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REVIEW ARTICLE

SARS CoV-2 AND OTHER REVERSE ZOONOSES: UNDERSTANDING THE HUMAN ANIMAL INTERFACE FOR DEVISING CONTROL STRATEGIES

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ABSTRACT

Destructive human activities have been ravaging nature and have also in certain situations paved the way towards emergence of diseases hitherto unknown. While a substantial number of the emerging diseases are known to originate from animals, there are many instances where humans have been responsible for causing infection in animals. Such "spill over" encountered in SARS CoV-2 raises alarm as it complicates the process of understanding the disease dynamics. Many other pathogens have been known to cause reverse zoonoses including Influenza viruses. The knowledge that have been gathered throughout the years from previous such occurrences can help the scientific community in designing the control and preventive protocols for arresting the spread of SARS CoV-2 among the human and animal population. In humans extensive vaccination is being practiced as an effective intervention strategy and the reverse zoonotic nature of the virus has given an impetus for assessing the feasibility of using similar vaccines in animals. However, to break the reverse zoonotic cycle capable of causing pandemics, a holistic approach is required to understand the pathogen movement at the man-animal interface which not only includes the viral properties like mutation rate, virulence characteristics etc but various other factors such as environmental changes, human interference etc. Effective biosecurity measures, artificial intelligence based monitoring systems and robust molecular epidemiological surveillance can help in preventing as well as predicting "spillover" of pathogens which will be critical for preventing pandemics in future.

Keywords: SARS CoV-2, Anthroponosis, Reverse zoonoses, Spill over, Emerging diseases

INTRODUCTION

The emergence of the Severe Acute Respiratory Coronavirus- 2 (SARS CoV- 2) brought day- to-day life to a screeching halt overwhelming the health care set up across the globe. The World Health Organization (WHO) declared COVID-19 as a pandemic in early 2020 (WHO, 2020) and since then a lot of dispute has been witnessed regarding the zoonotic origin of the virus (Chakraborty *et al.*, 2020). While the entire globe was engrossed with the development of COVID 19 vaccines for humans, in March 2021, Russia declared the development of the first SARS CoV-2 vaccine for animals Carnivac-Cov (Chavda *et al.*, 2021), bringing to the fore the importance of 'reverse zoonoses' which remains ignored at various levels.

Wild life trade, rapid destruction of animal habitat has brought man in close contact with the wild animals, resulting in a possible spill-over of previously unknown diseases between the two populations (WHO, 2020a). Many of the emerging viral diseases are zoonotic in nature. Under such circumstances, the huge population of infected people can become a possible source of infection for animals, and such an event is termed as reverse zoonoses (Ayudhya and Kuiken, 2021).

The present COVID 19 pandemic has presented a stiff task for researchers and even after strategies of quarantine, complete lock down and vaccination, the world is hit by new variants and surges every now and then (Sanyaolu *et al.*, 2021). Research has largely been dedicated on understanding the zoonotic transmission of SARS CoV-2 but lesser importance has been given in respect to its further transmission from humans to animals— 'anthroponosis' or 'reverse zoonosis' (He *et al.*, 2021). The devastating foot prints left behind by the Spanish Flu of 1918 can be taken in retrospection and the lessons learnt acknowledged for a stronger fight back against COVID 19. Spanish Flu is thought to have affected 500 million, killing 50 to 100 million people (Taubenberger and Morens, 2006). This review attempts to summarise the features of reverse zoonotic transmission and its significance in terms of the COVID-19 pandemic. Since various factors have a collective impact on the events that perpetuate reverse zoonoses in nature, careful assessment and recognition of these factors is indispensable for chalking out effective prevention and control mechanisms.

