigella species isolated from these wild creatures are *S. sonnei*, *S. boydii*, and *S. flexneri* (Nizeyi et al. 2001). These were found in sub-adults and grown-up gorillas aged from 6.0 to 11.9 years. The sharing of *Salmonella spp.* diseases among humans and gorillas has increased during previous years. The isolation of *Shigella spp.* interestingly from mountain gorillas may show upgraded reverse zoonotic transmission (Nizeyi et al. 2001).

Transmission of Zoonotic Viral Diseases

Viral infections such as dengue fever, yellow fever and zika fever, which mostly spread through arthropod vectors, can be justified by both anthroponosis and reverse zoonosis/zooanthroponosis, provided which host (human or mosquito) is considered the primary source of infection (Alekseev and Dubinina 2001). Conversely, infections such as Human Immunodeficiency Virus (HIV) which instigated in primates (LeBreton et al. 2007) and influenza virus attributed to avian species (Nelson and Vincent 2015), despite being originally identified as cases of zoonotic transmission, can now be termed as anthroponosis. Certain important viral pathogens of reverse zoonotic importance have been discussed in this chapter. Ironically enough, wild animals rarely come into direct contact with humans and due to their improbable presence in close vicinity, most cases of reverse zoonosis emerge between humans and wild animals as a consequence of contact with abiotic substrate contaminated with saprotoxic agents (Hubálek 2003).

Arboviruses

Arthropod-borne viruses are called as Arboviruses. Several of these viruses, namely Zika virus, Dengue fever virus and Yellow fever virus belonging to family *Flaviviridae*, exhibit reverse zoonosis. Moreover, Chikungunya virus, which has been classified into Alphavirus genera, is also considered an arbovirus (Kuno et al. 1998; Forrester et al. 2012). These arboviruses have been reported to involve urban, as well as sylvatic transmission cycles. In case of Dengue fever, the virus has been known to jump from human population to primates through the help of *Aedes aegypti* mosquitoes. Similarly, certain arboviruses endemic in wildlife populations have the potential to infect human hosts (Figueiredo, 2019). Therefore, consequent intermingling of sylvatic and urban cycles is quite common due to a myriad of mosquito species capable of viral transmission.

Zika Virus Fever

Aedes mosquitoes are responsible for the spread of this single stranded RNA virus in human and other animal populations (Nah et al. 2016). In 1947, Zika virus was isolated from primates in Uganda, West Africa. In following years, most of the outbreaks of Zika virus were seen in temperate regions of Asia and Africa. The virus, for the most part, cycled between monkeys and arboreal mosquitoes but instances of human infections were

sporadically reported. Zika virus experiences propagation in distinct sylvatic and urban cycles. However, in most cases zone of disease emergence for humans are areas where these cycles could overlap and co-exist. Previous investigations have postulated possible involvement of 47 animal species belonging to three orders (reptile, avian and mammal), other than primates and arthropod vectors (Singh et al. 2016). Another animal model studied antigenic response of Zika virus in pregnant rhesus macaques. To this end, Zika virus isolates from confirmed human cases were inoculated into pregnant rhesus macaques, resulting in propagation of viral bodies and detection up to 105 days after administration corroborating the probability of reverse zoonotic transference of viruses (Coffey et al. 2017).

Yellow Fever

Yellow fever is a flavivirus disease transmitted by arthropod vectors. It is an endemic to tropical regions of Africa and South America despite ample availability of vaccine. The spread of this disease across continents separated by vast oceans of water has been deliberated for several years now (Monath and Vasconcelos 2015).

However, Yellow fever is generally believed to have been introduced into American continent from West Africa approximately 400 years ago (Chippaux and Chippaux 2018). The disease was first reported amongst Europeans involved in the illicit slave trading business (Hamrick et al. 2017). It has been hypothesized that most probable source of the Yellow fever on the shores of new world may be attributed to the arrival of shackled infected individuals from West African countries, who were subsequently bitten by indigenous mosquitoes, thereby spreading virus to other humans upon next feeding (Yen et al. 2018). Regarding the concept of Reverse zoonosis, hypothesis suggesting anthroponosis of Yellow fever virus to un-infected *Aedes* species after feeding on diseased human is extremely noteworthy (Goenaga et al. 2012). In recent years, Yellow fever has been reported in non-human primates and other sylvatic communities living closely with un-vaccinated human populations (Figueiredo et al. 2018). An example of such a scenario was reported in Espirito Santo, Brazil, where PCR and immune-histologic examinations were performed on 22 deceased non-human New World primates and Yellow fever lesions were detected in 21 primates (Fernandes et al. 2017).

