Review of Emergence and Zoonotic Implication of Sars-Cov-2 (Covd 19) and its Associated Risk Factors

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Abstract: *SARS-CoV-2 (COVID-19) is Zoonotic pandemic viral disease which caused by Coronaviruses (CoVs) belong to the family Coronaviridae, which comprises a group of enveloped, positive-sensed, single-stranded RNA viruses World Health Organization declared the ongoing outbreak of lower respiratory tract infection caused by SARS-CoV-2 a Public Health Emergency of International Concern and also named the disease COVID-19. The COVID-19 outbreak once again proves the potential of the animal-human interface to act as the primary source of emerging zoonotic diseases. There are evidences suggest the possibility of an initial zoonotic emergence, from intermediate hosts such as bat, pangolins, and other wild animals in the origin of SARS-CoV-2, in addition to these some domestic animals like canine and feline are suspected as zoonotic emergence of the diseases. Identifying the possible zoonotic emergence and the exact mechanism responsible for its initial transmission will help us to design and implement appropriate preventive barriers against the further transmission and prevention of SARS-CoV2/COVID-19.*

Keywords: *challenges, control and prevention, COVID-19, zoonotic emergence*

Abbreviations: *SARS: Severe acute respiratory syndrome, MERS:Middle East respiratory syndrome, COVID-19: Coronavirus disease 19, SARS-CoV: Severe acute respiratory syndrome coronavirus; MERS-CoV: Middle East respiratory syndrome-CoV; ORF: Open reading frame; ACE2: Angiotensin-converting enzyme 2; DPP4: Dipeptidyl peptidase 4; SL-CoV: SARS-like coronavirus.*

1. INTRODUCTION

Infectious diseases that originate from animals and infect people comprise the majority of recurrent and emerging infectious disease threats and are widely considered to be one of the greatest challenges facing public health (Woolhouse and Gowtage-Sequeria, 2005; Heymann *et al.* 2015). Characterization of pathogen transmission events from wildlife to humans remains an important scientific challenge hampered by pathogen detection limitations in wild species. Disease spillover is probably vastly under-reported, particularly in remote regions where people have limited access to healthcare. Zoonotic disease spillover events are also difficult to detect, especially if the disease spectrum includes mild or non-specific symptoms, or if there is limited to no human-to human transmission. While the common characteristics of zoonotic diseases have advanced an understanding of disease transmission between animals and humans (Kreuder *et al.* 2015; Woolhouse and Gaunt, 2007; Woolhouse *et al.,* 2012), efforts to date have been hampered by sparse data.

The synthesis of epidemiological and ecological profiles of viruses and their hosts has enabled the detection of intrinsic virus and host features linked to species propensity to share viruses with humans (Stephens et al. 2016). For example, host phylogenetic proximity to humans and increased urbanization within a host distribution has been shown to be positively correlated with the number of zoonotic viruses in a species. Zoonotic disease richness has also been linked to larger geographical range and more litters earlier in life among rodents (Han *et al.,* 2015), geographical range overlap and more litters per year among bats (Luis *et al.,* 2013), and larger body mass, larger geographical range and phylogenetic diversification among carnivores (Huang *et al.,* 2015).

Characterizing epidemiologic features of viral transmission at the animal–human interface has also revealed a number of high-risk human activities that have enabled virus spillover in the past, particularly in situations that facilitate close contact among diverse wildlife species, domesticated animals and people (Kreuder et al. 2015). Moving from individual circumstances to

larger scale drivers requires a historical account of how humans have altered the nature of their contact with animals with implications for zoonotic spillover risk. Domestication of animals, human encroachment into habitats high in wildlife biodiversity and hunting of wild animals have been proposed as key anthropogenic activities driving infectious disease emergence at the global scale (Wolfe et al., 2005; Wolfe et al., 2007). Many of these same anthropogenic activities have been implicated as the drivers of wildlife population declines and extinction risk. The International Union for Conservation of Nature (IUCN) Red List of Threatened Species (IUCN, 2007) is the authority on global population trends for species, as well as criteria for a species to be listed as threatened with extinction. Pathogens shared with wild or domestic animals cause more than 60% of infectious diseases in man (Taylor *et al.,* 2001). COVID-19/SARS-CoV-2 is a pandemic disease that causes huge economic loss and leads frustration for human as worldwide. Hence, identifying the possible zoonotic emergence and the exact mechanism responsible for its initial transmission will help us to design and implement appropriate preventive barriers against the further transmission of COVID-19/SARS-CoV-2. Therefore, the objectives of this review are:

- To Review The Possible Zoonotic Emergence Of COVID-19/SARS-Cov-2 And Associated Zoonotic Links Between Human And Animal.

- To Review Associated Risk Factors For Emergence Of COVID-19/SARS-Cov-2.

- To Review Possible Prevention And Control Strategies Used For The Disease.

- To Review The Possible Challenges For Prevention And Control Of The Disease.

2. CORONA VIRUS

Coronaviruses were identified in the mid-1960s and known to infect humans and other animals, including birds and mammals. Epithelial cells in the respiratory and gastrointestinal tract are the primary target cells. Due to these characters, viral shedding occurs via these systems and transmission can occur through different routes, i.e., fomites, airborne or fecal-oral. To date, seven corona viruses have been shown to infect humans. Common human corona viruses *Beta corona virus* HCoVOC43 and HCoV-HKU1, as well as Alpha corona virus HCoV-229E, cause common colds and severe lower respiratory tract infections in infants and elderly, while *Alpha corona virus* HCoV-NL63 is found to be a significant cause of (pseudo) croup and bronchiolitis in children (Biscayart *et al.,* 2020).