Reverse zoonoses: mechanism of spill over: The process by which the transmission of a pathogen occurs from a reservoir host species to a recipient host species is known as Pathogen spillover (Lloyd-Smith *et al.*, 2009). Sometimes high number of infected human act as source of infection for animals hence the name is given "reverse zoonosis" where cross species spill over is observed (Haider *et al.*, 2020). Two main events are likely to occur during reverse zoonosis, either the infected animal becomes ill and then die or it becomes a virus reservoir that may reintroduce the infection into human population (Kuiken *et al.*, 2006). Occurrence of reverse zoonosis is likely not only via direct contact with infected human but also via contaminated biological matter (Franklin and Bevins, 2020). Usually species jump of virus occurs sporadically, where sufficient interaction between donor and recipient species takes place for sustainable transmission. Even different biological factors may favour the viral spill over, such as- expression of required receptors, presence of different enzymes or proteases etc. into the new host to enhance their replication efficiency (Wang *et al.*, 2013). After adapting to a new host, the virus eventually becomes low pathogenic but at the same time becomes more transmissible which is already seen in case of SARS-CoV-2. Coronaviruses have been known to cross the species barrier and in SARS-CoV1 spillover to human occurred through Masked palm civets and racoon dogs whereas in case of MERS it was through Dromedery camels (Petrosillo *et al* 2020). During the SARS outbreaks in 2002–2003 and 2003–2004, evidences suggest that four possible routes of transmission *viz*. animal-to-human, animal-to-animal, human-to-human and human-to-animal had occurred (Wang and Eaton, 2007).

Combination of several factors like landscape change, human behaviour and ecological disturbances all together play an important role for the viruses in switching hosts (Williamson *et al.*, 2020). After switching into new species the survival rate of the viruses into the new population depends on the density of the recipient species as well as the intermixing of both recipient and donor species (Ayudhya and Kuiken, 2021). Data says that such species jump was observed from human to pig during Influenza H1N1outbreak due to easy adaptation of the virus into the new host since both the human as well as pig infecting viruses were similar (Forgie *et al.*, 2011). Even in few studies wild captive animals were found to be positive for H1N1 which had come in contact with infected care takers and infected veterinarians (Martelli *et al.*, 2019). Since 2009, repeated introductions of pandemic H1N1 viruses from humans to pigs have enhanced the genetic diversity of swine influenza viruses threatening both the hosts (Nelson and Vincent, 2015). The human animal interface and the bi-directional aspect of disease transmission create opportunities for recurrent infection and outbreaks, forming a vicious loop and throws newer challenges for establishing control measures.

Lessons from previous episodes of reverse zoonoses: what we have learnt so far?: In Table 1, a list of reverse zoonotic events involving different pathogenic organisms is depicted which is a testimony to the disastrous possibilities that surround such events. Multi drug resistant human B2-O25:H4-ST131 CTX-M-15-type ESBL-producing *E. coli* strains are presumed to have continuous evolution causing significant public health threat (Ewers *et al.*, 2010). In context of *M. tuberculosis*, its presence in bovine tissue needs to be further confirmed by typing the mycobacterial strains from the animal attendants suffering from suspected tuberculosis infection since they are in constant contact with the animals (Mittal *et al.*, 2014).