Chikungunya Virus

Since its emergence in Asia during 1950s, Chikungunya virus (CHIKV) has caused severe, debilitating arthralgia, with severe morbidity in humans. It is believed that this disease probably spread across Europe and the Americas due to genetic mutations that resulted in the development of a protective glycoprotein envelop (Tsetsarkin et al. 2016). These revelations led to the rational conclusion that Asian strain of the virus propagating in urban cycles originated from ECSA

progenitor, which was introduced in the environment 50–430 years before 2000 (Volk et al. 2010).

Chikungunya virus, being a single stranded RNA alphavirus commonly referred as arbovirus, is typically spread by *Aedes* mosquitoes amongst humans and non-human primates, exhibiting high potential for spillover and spillback pathogenic events (Tsetsarkin et al. 2016). Chikungunya virus has been reportedly found capable of involving sylvatic mosquito species such as *Haemagogus leucocelaenus* and *Aedes terrens* for pathogenic transmission (Weaver 2014). Several *Aedes* species have been found to be enzootic transmitters of the disease. These vectors may be responsible for disease transmission between non-human primates and other vertebrates serving as amplification hosts (Tsetsarkin et al. 2016). Data confirming cross species transmission or anthroponosis with regards to vector borne Chikungunya virus is scarce, however in experimental studies *A. furcifer* has successfully transmitted virus from infected humans to African green monkeys (Mcintosh et al. 1964). Moreover, Senegalese baboons (Monlun et al. 1993) and Congolese chimpanzees (Osterrieth et al. 1960) have also been found seropositive for this virus without clinical manifestation of any malady. Seroprevalence of this virus in non-human primates of Bahia state residing in peri-urban areas also suggests Reverse zoonosis (Forrester et al. 2012; Ndenga et al. 2017).

Dengue Fever

Dengue virus belongs to genus *Flavivirus*, which is also known as an arbovirus. Mosquito, such as *Aedes* spp., are vectors responsible for spreading this virus. Not unlike other arboviruses, Dengue virus and its reservoir vector concurrently arrived the Americas probably as a consequence of slave trade (Hanley et al. 2013). In 2009, a French study undertaken at one of its colonial territories in Guiana reported endemicity and seroprevalence of Dengue virus types 1 to 4 amongst all kinds of mammalian hosts including primates, rodents, bats and marsupials (Fouque et al. 2006). The rationalization for suggesting cross carrying of viral strains between sylvatic and urban vectors has been reinforced by studies conducted in Brazil, Ecuador, Peru and Colombia, where a common backyard mosquito *Aedes albopictus* found in urban and peri-urban areas was identified as a carrier for Dengue virus type 3 (Usme-Ciro et al. 2008). Likewise, *Haemagogus leucocelaenus*, a mosquito purely feeding upon wildlife, was discovered to carry Dengue virus type 1 in the state of Bahia (De Figueiredo et al. 2010). Presence of antibodies has also been used as an indicator to confirm the presence of sylvatic lifecycles in the case of Dengue virus. A study in the *Sapajus xanthosternos* and *Leontopithecus chrysomelas* primates indigenous to Atlantic forest of Bahia revealed the presence of antibodies against Dengue virus type 1 and 2 (Catenacci et al. 2018). Similarly, Dengue virus type 3 antibodies have been reported in Sloths (*Bradypus torquatus*) as well (Catenacci et al. 2018).