Corona viruses (CoV) are a family of RNA (ribonucleic acid) viruses. They are called corona viruses because the virus particle exhibits a characteristic 'corona' (crown) of spike proteins around its lipid envelope. CoV infections are common in animals and humans. Some, but not all strains of CoV can be transmitted between animals and humans. A wide range of animals is known to be the source of corona viruses. For instance, the Middle East respiratory syndrome corona virus (MERS-CoV) originated from camels and the Severe Acute Respiratory Syndrome (SARS) originated from civet cats. In humans, CoV can cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (caused by MERS-CoV), and Severe Acute Respiratory Syndrome (caused by SARS-CoV)(Federation of Veterinarians of Europe, 2020).

Coronaviruses are enveloped, positive stranded RNA viruses of mammals and birds. These viruses have high mutation and gene recombination rates, making them ideal for pathogen evolution.1 In humans, coronavirus is usually associated with mild disease, the common cold. Previous emerging novel coronaviruses, such as SARS-CoV and Middle East respiratory syndrome corona virus (MERS-CoV), which emerged in the Middle East in 2012, were associated with severe and sometimes fatal disease. MERS-CoV was less pathogenic than SARS-CoV, with the most severe infections mainly in individuals with underlying illnesses. Clinically and epidemiologically, the contemporary 2019-nCoV in China seems to resemble SARS-CoV. The genome of 2019-nCoV also appears most closely related to SARS-CoV and related bat coronaviruses.2 The infection has now spread widely, with phylogenetic analysis of the emerging viruses suggesting an initial single-locus zoonotic spillover event in November, 2019,3 and subsequent human to-human transmission.

The SARS epidemic in 2003 was followed soon after by avian influenza H5N1 in 2006, centered on the Asian continent and Middle East. Other surprising viral zoonoses that have caused serious disease include Nipah encephalitic virus in pigs and humans in southeast and south Asia

in 1999–2014, and large-scale Ebola virus epidemics in 2014–16 and 2018–19 in west and central Africa. Taken together, these events ring alarm bells about disease emergence in the 21st century, and the importance of human diseases originating from indiscriminate contacts with infected animals.

The emergence of novel corona virus (CoVs) and their wide host range may be due to instability of the replicase enzyme, RNA dependent RNA polymerase, polybasic furin cleavage site, and O-linked glycans, lack of proofreading mechanism, a higher rate of mutations in the RBD of spike gene and genetic recombination (Su *et al.,* 2016; Chen 2020; Patel and Jernigan, 2020). Researchers also showed that SARS-CoV and SARSCoV-2 (2019-nCoV) both use ACE2 as a similar cell entry receptor (Zhou *et al.,* 2020a). Due to the mutation in the RBD region of S gene of CoVs, the hostrange get expanded to infect other host species of animals or humans, pathogenicity and transmissibility of virus may further get altered and increased, becoming a matter of global worry (Chen, 2020; Patel and Jernigan, 2020).

Animal CoVs have been known since late 1930s. Before the first isolation of HCoV-229E strain B814 from the nasal discharge of patients who had contracted common cold, different CoVs had been isolated in various infected animals, including turkey, mouse, cow, pig, cat and dog [21-26]. In the past decades, seven HCoVs have been identified. A brief summary of the history of HCoV discovery in chronological order (Table 1) would be informative and instructive.

Table1: *Characteristics of the Emergent Zoonotic Corona viruses of the Century Responsible for Severe Acute Respiratory Syndrome (SARS-CoV), Middle Eastern Respiratory Syndrome (MERS-CoV) and SARS-2-CoV-19 (COVID 19)*

Epidemiological, clinical and biological characteristics	SARS-CoV	MERS-CoV	SARS CoV-2 (Covid - 19)
Distribution	Pandemic	Epidemic	Pandemic
Origin	Guangdong province, south china	Saudi Arabia	Wuhan, Hubei province, china
Naural reservoir	Bat	Bat	Bat
Viral sequence	Weiss and Navas-Martin 2005; Li et al.,2006	Song et al., 2019, Ramadan and Shaib 2019).	89% similarity with SARS-CoV, 64% with MERS-CoV Lu et al., 2020; Benvenuto et al., 2020
Probable/suspected intermediary host	Palm-civet Others**	Camel/dromedary llama, alpaca, market civets	Not-known Pangolins?
Transmission	Human-to human spread	Human-to human spread Other	Human-to human spread Other
Pathogenicity (involved receptor)	ACE-2§	DPP4 or CD26§§	ACE-2§
Total number of infected persons in the World	More than 8,098	2,490^	More than 207,800
Incubation period	2-7 days	7-12 days	2-14 days
Global deaths	774	858^	More than 8,657
Main symptoms	influenza-like symptoms, fever, chills, dry cough, shortness of breath	Fever, chills, cough, shortness of breath, myalgia, and malaise	influenza-like symptoms, fever, dry cough, headache, myalgia malaise, diarrhoea, shortness of breath
Lethal disease	Acute Respiratory Distress Syndrome (ARDS)	Rapidly progressing pneumonia,possible renal failure	Severe pneumonia†
Patients facing life-threatening and or death	Elderly and persons with pre existing conditions	Elderly and persons with pre existing conditions	Elderly and persons with pre existing conditions
R0 ††	2-5	< 1	1.4-5.5
Case Fatality Rate	9.6%	34.5%	05-3% ¥
Children	5.7%	1%	Infrequently reported ¥¥

Key: Horseshoe bats* (Rhinolophus Hypposideros Bat); raccoon dogs and Chinese ferret-badger**; droplets, via direct person-to-person contact°; close contact with: respiratory secrets, urine, unpasteurized milk, saliva, uncooked meat of camels and/or dromedaries or other camelids°°; ACE-2, Human angiotensin-converting enzyme-2 §; DPP4 or CD-26, Human dipeptidyl peptidase §§; reported by WHO from 2012 through 30 November 2019 ^; 14.9% of those who have comorbidity such as hypertension, diabetes, cancer, immunosuppression, hearth or renal failure†; R0; viral transmissibility†† (if R0 is less than 1, each existing infection causes less than 1 new infection); in Wuhan, 2.9-3-5%; 0.4% in rest of China ¥; no death under 10 year