The occurrence of zoonotic enteric bacteria in seabirds has been reported even from the Antarctic and sub-antarctic region. The presence of Salmonella serovar (ser. Enteritidis) and Campylobacter species (e.g. *C. jejuni*) typically associated with human infections suggest reverse zoonosis from humans to seabirds. The opportunistic seabirds, notably skuas (Stercorarius) facilitate further spread of zoonotic agents among Antarctic wildlife (Cerdà-Cuéllar *et al.*, 2019). The role of migratory birds in the transmission patterns holds a great importance in case other pathogens and their vectors also (McCoy *et al.*, 2012). Furthermore, both social and ecological factors together act as precipitating factors towards disease transmission between human and nonprimates through habitat and shared water resource in case of some enteropathogens (Nizeyi *et al.*, 2001). Reportedly, genotype 4 of human HEV strain is found to breach species barriers leading to infection in pigs (Feagins *et al.*, 2008). Long term evolution of Lassa virus is thought to occur in rodents with intermittent spill over to humans but seroprevalence shows that 70% seropositive human are with no symptoms and they excrete the viruses upto 60 days in urine. These contaminated domestic surfaces are accessible to rodents and also act as potential source for further spread of infection (Olayemi *et al*., 2020). Again, the segmented nature of the Rotaviral genome makes the virus capable of reassorting its genome with rotavirus strains from different host species. It has also been observed that some virus strains might have been transmitted to another species as a whole genome constellation (Palombo, 2002). Sequencing of H1N1 during pandemic human influenza revealed that it accommodated unique reassorted genes from viruses of Eurasian and North American pigs which was further introduced into the pig farm reflecting pattern of human to animal transmission (Howden *et al*., 2009). Potential human-to-animal transmission of SARS-CoV has also been reported in cats and pigs. In an incidence in China, the genome sequence of the pig isolate was found to be closely related to the human isolate and was only distantly related to SARS-CoVs of animal origin (Wang and Eaton, 2007). Evidences of bat derived coronaviruses adopting a functional gene from reoviruses has also been reported (Huang *et al*., 2016). The S2 domain of the spike protein of coronavirus i.e. carboxyl domain contains two heptad repeats which is grouped with other classes such as Ebola GP2, Influenza virus Haemaglutinin and HIV env-1 etc (Bosch *et al*., 2008). Reportedly the host range expansion is contributed by mutation in this S2 domain (McRoy and Baric, 2008). Many coronaviruses are seen to be accomplished at maintaining the persistent infection in their respective hosts where mutational events have happened either to recognize new receptors or to alter the affinity for the existing receptors through downregulating the receptor expression in the carrier host cells (Baric *et al*, 1999).

Reverse zoonoses in SARS CoV-2

Viral characteristics: Corona viruses infect different animal species like bats, swine, equines, bovine, feline, canine, Camelids, civets etc that can act as intermediate hosts (Ye *et al*., 2020). It is said that the origin of all human corona viruses is from animals, mostly bat which acts as natural host as seen in HCoV-NL63, MERS-CoV, HCoV-229E, SARS-CoV. Whereas, the probable origin of other two HCoV-OC43 and HKU1 is thought to be rodents (Su *et al*., 2016). However, debates are still on whether the origin ofSARS-CoV-2 is zoonotic or laboratory engineered which might have accidently or deliberately leaked from the research lab in Wuhan, China. Certain theories claim that the outbreak occurred in the food market that was 300 yards away from the Wuhan research lab (Bolsen *et al*., 2020). The virus has been predicted to come from bat either as direct transmission to human or via intermediate host Malaysian pangolin (Li *et al*., 2020). But, protein sequence analysis and phylogenetic study showed possibilities of involving other intermediate hosts like turtles ,snakes etc. since similar receptors are found in them (Liu *et al*., 2020). Reportedly, not only the snake or turtles but animals under Bovidae or Cricitidae could be possible intermediate hosts based on study of the Receptor Binding Domain (Luan *et al*., 2020). SARS -CoV-2 viruses showed 96% (Zhou *et al*., 2020) and 91% identity (Zhang *et al*., 2020) respectively with corona viruses isolated from horseshoe bat and Malaysian pangolin respectively.