Influenza Virus

There have been reported cases of Influenza A virus subtype H₁N₁ being transmitted from humans to wild, companion and domesticated mammals due to contact through abiotic elements of environment (de Jong and Hien 2006; Morens and Taubenberger 2010; Messenger et al. 2014). This phenomenon is justified by the fact that the said virus is extremely resilient and capable of mass infections without any reservoir host or biological vector (Zambon 2014). Most viruses have a narrow host range, however, antigenic shift, drift and point mutations could be responsible for cross species infections (Zimmer and Burke 2009; Ma et al. 2018). In 1990s, a wild seal admitted to Dutch seal rehabilitation center was reported to be infected with human influenza B virus (Osterhaus et al. 2000). The close proximity, with humans cohabiting in close quarters with companion animals, increase the probability of Reverse zoonosis several folds, especially in case of Influenza virus that may be transmitted through contact with soft, porous surfaces (Mukherjee et al. 2012). An incidence confirming this deduction was reported in 2009, when household pet ferrets were naturally infected with human H₁N₁ strain (Swenson et al. 2010). Viral infections jumping across species are not exclusively seen only in companion animals, but several studies have reported such incidences in livestock as well (Janke 2014). However, the underlying factors, such as contact with contaminants, remain the primary cause of such instances. In Norway, a flock of turkeys contracted Influenza type A H₁N₁ virus from a diseased farm hand. Phylogenetic analysis of isolates from both species revealed identical set of strains infecting both of them (Kulberg Sjurseth et al. 2017). The transmission of H₁N₁ from humans to pigs is extremely widespread and cases have been identified throughout the South-East Asia (Song et al. 2010), Europe (Chastagner et al. 2019) and Canada (Howden et al. 2009).

Coronavirus

Wild animals in captivity and sanctuaries have reportedly been victims of Reverse zoonosis, especially in the case of coronavirus. Contrary to popular belief, coronavirus existed before COVID-19 outbreak in both humans and animal species (Ng and Hiscox 2020). Previously, symptoms and genetics of coronaviruses afflicting human and animal hosts were distinct. However, it was vexing when coronavirus isolates from a 2007 outbreak in Alpacas was evolutionarily quite similar to that of human coronavirus. This discovery has suggested the human to alpaca mode of transmission. Moreover, these findings have become succinctly significant in the light of recent events when a genetic relative of the same coronavirus is wreaking havoc on human population (Crossley et al. 2012). In 2016, a similar instance of human coronavirus (HCoV-OC43) transmission to wild chimpanzees housed at Tai National Park, Côte d'Ivoire was reported to cause common cold (Mackay et al. 2012). Through the years, coronavirus has been detected in all classes of the

animals, ranging from ungulates to carnivores, iterating plausibility of coronavirus host switching (Patrono et al. 2018).

COVID-19

Recent COVID-19 pandemic has caused scientists to investigate the ability of household pets to serve as carriers or reservoirs of this virus. Experimentation has suggested the transmission and clinical incidence of the disease in cats and ferrets (Shi et al. 2020). The water droplets contaminated with SARS-CoV-19 virus can be transmitted to cats. The fecal samples from inoculated cats exhibited viral shedding within 3-5 days. Moreover, viral RNA samples were also collected from upper and lower respiratory tract. Severe lesions were observed in lungs of kittens and mucosae of upper respiratory tract (Shi et al. 2020). Some instances of natural transmissions were reported in domesticated cats, while most experimental investigations were conducted in laboratory settings (Bosco-Lauth et al. 2020). In addition to cats, ferrets have also been observably prone to reverse zoonosis on account of COVID-19 virus (Monchatre-Leroy et al. 2021). In experimental settings, ferrets were inoculated with samples obtained from Huanan Seafood Market in Wuhan, China and clinically positive humans causing subsequent shedding of virus. Virus successfully replicated in the upper respiratory tract mucosae and remained detectable in rectal samples for prolonged period without causing death. Thirteen days post inoculation of viral isolates, mild peri-bronchitis along with other marked symptoms associated with COVID-19 were observed. Serum antibodies against SARS-CoV-2 were also detected (Shi et al. 2020). Contrarily, low susceptibility was seen after inoculation of virus into Beagle dogs whereby, only 50% of them seroconverted after 14 days (Shi et al. 2020). However, such findings were not observed when chicken, ducks and pigs were inoculated, as these species remained seronegative even 14 days after infection (Shi et al. 2020).