2.1. Sars Cov2 (Covid 19)

SARS-CoV-2 is classified as a novel *Betacoronavirus* belonging to the *Sarbecovirus* subgenus of Coronaviridae family. This virus has never previously been identified in humans. Never the less, information coming from the scientific world is constantly evolving. The novel coronavirus sequencing enabled the laboratories from different countries to produce specific diagnostic real-time RT-PCR methods for detecting the SARS-CoV-2 infection (Zhu et al., 2020). The genome sequence of SARS-CoV-2 is about 89% identical to bat SARS-likeCoV and 82% identical to human SARS-CoV (Lu *et al.,* 2020). SARS-CoV-2 is reported as using the same cell entry receptor as SARS-CoV (Zhai et al., 2020), ACE2, to infect humans, so clinical similarities between the two viruses are expected, particularly in severe cases. Phylogenetic analysis of novel SARS-CoV-2 has shown that it is a product of recombination with previously identified bat coronaviruses. However, significantly, SARS-CoV-2 is only closely related to the specific bat SARS-like coronavirus isolated from *Rhinolophus sinicus* in 2015 in China (MG772934.1).

The SARS-CoV-2 origin is still discussed although the initial cases have been associated with the Huanan South China Seafood Market. As with SARS-CoV and MERS-CoV, SARS-CoV-2 almost certainly originated in bats (Zhai *et al.,* 2020). The most recent analysis of the SARSCoV-2 genome has found that it shares 96 percent of its RNA with a coronavirus which was previously identified in a specific bat species in China (Benvenuto *et al.,* 2020; Giovanetti *et al.,* 2020). Such hosts may

increase the viruses' genetic diversity by facilitating greater numbers of different mutations. Although SARS-CoV-2 can cause a severe respiratory illness like SARS and MERS, evidence from clinics has suggested that this virus is generally less pathogenic than SARS-CoV, and much less than MERS-CoV (Velavan and Meyer, 2020).

The Covid-2019 pandemic emerged as an outbreak rapidly and spread to China and other countries, including the United States, killing at the time of writing 3,194 people with more than 81,000 confirmed cases of infection of Chinese nationality (99%), along with approximately 5,415 deaths in predominantly elderly people (age range 58-101 years) and more than 126,000 confirmed cases in 166 countries (Jernigan, 2020). In just 2 and half months SARS-CoV-2 has caused more victims than SARS-CoV in about 8 months and MERSCoV in eight years (Hui *et al.,* 2020).

2.1.1. Clinical signs of covid 19

Coronaviruses can cause severe diseases in humans and animals, as has been stated recently by Biscayart et al. 2020).

- **In animal:** Coronaviruses (CoVs) infect man as well as domestic and wild animal species and usually infections remain sub-clinical in most cases (Ji *et al.,* 2020a; Li *et al.,* 2020a; Salata *et al.,* 2020). Among the four genera in the Coronaviridae family, Alpha corona virus and Beta corona virus usually infect mammals and have probable bat origin, while Gamma corona virus and Deltacoronavirus infect birds, fishes, and mammals and are assumed to have swine origin (Woo *et al.*, 2012; Hu *et al.* 2017; Cui *et al.* 2019). The genus Beta corona virus possess potential zoonotic pathogens like SARS-CoV and MERS-CoV which have bats as primary host and palm civet cat and dromedary camels as intermediate hosts, respectively (Wang and Eaton, 2007; Ar Gouilh *et al.,* 2018; Ramadan and Shaib, 2019). The clinical form varies from enteritis in cattle, horses and swine, upper respiratory tract disease in cattle, dogs, felines, and poultry, and common cold to highly fatal respiratory infections in humans (Dhama *et al.,* 2020a, 2020b).

- **In human**: An early study conducted in January 2020, among 41 patients (median age 49 years), positive for SARS-CoV-2 infection (the causative agent of COVID-

19), found that half of them had underlying diseases, including diabetes 20%, cardiovascular disease 15%, and hypertension 15%. Their symptoms were mainly fever 98%, cough 76%, and fatigue 44%. The COVID-19 severe complications in such patients included respiratory distress syndrome 29%, RNA aemia 15%, acute cardiac injury 12%, and other secondary infections. Of the total infected patients, 32% were admitted to an Intensive Care Unit (ICU). The death rate was 15% (Bastola et al., 2020).

Patients with mild symptoms were reported to recover after 1 week while severe cases were reported to experience progressive respiratory failure due to alveolar damage from the virus, which may lead to death (Li et al., 2020). Cases resulting in death were primarily middle-aged and elderly patients with pre-existing diseases (tumor surgery, cirrhosis, hypertension, coronary heart disease, diabetes, and Parkinson's disease) (Li et al., 2020).

2.1.2. Diagnosis

For patients with suspected infection, the following procedures have been suggested for diagnosis: performing real-time fluorescence (RT-PCR) to detect the positive nucleic acid of SARS-CoV-2 in sputum, throat swabs, and secretions of the lower respiratory tract samples [(Li et al., 2020; NHC and CDC 2020.).

2.1.3. Treatment

There is no specific treatment for this disease so the approach used to treat patients with coronavirus-related infections is to treat the clinical symptoms (e.g. fever). Supportive care (e.g. supportive therapy and monitoring oxygen therapy, fluid management and antivirals) can be highly effective for those infected.

2.1.4. Prevention and control

In accordance with advice offered by the WHO, as a general precaution, when visiting live animal markets, wet markets or animal product markets, general hygiene measures should be applied, including regular hand washing with soap and potable water after touching animals and animal products, avoiding touching eyes, nose or mouth with hands, and avoiding contact with sick animals or spoiled animal products. Any contact with other animals possibly living in the market (e.g., stray cats and dogs, rodents, birds, bats) should be strictly avoided. Attention should also be taken to avoid contact with potentially contaminated animal waste or fluids on the soil or structures of shops and market facilities (Federation of Veterinarians of Europe, 2020).