The genome size of coronavirus is variable from 27317 to 29903 nucleotides and GC content is ~38% (Mohanta, 2020) with few notable features observed in the viral genome. Total of six amino acids present in the Receptor Binding Domain (RBD) are highly variable and it determines the host range (Wu *et al*., 2020; Wan *et al*., 2020). Presence of poly basic cleavage site in the spike proteins junction along with proline residue to form a turn for addition of O-linked glycans which determines transmissibility. This is not observed in other lineage B Beta coronaviruses but found in few from lineage A (Andersen *et al*., 2020). Whole genome of coronavirus is comprised of four structural proteins along with 16 non structural proteins and several accessory proteins. 149 mutation sites are observed across this whole genome (Tang *et al*., 2020). The calculated evolutionary rate of coronavirus is 10^{-4} nucleotide substitution in each site per year (Su *et al*., 2016) and hence SARS-CoV-2 is thought to be a fresh lineage of Beta CoV with sequence homology to Bat coronavirus causing SARS (Zhou *et al*., 2020). Mutation in the NSP2 and NSP3 determines the infection capacity (Wu *et al*., 2020). A study pointed out that homologous recombination can occur in the spike glycoprotein genes between bat corona virus and other corona viruses of unknown origin (Ji *et al*., 2020).

Reverse zoonotic events of SARS-CoV-2: wild animals:In April, 2020, the world came to light about the first episode of SARS-CoV-2 associated reverse zoonotic event in wild felines, when a Malayan tigress at the New York based Bronx Zoo was tested positive for SARS-CoV-2 along with another Malayan tiger, two Amur tigers and three African lions (McAloose *et al*., 2020). Further epidemiological and diagnostic investigation suggested that there was a close evolutionary relationship between the viral strains in the tigers and those in the tiger keepers.

In India, the first instance of reverse zoonotic event of SARS-CoV-2 took place at Hyderabad's Nehru Zoological Park, when eight Asiatic lions were tested positive for SARS-CoV-2 by RT-PCR (Deshpande, 2021). Two lions of Etawah Safari Park, Uttar Pradesh (Jha, 2021), 10 lions of Vandalur Zoo, Chennai (Sidharth, 2021) and 28 elephants of Madumalai Tiger Reserve, Tamil Nadu (Chandrababu, 2021) were also diagnosed with SARS-CoV-2.

Reverse zoonotic events of SARS-CoV-2: Farm/ companion animals: The Netherlands reported the first cases of diagnosis of SARS-CoV-2 in mink farms during April, 2020. Out of the minks which were tested, 66 (68%) were found to be positive for the virus or having antibodies to SARS-CoV-2. The genome sequences generated from the employees of seven different mink farms were nearly identical to the mink sequences from the same farm (Munnink *et al*., 2021).

Similarly, several mink farms in the United States, Denmark, France, Greece, Italy, Spain, Sweden, Poland, Lithuania and Canada faced the consequences of SARS-CoV-2 infection (Munir *et al*., 2020).

Among companion animals, a male Pomeranian was the first to be diagnosed with SARS-CoV-2 in February, 2020 in Hong Kong. The owner of the dog and the female domestic help were also reported to be positive for SARS-CoV-2. Another German shepherd, belonging to a Hong Kong based owner, tested positive for SARS-CoV-2 RNA. The viral sequences obtained from the dog and the owner were found to be identical across the full genome (29,764 nucleotides) (Sit *et al*., 2020). Such reports of SARS-CoV-2 associated reverse zoonotic events in dogs were also reported from the USA and the Netherlands (Munir *et al*., 2020).

The first report of human-to-domestic cat transmission of SARS-CoV-2 came from Belgium in March, 2020 (Bryner, 2020). Hong Kong, USA, China, France, Spain, Germany, Russia and the Netherlands are the other countries which have reported transmission of SARS-CoV-2 from human to domestic cats (Munir *et al*., 2020).

Experimental infection of SARS-CoV-2: Experimental infections of SARS-CoV-2 conducted on dogs, cats, pigs, poultry, ferrets (Shi *et al*., 2020), hamsters (Chan *et al*., 2020), rhesus macaques (Melin *et al*., 2020), African green monkeys, fruit bats (Wan *et al*., 2020) and many other species has revealed that these animals are susceptible to the disease. Out of these, the rhesus macaques, fruit bats, Golden Syrian hamsters, ferrets, deer mice and cats are found to be highly susceptible (Munir *et al*., 2020).