Measles

Measles is a common pediatric infection of viral origin caused by measles virus (MeV), which is a member of the genus Morbillivirus. Phylogenetic evidence has suggested that MeV has evolved from Rinderpest virus (RPV) around the 11th to the 12th century and is commonly associated with infections in cattle (Furuse et al. 2010). Since then, measles has wreaked havoc on human populations, causing high morbidity and mortality in infected individuals (Hilleman 1992). The outbreak reported in 1996 amongst 94 primates has since then been identified as an instance of Reverse zoonosis following urine and serum analysis were found positive for measles specific IgG and IgM antibodies. A reverse transcriptase-polymerase chain reaction was also employed for confirmatory virus isolation (Willy et al. 1999). The incidence of measles outbreak in humans precisely during the same period legitimized the said claims (Willy et al. 1999).

Rhinovirus-C

Rhinoviruses, which belong to the family Picornaviridae and genus Enteroviridae, are responsible for causing common cold in humans (Matsuzawa 2020). Interestingly, human rhinovirus-3 was never thought to be capable of jumping species. However, several reports in non-human primates with severe flu-like symptoms have indicated a spillover effect into sylvatic communities (Velayudhan et al. 2006). Outbreak of human rhinovirus-C (HRV-C) in 2013 amongst chimpanzees has been identified by the presence of universal homozygosity for the 3 CDHR3-Y529 allele (cadherin related family member), which is a receptor that drastically increases susceptibility to rhinovirus-C infection and asthma in humans. Susceptibility of chimpanzees to a highly pathogenic virus implicates inevitable spillback into human hosts (Scully et al. 2018).

Pneumo Viruses

Human metapneumovirus (also known as MPV, Pneumoviridae, Metapneumovirus) and a human respirovirus-3 (also known as HRV3, Paramyxoviridae, Respirovirus, or formerly as parainfluenza virus-3) have been found as causative agents for spread of respiratory infection amongst Ugandan Chimpanzee community (Negrey et al. 2019).

Human respiratory viruses have become a major threat to wild non-human primate communities (Dunay et al. 2018). These respiratory maladies have become predominant causes of the disease and mortality amongst apes in wildlife sanctuaries of Uganda (Emery Thompson et al. 2018) and Tanzania (Lonsdorf et al. 2018). Reverse zoonosis of human respiratory pneumoviruses has also been reported in gorillas from Congo (Grützmacher et al. 2018) and Central African Republic (Grützmacher et al. 2016).

Parasitic and Fungal Anthroponosis

In a similar fashion of other infectious agents, parasites and fungi also make their way between humans and animals. Most of the time parasitic cycle of transmission is slower than that of bacteria and viruses due to involvement of intermediate transporters and nature of slow growth in case of parasites. However, parasites are able to share different hosts, including humans and animals. The fungal kingdom contains as many as 6 million species and is important in terms of the breadth and depth of its effects in areas of public health, animal health, environment, biomedical and agriculture (Taylor et al. 2014). Fungi can be naturally transmitted between animals and humans in both directions and in some cases cause significant public health problems. A large number of fungi associated with zoonotic and reverse zoonosis transmission are among the group of the most common fungal diseases worldwide. It is, however, notable that some fungal diseases have failed to attract sufficient attention in international one health efforts, leading to

insufficient attention on their preventive strategies (Seyedmousavi et al. 2015).

Cryptosporidium parvum

A parasitic disease in the intestinal tract of mammals, called cryptosporidiosis, is caused by *Cryptosporidium* (*C.*) *parvum*. The infection of *C. parvum* is mainly manifested by watery, non-bloody acute diarrhea. The presence of cryptosporidiosis disease in livestock has become a considerable glitch both for animal wellbeing (together clinical and subclinical) and commercial harms (Santín 2013). These effects are due to growing veterinary amenities and work expenses, aggregate animal health-carefulness rate, and deteriorating the growth of animals along with high mortality. *Cryptosporidium parvum* was one of the most prevalent parasitic species in animals, infecting 30% of buffaloes at farm level (Inpankaew et al. 2014).