Standard recommendations issued by WHO to prevent infection spread include regular hand washing, covering mouth and nose when coughing and sneezing, and thoroughly cooking meat and eggs. Avoid close contact with anyone showing symptoms of respiratory illness such as coughing and sneezing. Raw meat, milk or animal organs should be handled with care, to avoid cross contamination with uncooked foods, as per good food safety practices. Further recommendations from WHO (https://www.who.int/health-topics/coronavirus#)

Efforts for rapid diagnosis, strict vigilance, appropriate isolation, and quarantine procedures to halt its further spread, enhanced surveillance and monitoring, strengthening of medical facilities and intensive care units, networking programs, rapid communication and providing updates, knowledge awareness of its public health risks to the general population, high efforts to develop effective vaccines and therapeutics/drugs are being explored optimally. International collaborative efforts and readiness to tackle further heightened emergency to a level of pandemic potential along with following suitable One health approach to combat this emerging virus haunting the lives of billions of human population are being followed effectively (Bonilla-Aldana et al., 2020; Dhama et al., 2020a, 2020c; Malik et al., 2020b.

Vaccines appear to be the long-lasting solution for the COVID-19 pandemic. However, currently, there are no vaccines available against it (Shang et al., 2020; Chen et al., 2020). Clues are being taken from the viral structures, pathogenesis, and related corona viruses (Shang et al., 2020). Various vaccines are being evaluated by different institutes and companies (Shang et al., 2020), with a few under trials. Moderna, Cambridge, Ma, USA, a biopharma company, started with the mRNA-1273 vaccine in collaboration with CanSino, Hong Kong Special Administrative Region, China (Flanagan, 2020). The University of Alabama at Birmingham (UAB), Birmingham, Al, USA, in coordination with Altimmune Inc., Gaithersburg, Md, USA, is developing an intranasal vaccine against COVID-19 and named it as AdCOVID on the pattern of pandemic influenza vaccine and inhalation anthrax vaccine (Hansen et al., 2020).

There is a need for strengthening infrastructure and capacity building with a trained workforce, hospital, health workers to identify the SARS affected patient with the isolation of patients after being doubted for COVID-2019. To apply any prevention, measure the first and foremost step is to diagnose the case with accuracy and speed. While confirming any deadly case, the guidelines of Centers for Disease Control and Prevention (CDC) must be adopted. As the suspected case is a good source of nosocomial spread, the health workers must follow all the precautionary practices while handling the COVID-2019 case. Notably, a facility with negative air pressure is recommended for keeping confirmed patients of SARS-CoV-2. The applications of telemedicine having tele-visits and supervision, monitoring, interpretation, and consultation (Serper and Volk, 2018) have proven effective in mitigating chronic diseases. The tele-model has been applied on present-day COVID-19 pandemic, especially in the remote areas having limited medical backups saving both manpower as well as resources (Au, 2020).

Further spread of SARS-CoV-2 can be controlled by immediate isolation of confirmed cases along with contact tracing. According to the analysis made by using transmission models, the COVID-19 outbreak could be controlled within three months by following active contact tracing in combination with the isolation of infected individuals (Hellewell et al., 2020). It is not the first time that live-animal markets in China have been identified as the epicenter of emerging novel zoonotic diseases. For preventing the likelihood of another zoonotic outbreak, closure of all the live-animal markets is a necessity (Peeri et al., 2020).

3. ANIMALS AND ZOONOTIC LINKS OF SARS-COV-2/COVID 19

Amongst CoVs, recent zoonotic ones such as SARS-CoV, MERS-CoV, and SARS-CoV-2 gained higher importance due to the severity of disease in humans and their global spread (Rothan and Byrareddy, 2020). SARS-CoV-2 has features that are similar to both SARS-CoV/MERS-CoV and the four community-acquired HCoVs. It is highly transmissible like community-acquired HCoVs, at least for the time being. However, it is more pathogenic than community-acquired HCoVs and less pathogenic than SARS-CoV or MERS-CoV. The emergence of novel CoVs and their wide host range may be due to instability of the replicase enzyme, RNA dependent RNA polymerase, polybasic furin cleavage site, and O-linked glycans, lack of proofreading mechanism, a higher rate of mutations in the RBD of spike gene and genetic recombination (Su et al., 2016; Chen, 2020; Patel and Jernigan, 2020). Researchers also showed that SARS-CoV and SARSCoV-2 (2019-nCoV) both use ACE2 as a similar cell entry receptor (Zhou et al., 2020a). Due to the mutation in the RBD region of S gene of CoVs, the host range get expanded to infect other host species of animals or humans, pathogenicity and transmissibility of virus may further get altered and increased, becoming a matter of global worry (Chen, 2020; Patel and Jernigan, 2020).

While searching the source of SARS-CoV-2, it was observed that the initially infected individuals had a common exposure spot. It was South China Wet Seafood wholesale market in Wuhan, Hubei Province, China, where restaurants are famous for offering various small and large domestic animals, wild animals, and live animals including poultry, rabbits, bats, snakes, pangolins, turtles, hedgehogs, badgers, and marmots for human consumption (Hu et al., 2015; Hui et al., 2020; Ji et al., 2020b; Liu et al., 2020a, 2020b; Lu et al., 2020b; Wang et al., 2020; Wu et al., 2020b). The initial inferences from Wuhan Seafood Market hypothesised animal source attachments and wild animals for the spillover of SARS-CoV-2. Findings indicated the probability of a zoonotic basis, as CoVs keep on circulating between various animal species, vertebrate, and humans due to a broad host range (Figure 1). It was assumed that SARS-CoV-2 got initially transmitted from animals to humans, followed by maintaining via human-to-human transmission (Hui et al. 2020; Ji Figure 1. Zoonotic links of SARS-CoV-2. Bat has been reported as the reservoir source of SARS-CoV-2. The intermediate host is not yet elucidated clearly and presently snake and/or pangolins are reported to the intermediate host. Reports regarding the transmission of SARS-CoV-2 from human to animal have been speculated. Study also shows that SARS-CoV-2 replicate poorly in pig, chicken and duck while ferrets and cats are susceptible (Nishiura et al., 2020).