Table 1: Reverse zoonotic events reported from different geographical location worldwide

Causative agent	Reservoir host	Animal infected	Location	Reference
Mycobacterium tuberculosis	Human	Cattle	Uganda	(Adesokan *et al*., 2019)
Human Metapneumovirus	Human	Chimpanzees	USA	(Slater *et al*., 2014)
Human B2-O25:H4-ST131 CTX-M-15-type ESBL-producing E. coli strains	Human	Dogs	Europe	(Ewers *et al*., 2010)
Tuberculosis	Human	Elephant	France	(Laine, 2018)
Salmonella serovar (ser. Enteritidis)	Human	Sea birds	Antarctica	(Cerdà-Cuéllar *et al*., 2019)
Campylobacter	Human	Mountain gorilla	Uganda	(Nizeyi *et al*., 2001)
Genotype 4 human Hepatitis E virus	Human	Pig	United States	(Feagins *et al*., 2008)
Lassavirus	Human	Rodents	West Africa	(Olayemi *et al*., 2019)
Rotavirus	Human	Sheep	Haryana	(Choudhury *et al*., 2017)
Influenza Virus A (H3N2)	Human	Pig	Nigeria and Ghana	(Adeola *et al*., 2016)
VIM-2 carbapenemase-producing *Pseudomonas aeruginosa*	Human	Dog	Brazil	(Fernandes *et al*., 2018)
Human-related metapneumovirus	Human	Chimpanzees	Western Tanzania	(Kaur *et al*., 2008)
Measles virus	Human	Japanese Macaques	Yongin, Korea	(Choi *et al*., 1999)
human influenza A (H1N1)	Human	Pig	Nigeria	(Anjorin *et al*., 2020)
Mycobacterium tuberculosis	Human	Dogs	Federal District, Brazil	(de Sousa *et al*., 2018)
Mycobacterium tuberculosis	Human	Cattle	Eastern Cape Province, South Africa	(Hlokwe *et al*., 2017)

DISCUSSION

The scientific community is expected to anticipate reverse zoonotic events to appraise the concerned authorities and bridge the gaps to strengthen the monitoring and control policies. Reverse zoonoses not only affects the susceptible companion animal populations abruptly but also pose a greater threat to wildlife. It may diminish or even wipe off the wild population by destroying and disrupting the local biodiversity, niche, ecological balance and dynamic equilibrium (Daszak *et al*., 2000). Since the inception of the COVID 19 pandemic, some scientists have shared their concerns about the impact of coronavirus in animals. In light of that, Russian researchers developed the first COVID-19 vaccine named Carnivac-Cov/Karnivak-Kov, for animals specifically designed for carnivores (Andrew, 2021). In fact an amalgamation of clinical, epidemiological, sequencing analysis, and laboratory investigations are crucial for the risk assessment for animals and humans associated with reverse zoonosis outbreaks of influenza or COVID-19 (Ayudhya and Kuiken, 2021). Only a few sero-surveillance studies have been conducted for SARS-CoV-2 in domestic dogs, cats, and mink, suggesting further sero-surveillance studies in human animal interfaces can give insights regarding cross-species transmission (Munnink *et al*., 2021; Zhang *et al*., 2020). Robust sero-surveillance in susceptible as well as other animal species is paramount to determine whether the risk factors perpetuating reverse zoonoses in certain situations actually exist. Considering the threat of transmission of infection from human to pet animals, few precautions should be adopted like isolation of infected individual and the surrounding animals, proper hygiene and usage of personal protective equipment. Sero-surveillance of random pet animals should be performed which live in close contact with infected humans (Naveenkumar *et al*., 2020).