The parasite can be transmitted by two routes, including direct and indirect methods of transmission. Direct transmission occurs through feco-oral route by unintended ingestion that leads to the excretion of *Cryptosporidium* oocytes in feces. A parasite adopts various routes for its transmission from humans to animals or vice versa and for human to human transmission (Hubalek 2003). In humans, it causes infection by living in the epithelial exteriors of the intestines, distributed from stool or feces, and/or filthy in the atmosphere (environmental contamination). There are only a few studies for animals that demonstrate the influence of nitazoxanide drug contrary to clinical contaminations of *Cryptosporidium* spp. in which this nitazoxanide drug might reduce *Cryptosporidium* oocysts in defecation. Nevertheless, this drug is not being used commonly in animals (Ghazy et al. 2015). There is an extensive need to practice the preventive measures to reduce the spread of *Cryptosporidium* spp. particularly in livestock. By mitigating different factors, namely congestion in farmhouses, cross contamination by workers and contact with animals which bear greater risk of infection (Robertson et al. 2020).

Trichuris trichiura

Trichuris (*T.*) *trichiura* is a species that can be found in the tropical and temperate areas around the globe, however, mostly found in the dampness of the tropics (Roberts and Janovy Jr, 2000). This parasitic specie is also named as whipworm and infects animals and humans. There are two situations, namely deprived sanitation and poor environment, required for dispersion of *T. trichiura* and for the development of worm. These environmental conditions comprise a moisturizing moderate climate, wet soil, low lights and lot of rainfall (de Silva et al. 2003). The eggs of *T. trichiura* have been detected in the feces of some pigs, dogs and cats in tropical areas with poor sanitation, raising the possibility of reverse zoonoses. *T. trichiura* was also identified in mountain gorillas, and there are possibilities that these parasites

belong to human origin (Sleeman et al. 2000). A recent study in Thailand found that more than half of the *Trichuris*-positive fecal samples from dogs contained the human parasite *T. trichiura*, as identified by PCR. Likewise, more than half of the fecal samples from dogs and cats in Malaysia were found to contain eggs identified genetically as from *T. trichiura*. Whether these animals were infected with adult worms or simply shedding eggs acquired from the environment is currently unclear. (Phosuk et al. 2018; Mohd-Shaharuddin et al. 2019).

Blastocystis spp

Blastocystis is a genus in the Stramenopile group that is very diverse, comprising brown algae, slime nets, diatoms and group of water molds. These *Blastocystis* are eukaryotic organisms that are unicellular and anaerobic in nature (Hoevers and Snowden 2005). It is the most common parasitic protist globally and also a pluralistic enteric parasite found worldwide (Ahmed and Karanis 2018). The virulence mode of action of *Blastocystis* is not fully described yet. Although, it has pathogenic potential but its capability to cause gastrointestinal and various other infections has been questioned (Mohamed et al. 2017). A vast variety of animals, such as invertebrates, reptiles, amphibians, birds, mammals and humans, are infected by *Blastocystis* (Ahmed and Karanis 2018). One of the most common parasites that infect humans globally is the *Blastocystis*, as it is extensively spread worldwide. The commonly acknowledged pathway of transmission is the feco-oral diffusion and current investigations have revealed that spread occurs merely through the cyst form of the parasite (Yoshikawa et al. 2004). However, when ingestion of the cyst takes place, its life cycle is started. Different forms of cyst develop after ingestion, which possibly will turn into cyst forms sequentially. The transmission cycle is repeated when cysts are released into environment through humanoid feces to infect the humans and other animals. The contamination caused by *Blastocystis* parasites can take place by different species either through zoonosis or reverse zoonosis (Noël et al. 2005). However, studies found zoonotic isolates having large potential and stay problematic in recognizing the host roots and communication ways. *Blastocystis*, whether commensal, pathogen, or part of human microbiota, is still ubiquitous parasite cycling among humans, animals and environment. Evolution of this parasite is increasingly reported almost everywhere worldwide involving animals, humans, and even water. However, *Blastocystis* still remains underestimated and underreported in comparison to other protozoa (Ahmed and Karanis 2018).