For the time being, it is understood that the SARS-CoV-2 is closely related to the bat corona virus that was isolated from horseshoe bat, the species of bat that is considered to be a maintenance host of previous SARS-related CoVs. Hence, SARS-CoV-2 might have

emerged from the sequential recombination occurring between the precursors of SARS-related corona viruses. Based upon codon usage bias snake SARS-CoV-2 was proposed as the reservoir of SARS-CoV-2 (Ji *et al.,* 2020a). However, later this proposal was contradicted by several researchers. This is the reason for suspecting the presence of an intermediate animal host that is responsible for the zoonotic spill-over to humans (Weiss and Leibowitz, 2011; Murdoch and French 2020).

Similarly, not only from bats, but corona virus associated with SARS was transmitted from human beings to pigs (Chen *et al.,* 2005). It is pertinent to mention that pigs had been predominant species for the evolution of many new strains of Influenza A virus in the past when present in close association with avian and human species and as bat CoVs are infecting pigs, the possibility of evolution of any new virus involving influenza and corona cannot be excluded including the current scenario of growing SARS-CoV-2 cases, such hypothesis needs explorative studies (Brown 2001; Dhama *et al.,* 2012; Malik et al., 2020a). Provided conditions, at any point in time, pigs which serve as a mixing vessel of influenza viruses (Ma *et al.,* 2009) need to be taken with caution as they remain in proximity with man and domestic-sylvatic cycles involving contact with many wild animals and then the situation may get worsen (Ma *et al.,* 2008).

However, for the time being, findings of Shi *et al.* (2020) have not revealed significant susceptibility of pigs to SARS-CoV-2. Bats, civets, and camels have been the recent animal carriers of human CoV infections (Cui et al., 2019). Of the latest, bats (Wu et al. 2020b) and pangolins (Zhang *et al.,* 2020a) are considered to be the probable sources of origin of SARS-CoV-2 (Andersen et al. 2020). Still, actual intermediate host and nature of emergence are yet to be explored. Two scenarios of the emergence of SARS-CoV-2 are being projected. First is that natural selection of viruses that may have occurred in an animal host before transmission to humans and the second is that natural selection of viruses has occurred in humans after zoonotic transmission (Andersen *et al.,* 2020). Advanced studies involving cell culture or animal models can help in clarifying these hypotheses (Ge *et al.*, 2013; Andersen *et al.,* 2020).

3.1. Suspected Reservoir Host for Sarscov-2/ COVID 19

3.1.1. Bats

Bats are known to be reservoir hosts for several human viruses, including rabies, Marburg, Nipah, Hendra, and the severe ats are known to be reservoir hosts for several human viruses, sever acute respiratory syndrome coronavirus (SARS-CoV) (Calisher *et al.,* 2006). Bats are ideal reservoir hosts for CoVs, as viruses are persistently present in bats and being asymptomatic. They travel across the forests in search of food and transmit the virus to a variety of hosts they come in contact with (Fan *et al.,* 2019). In the current COVID-19 pandemic, laboratory findings confirmed that SARSCoV-2 is also 96% identical to the bat CoV at the genomic level, and hence bats may be the primary source of this zoonotic spillover (Tang *et al.*, 2006; Rodriguez-Morales *et al.,* 2020b; Zhou *et al.,* 2020a).

3.1.2. Pangolins

Not only from bats, corona virus has been isolated from Malayan Pangolins also, and RBD in S protein of SARS-CoV-2 was nearly the same as that of Pangolin-CoV, and thus pangolins might be the intermediate host of SARS-CoV-2 (Xiao *et al.,* 2020). This is also supported by the findings of Zhang et al. (2020a). Interestingly, the coronavirus isolated from pangolins (SRR10168377 and SRR10168378) did not have the RRAR motif. The SARS-CoV-2 virus isolated from the infected individuals showed higher similarity to the Beta CoV/bat/Yunnan/RaTG13/2013 virus compared to the ones that were isolated from the pangolins (Li *et al.,* 2020b).

Pangolins are highly sought for their scales, which are used in traditional Asian medicine, as well as their meat, which is considered a delicacy in some Asian and African communities. As a result, they have become the most trafcked animal in the world, with these high levels of trade threatening their survival. International trade in pangolins has been illegal since 2016, but the trade has by no means ceased(https://cites.org/sites/default/fles/eng/co m/sc/69/E-SC69-57-A.pdf).

Several recent studies based on metagenomic sequencing have suggested that a group of endangered small mammals known as pangolins (*Manis javanica*) could also harbor ancestral beta-CoVs related to SARS-CoV-2 (Lam et al., 2020). These novel pangolin CoV genomes share 85-92% nucleotide sequence homology with SARS-CoV-2. However, they are equally closely related to RaTG13 with about 90% identity at the level of nucleotide sequence. They cluster into two sub-lineages of SARSCoV-2-like viruses in the phylogenetic tree, one of which share a more similar receptor binding domain (RBD) with SARS-CoV-2, with 97.4% amino acid sequence identity (Lam et al., 2020).

In stark contrast, the RBDs of SARS-CoV-2 and RaTG13 are more divergent, albeit a higher degree of sequence homology genome-wide. An earlier study on diseased pangolins also reported the detection of viral contigs from lung samples, which turn out to be similarly related to SARS-CoV-2 (Liu et al., 2019). This study adopted different assembly methods and manual curation to generate a partial genome sequence comprising about 86.3% of the full-length viral genome (Liu et al., 2019). We cannot exclude the possibility that pangolin is one of the intermediate animal hosts of SARS-CoV-2 (Lam et al.. 2020). However, currently there is no evidence in support of a direct pangolin origin of SARS-CoV-2 due to the sequence divergence between SARS-CoV-2 and pangolin SARS-CoV-2-related beta-CoVs.