Previous studies have cited that susceptible workers working in animal farms involved in daily handling have a potential for transmission of Influenza virus between humans and pigs (Chastagner *et al*., 2019). Human influenza viruses as well as Human tuberculosis can easily disseminate from infected farm workers' secretions and excretion to the farm animals. (Adesokan *et al*., 2019; Adeola *et al*., 2016). Establishing vaccination status and good hygiene practices among key individuals like vets, employees, suppliers along with their families will help minimise the risk of bidirectional transmission and the emergence of a novel strain due to genomic re-assortment (Ramirez *et al*., 2006). Biosecurity measures are one of the cardinal measures to embrace at the human- animal interface to minimise spread of infection to animals from human contact (Krueger and Gray, 2013).

Geographic Information System (GIS) has found wide application across various scientific disciplines and in the ongoing COVID-19 pandemic too it has played a crucial role in deciphering the spatial clustering and transmission trend of the disease. In the early stages of the pandemic, near-real-time GIS based tracking of COVID-19 cases was made possible by the John Hopkins University (Dong *et al*., 2020). In a similar way, better prevention and control of reverse zoonoses is possible through multifactorial monitoring approach. For example, location-based services, geographic information systems, and artificial intelligence can aid in ascertaining the movement trajectory of the animal owners and their probable contact with COVID-19 infection (Yang *et al*., 2021). Also, daily movements of livestock farm animals can be scanned by global positioning system equipped wearable devices for disease detection and health status monitoring (Jia and Yang, 2020). An emerging discipline namely spatial life course epidemiology, which includes the study of evolving agents, mobile hosts and changing environments (Jia and Yang, 2020a) uses advanced technologies to not only recognize when and where a disease occurs but also determine how exposures occurred previously so that the causative agent can be identified for designing intervention strategies and policy change (Jia, 2019).

The all-inclusive "One Health" approach needs to be strengthened involving public health experts, government and nongovernmental health organizations, economists and ecologists, etc., for reviewing and scrutinizing policies necessary for the prevention of outbreaks (Jorwal *et al*., 2020). Further, adequate intensive data help in regulating and generating scientific discovery. Herein, the concept of precision public health is noteworthy since it incorporates different types of data *viz.* genomic information, satellite imaging, mobile phone and social media usage information to enhance the power of epidemiology. The challenge lies in selecting the most relevant data and recognizing new types of data when they become available (Bedford *et al*., 2019). In general, better awareness about reverse zoonoses is required at an individual level among the vulnerable population. Moreover, in absence or lack of strict regulations concerning containment protocols for animals, especially for home pets, there is a high likelihood of transmission and consequent increase in the number of infections among animals. Resources should be reserved for high-risk category animals (e.g., pets of confirmed COVID-19 patients) for easy SARS-CoV-2 detection and also for management of infected and at-risk animals, especially at the farm (Jia *et al*., 2021).

The varied episodes of reverse zoonoses are a lurking peril which have the potential to disrupt the delicate ecological balance leading to catastrophic consequences. Constant vigilance and assessment involving both human and animals is needed, specifically in context of the COVID 19 pandemic which has been witnessing the emergence of new variants of the virus. Putting an end to the SARS-CoV-2 infections in animals could be indispensable for pandemic recovery, as well as for future preparedness. A pandemic of such a magnitude requires an equally robust control approach incorporating the age-old proven mechanisms of disease control coupled with new age technology. The complexities involving disease dynamics at the human animal interface magnifies the challenges posed to the researchers and therefore well strategized, collaborative approach is needed to find an altruistic and long-lasting solution.

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Author contribution: SMG – Conceptualized, designed and wrote the draft. HD, SAA, CG- Wrote the draft. TD and SN- Collected the data. DPB and PD: Designed the review and analysed the data; SD and GKS- Critically revised the draft

Statement of novelty: This review attempts to analyse various instances of reverse zoonoses that have been encountered in the past highlighting their significance in the transmission as well as evolution pattern of microorganisms. While majority of the literature available have only provided data regarding reverse zoonotic events, our review seeks to correlate the factors that initiate and help in the persistence of reverse zoonoses in order to critically point out the probable areas that need immediate attention for prevention of such occurrences in future by taking SARS CoV-2 as a reference.

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