Encephalitozoon intestinalis

Encephalitozoon (E.) intestinalis is one of the most predominant *Encephalitozoon* species found in humans around the world. This species has been found to occur in numerous, principally native, mammalian species, for example cattle, pigs, goats, donkeys, dogs or gorillas

(Hinney et al. 2016). Animal to human and human to animal transmission has been proposed to be an important source of infection. Human associated *Encephalitozoon* spp. was found in waterfowl in Slovakia (Malčėková et al. 2013). Several case reports of this parasite transmission in captive wild birds have been described. Subsequent studies on larger populations showed that asymptomatic infections in captive wild birds are widespread (Phalen et al. 2006). Close interaction between humans and non-human primates can create routes for the transmission of this zoonotic disease in both directions (Graczyk et al. 2002).

Candida albicans

Species of *Candida*, a yeast like fungus, cause a localized mucocutaneous disease called “Candidiasis” (Hani et al. 2015). Candidiasis is prevalent all over the world in humans and animals. Many animal cases were reported that had the same isolates as those of humans (Wrobel et al. 2008). Canine isolate was obtained from a graduate student-owned dog and two feline isolates were obtained from animals at the Champaign County Humane Society analysis of the domestic animals. *Candida albicans* isolates showed that the cats and dogs were colonized with common human isolates. The pets tested were all indoor animals that were in close contact with humans (Wrobel et al. 2008). Parakeet (bird) was found infected with *C. albicans*. It was also a case of reverse zoonosis (Kumar et al. 2017). Ingestion of contaminated food or drinking water is the usual means of transmission. Contaminated environment, such as litter from diseased and game bird rearing in the same amenities and areas contaminated with human waste, are suggested as sources for Candidiasis exposure to birds (Kumar et al. 2017). The consensus drawn from various texts is that *C. albicans* is associated mainly with humans, other mammals, and avian species (Wrobel et al. 2008).

Trichophyton rubrum

Trichophyton (T.) rubrum belongs to phylum Ascomycota. It is dermatophytic, anthropophilic, saprotrophic fungus and exclusively clonal, which colonizes the upper layers of dead skin cells (Gräser et al. 1999). *Trichophyton rubrum* is a cosmopolitan, anthropophilic species and is the most usual causative agent of human dermatophytosis across the planet. Despite being anthropophilic, this dermatophyte is also infrequently found to be reason of dermatological disease in dogs. Therefore, *T. rubrum* can also be considered as an anthroozoonotic and zooanthroponotic pathogen (Overgaaauw et al. 2020).

Microsporium gypseum

Microsporium gypseum is a soil-associated dermatophyte that is recognized to colonize and infect the upper layer of skin in mammals (Samanta, 2015). Tinea or ringworm is the fungal infection, which affects external body parts. It

is one of the fungal diseases which are transferred from humans to animals and humans to humans (Summerbell and Howard, 2003). People engaged in experimentation and handling with laboratory animals can also be at risk of contracting the infection, if the animals were predisposed to a certain region (Ranganathan and Balajee 2000). Animals such as cattle, which repeatedly come in contact with soil, are predominantly affected by this fungus, but equines, rodents, apes and canines have a disposition to acquire it (Messenger et al. 2014). A dog was found positive with *M. gypseum*, which is a case of zoonosis (Sharma et al. 2009); though the soil is usually considered as the prime reason of infection. Analytically, at least 10 fungal spores must deposit on a keratin rich skin surface of animals or humans to manifest a fungal infection (Messenger et al. 2014). Diagnosis is usually made on the shape of the fungus on the host through a sample culture.

Conclusion

Reverse Zoonosis is a reality and is playing an important role in the sufferings of the animals. During the past few decades, human animal interaction, especially with the wild life, has increased. Transmission of interspecies pathogens could be direct or through vectors. All types of pathogens i.e., bacteria, viruses, protozoa, and fungi have capability of reverse zoonosis. Although it is difficult and labor extensive work to consider animal factors while studying a disease outbreak in humans, yet it is need of the time, as the evidences are strong for inter species disease transmission. The countries having higher population density like Pakistan, have higher chances of human to animal transmission of pathogens, as they are residing in close vicinity. There is need to focus on this aspect of research and study in Pakistan. In the light of COVID-19 disaster, the thinking horizon of the scientist has now changed. There will be more focus on 'One Health' for one globe rather than only human health. Because health is important, host specie doesn't matter now.

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