3.1.3. Canines and Felines

Till now, SARS-CoV-2 infection has been noticed in two dogs; both are reported from Hong Kong (Almendros 2020a). The first case was reported in a 17-year-old Pomeranian dog that gave positive RTPCR results in both oral and nasal samples (Almendros, 2020a; American Veterinary Medical Association, 2020). Even though the initial serological test gave a negative result, the blood samples taken in the later stages gave weak positive results. This might be due to the fact that formation of antibody can take 14 days or more (Almendros and Gascoigne, 2020b). A report of seroconversion in dogs indicates that the animal has produced antibodies against SARS-CoV-2. This is suggestive of a weak infection in the dog that resulted in an immune response. Hence, the findings are suggestive of a true infection in dogs caused by human-to-animal transmission (Almendros and Gascoigne, 2020b). Similarly, another case of SARS-CoV-2 infection was reported in a German Shepherd Dog in Hong Kong. It is interesting to note that both the cases of canine SARS-CoV-2 infections were reported in dogs that were living in close contact with SARS-CoV-2 positive owners (American Veterinary Medical Association, 2020). Currently, there is no substantial evidence that dogs get SARS-CoV-2 infection, or can transmit this virus to human beings (Almendros, 2020a).

Two cats, one from Belgium and another from Hong Kong, were also tested positive for SARS-CoV-2 (American Veterinary Medical Association, 2020). The scientists from Harbin Veterinary Research Institute have reported that cats can get infection with SARSCoV-2 under experimental conditions and can transmit to other susceptible cats that are housed together (Mallapaty, 2020; Shi *et al.,* 2020). The findings are based on experimental inoculation and may not be accurate in natural conditions. None of the infected cats showed any signs of illness, indicating the low potential for transmitting the infection (Mallapaty, 2020). A serological study was conducted among the cats of Wuhan that observed the presence of SARS-CoV-2 neutralizing antibodies. This indicates that cats can get SARS-CoV-2 infection under natural conditions resulting in an antibody response (Zhang *et al.,* 2020b). However, among the cats that tested positive, a higher titre of neutralizing antibodies was seen in the cats that were living in close contact with SARS-CoV-2 positive owners (Zhang *et al.*, 2020b). Recently, a Malayan tiger maintained in the Bronx Zoo of New York City, NY, USA was also tested positive for SARS-CoV-2. The "Big cat" is suspected to be infected by SARS-CoV-2 positive asymptomatic zookeeper. These carnivores were tested for SARS-CoV-2 when they started showing signs of mild respiratory illness (United States Department of Agriculture, 2020).
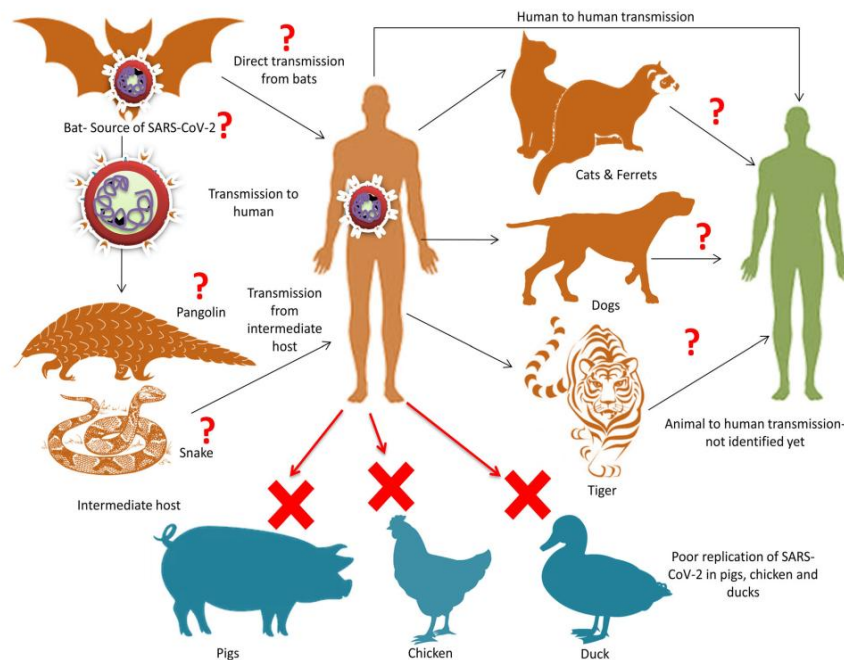
Figure 1: *Zoonotic links of SARS-CoV-2. Bat has been reported as the reservoir source of SARS-CoV-2. The intermediate host is not yet elucidated clearly and presently snake and/or pangolins are reported to the intermediate host. Reports regarding the transmission of SARS-CoV-2 from human to animal have been speculated. Study also shows that SARS-CoV-2 replicate poorly in pig, chicken and duck while ferrets and cats are susceptible (Nishiura et al., 2020).*

The culinary habits of Chinese people involve the consumption of wild animal meat. The common motivation that is responsible for the human consumption of wild animal meat in China is due to their believed medicinal value as well as the health promoting effects associated with the consumption of certain wild game animal meats and their products (Harypursat and Chen 2020). The circumstantial evidence that links the first case of COVID-19 to the Huanan South Seafood Market that sells various exotic live animals and our previous knowledge that coronaviruses are animal-derived made us conclude the possible zoonotic transmission in SARS-CoV-2. Nevertheless, it is too early to jump into conclusions since our knowledge of the primary source of infection is limited (Jalava 2020). Identifying the origin of SARS-CoV-2 will help us to unravel the exact mechanism responsible for its initial transmission. After attaining a remarkable progress in developing field oriented as well as high accuracy lab-based diagnostics, much attention has been paved upon developing effective vaccine and therapeutics for blocking person-person transmission, old age infections and health-care workers infection (Chen et al. 2020). That is critical for developing appropriate preventive and control strategies against the fast-spreading SARSCoV-2 infection. Looking at the beneficial propositions of hydroxychloroquine a

multicentric randomised study is underway to assess its effectiveness as a prophylactic measure in curbing secondary SARS-CoV-2 infections as well as associated clinical symptoms progression reducing overall the spread of the virus (Mitja and Clotet, 2020).

4. RISK FACTORS FOR EMERGENCE OF COVID- 19

Sequence comparison of civet viruses suggested evolution was ongoing; this was further supported by high Seroprevalence of antibodies against SARS-CoV among civet sellers, suggesting previous cross-species transmission events without necessarily human-to-human transmission.[7,8] Similarly, early Ebola virus was mostly associated with bush meat and its consumption in Africa; Nipah virus is associated with date palm sap, fruit, and domestic pig farms; MERS is associated with the camel livestock industry; and H5N1 arose from viral evolution in domestic and wild birds, to ultimately bring all these cases to humans. The 2019-nCoV is another virus in the pipeline that originated from contact with animals, in this case a seafood and animal market in Wuhan, China (Guan *et al.,* 2003; Kan *et al.,* 2005).

4.1. Climate Change

The drivers of zoonotic diseases are changes in the environment, usually the result of human

development or climate change. Example: Bat-associated viruses, thought to be the cause of the latest corona virus, emerged from the loss of bat habitat from deforestation and agricultural expansion. Logging, mining, road building in remote places, dam building, irrigation, coastal development, rapid urbanization, population growth all lead to biodiversity loss. Another is fire, such as the Amazon blazes last year. In its aftermath, altered habitat can yield less food, sending foraging wildlife into contact with nearby humans, creating vectors for zoonotic bacteria, viruses and parasites. As the World Economic Forum (WEF) recently noted, the world has lost 60 percent of all wildlife in the last 50 years while the number of new infectious diseases has quadrupled in the last 60 years (Joel, 2020).

Climate change, altering and accelerating the transmission patterns of infectious diseases. Already, the roughly 1 degree Celsius rise in mean global temperatures is altering the abundance, genetic composition, behavior and survival of some species. And it's a vicious, downward cycle: The decline of species threatens the ecosystem services nature provides that, among other things, help to regulate the climate. The focus on biodiversity builds on a growing movement toward nature-based solutions, which harness the power of ecosystem services to mitigate effects of the climate crisis, unsustainable food systems, water pollution and other environmental challenges. Companies already were leaning into the topic, led by a global coalition called Business for Nature. It was to be a packed schedule of meetings and negotiations, all focused on nature. The links between pandemics and biodiversity are becoming better understood and appreciated. So much so that we're seeing the growth in an emerging discipline, planetary health, focusing on the connections among the well-being of humans, other living things and nature's ecosystems(Joel, 2020).

4.2. Human –Animal Interaction

Repeated human-animal interactions either in the market or in the animal industry without using proper environmental biosecurity were considered as the significant risk factors for the emergence of zoonotic diseases, particularly in the rural communities of southern China (Daszak 2020). After these reports, China has put temporarily ban on the sale of wildlife and trading of bats following CoV infection. Furthermore, Wuhan animal food market is also

kept closed so that further zoonotic transmission of SARS-CoV-2 and evolution of any new viral variant can be prevented. It is also recommended to avoid any contact with farm or wild animals without the use of personal protective equipment (Benvenuto *et al.,* 2020).

Now there is need to draft surveillance strategies and preventive guidelines to have in-depth analysis of bat origin Betacoronavirus, especially in the Rhinolophus bat family as in the past SARS, MERS, and now SARSCoV-2 epidemic have created panic, and from epidemic, it has turned to pandemic (Daszak *et al.,* 2020). In a nutshell, bats appears as the natural reservoir or source of origin for SARS-CoV-2 (Li *et al.,* 2020a) that causes zoonotic infection in humans through an intermediate host yet to be deciphered with recent investigations on pangolins, ferrets and possibly snakes. However, the future explorations might reveal the actual intermediate host of SARS-CoV-2 responsible for zoonotic transmission (Almendros 2020a; Zhang *et al.,* 2020a).

4.3. Human Cultural and Traditional Practices

Some researchers opined that traditional cooking practices of China are also responsible to some extent for the occurrence of novel CoV infection in humans because as per the Chinese food customs live-slaughtered animals are considered more nutritious, but at the same time, people get exposure to possibly all/any types of pathogens (SARS-CoV, Nipah virus, Hepatitis A virus, Hepatitis E virus, Norovirus, Rotavirus, Highly Pathogenic Avian Influenza virus) present in the offered food items (FAO/WHO 2008).

It was South China Wet Seafood wholesale market in Wuhan, Hubei Province, China, where restaurants are famous for offering various small and large domestic animals, wild animals, and live animals including poultry, rabbits, bats, snakes, pangolins, turtles, hedgehogs, badgers, and marmots for human consumption (Hu *et al.,* 2015; Hui *et al.* 2020; Ji *et al.* 2020b; Liu *et al.* 2020a, 2020b; Lu *et al.* 2020b; Wang *et al.* 2020; Wu et al. 2020b). The initial inferences from Wuhan Seafood Market hypothesised animal source attachments and wild animals for the spillover of SARS-CoV-2.

In China, bats are not only sold for food purposes in live-animal markets, but they are an integral part of Traditional Chinese Medicine (TCM) and wild bats are used to obtain bat-

derived compounds. Although bats have commercial value, they pose a severe risk of acquiring any new zoonotic infection (Riccucci 2012; Wassenaar and Zou 2020).

4.4. Pathogen Mutation

The SARS corona virus HKU1 (CoV HKU1), isolated from patients in Hong Kong from 2003 to 2005, was divided into three clusters: genotypes A, B, and C. However, the phylogenetic analysis of different genomic regions showed that the nucleotide sequences of putative proteins (nsp) 4 to nsp6 of the genotype A strains were clustered with the genotype B strains, while nsp7 and nsp8 and from nsp10 to nsp16 from the genotype A strains were clustered with the genotype C strains, suggesting that genetic recombination between genotypes A and B generated genotype C. This genetic recombination in corona viruses could easily generate novel corona virus genotypes or species that could cross host species barriers and cause the emergence of major zoonotic diseases (Woo *et al.,* 2006)

Table2: *Factors affecting infectious disease emergence (Rabozzi et al., 2012)*

Factor	Specific factor	Disease emergence
Ecological changes	• Climate change • Changes in water ecosystems • Deforestation/reforestation • Flood/drought • Famine	• Rift Valley fever • Argentine haemorrhagic fever, Hantaan or Korean haemorrhagic fever • Hantavirus pulmonary syndrome in the southwestern United States of America
Human behavior international travel and commerce	• War • Population migration (movement from rural areas to cities) • Economic impoverishment • Urban decay • Factors in human behaviour (such as the commercial sex trade, outdoor recreation and activities…) • Worldwide movement of goods and people • Air travel	• HIV and other sexually transmitted diseases • Dengue • Rat-borne hantaviruses • Introduction of cholera into South America, dissemination of O139 (non-O1) cholera bacteria (via ships)
Technology and industry Developments (food)	• Globalization of food supplies • Changes in food processing and packaging	• Food production processes: haemolytic uraemic syndrome certain *Escherichia coli* strains from cattle contaminating meat and other food products), bovine spongiform encephalopathy, Nipah virus (pigs), avian influenza, severe acute respiratory syndrome (probably)
Technology and industry Developments (health care)	• New medical devices • Organ or tissue transplantation • Drugs causing immunosuppression • Widespread use of antibiotics	• Ebola • HIV • Creutzfeldt-Jakob
Microbial adaptation and change	• Microbial evolution as a response to selection in the environment	• 'Antigenic drift' in influenza virus • Possibly genetic changes in severe acute respiratory syndrome, coronavirus in humans • Development of antimicrobial resistance (HIV, antibiotic resistance in numerous bacterial species, multi-drug-resistant tuberculosis, chloroquine-resistant malaria)
Breakdown of the host's defenses	• Immunodepression • Imunnodeficiency resulting from HIV infection	• *Mycobacterium bovis* • *Listeria monocytogenes* in humans
Breakdown in public health or control measures	• Lack ofor inadequate sanitation and vector control measures	• Tuberculosis (mainly in the United States of America) • Cholera in refugee camps in Africa, resurgence of diphtheria in the former Soviet republic and Eastern Europe in the 1990s

HIV: human immunodeficiency virus.

5. CHALLENGES OF MANAGING ZOONOTIC INFECTIONS (LIKE COVID 19)

Many viral pathogens causing emerging zoonotic infections in humans originated from animals (specifically wildlife) or from products of animal origin. Knowledge of extra-human reservoirs of these pathogens remains essential for understanding the epidemiology and potential control measures of these zoonotic diseases. There is also inadequate transparency regarding timely reporting of emerging zoonotic infections to WHO or any other international agency that is mandated to investigate and respond appropriately for global health security. Often medical authorities in the countries deny the existence of human cases, making it difficult for these agencies to understand the epidemiology, disease progression and use the opportunity to understand which methods work and do not work for control of these diseases in different settings(Malik *et al.,* 2012).

Globalization has resulted in the unparalleled passage of people, animals and goods across national borders, which in turn has fuelled the international spread of zoonotic infections. Many of the zoonoses are trans-boundary diseases, they spread across borders from their origin, to impact on trade, commerce, tourism and consumer confidence with devastating economic consequences. The experiences drawn from the region have shown that most of the zoonotic infection outbreaks have occurred in remote areas, making it sometimes impossible to provide public health services to these hard-to-reach populations (Jones *et al.,* 2008).

The detection and diagnosis of the disease has been considerably delayed due to difficulties in deploying teams for field investigation, lack of appropriate and safe sample shipment mechanism, lack of appropriate laboratory diagnostic facilities on-site or in-country, and insufficient capacities of the countries to plan, mobilize and implement appropriate control measures in such settings and to monitor the progress of control measures in geographically dispersed areas. The detection of these disease threats require functional sub-national surveillance capacity and therefore the need for investing in strengthening subnational outbreak surveillance and response capacities in the countries frequently affected by these diseases(Madani *et al.,* 2003).

The major limitation in controlling the zoonotic infections in the region include the lack of effective collaboration between the animal and human health sectors under the concept of "One Health" approach, which links the human with the animal health sector integrating the animal and human disease surveillance and response system that could, otherwise have helped controlling the zoonotic infections in animal reservoirs, enable early outbreak detection, and prevent deadly epidemics and pandemics (Malik et al., 2012).

6. CONCLUSION AND RECOMMENDATIONS

SARS-CoV-2 (COVID-19) is pandemic viral disease that affects respiratory system of human. It is suspected that originated from animal species like bat, pagolions, canines and felines as many researches indicated. The disease is transmitted highly from human to human and can cause huge human death and economic loss for the treating the case and controlling the disease.

Based on the above conclusion, the following recommendations were forwarded:

- Research should be continued investigations in this area to elucidate the evolutionary pathway of SARS-CoV-2 in animals, with important implications in the prevention and control of COVID-19 in humans.

- There should be collaboration between human medical professions and veterinary professions to avoid such zoonotic infectious diseases

- Restrictions should be made on factors such as land-use change and deforestation that may increase overlap of wildlife and humans, enhancing zoonotic disease transmission.

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