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# Zoonotic origin of SARS-CoV-2

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***Abstract***
*Zoonotic disease is an infectious illness causes by a pathogen that is moved from an animal body to humans. SARS-CoV-19 is believed to be of zoonotic origin. The virus were detected from throat or rectal swabs of five domestic cats, one of which had antibodies reactive with SARS CoV. SARS-CoV and MERS are not well adapted to human, SARS-CoV2 is believed to have evolved from those viruses. These data are consistent with SARS animal transmission studies which revealed that the respiratory tract of both mice and cats can be experimentally infected with SARS CoV, although infections in both species remained sub-clinical. SARS-CoV-2 shares 96.2% nucleotide homology with a bat CoV isolated from Rhinolophusaffinisbats. About to 75% of emerging infectious diseases are found to be zoonotic in nature. Epidemiological and phylogenetic results have been presented suggesting that SARS evolved from a wild animal host, but no definitive evidence yet exists to prove this hypothesis. The recently emerged SARS in healthy adults surprised the medical community, but veterinary coronavirologists have long recognized the potential of CoVs to produce lethal infections in young animals. Coronaviruses cause a broad range of diseases in both domestic and wild animals, poultry (such as chickens, turkeys etc.) and rodents ranging from mild to severe enteric, respiratory or systemic disease, as well as minor colds in humans.*

***Keywords:*** *Zoonosis, SARS-CoV, SARS-CoV-2, MERS*

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## I. Introduction

Zoonotic disease or Zoonosis is derived from greek (Zoon "animal" and nosos "sickness" is an infectious illness caused by a pathogen (such as Bacterium, Virus, Parasite etc.) that is moved from an animal body to humans [1].

Majority of today's diseases such as Ebola Virus, HIV, and Corona Virus etc. are believed to have been originated from animal hosts. Of about 1,415 pathogens known to infect humans, 61% were found to be zoonotic [2]. Most human diseases originated in other animals; however, only diseases that routinely involve non-human to human transmission, such as rabies, are considered direct zoonosis [3].

Zoonotic diseases can be transmitted from animals via a number of mechanisms, SARS_COVID19 is believed to have been brought to humans from animals through hunting and Bush meat.

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The Human version of this pathogenic illness was identified in December 2019 in Wuhan, China, and has since spread throughout the globe, resulting in global pandemic [4]. The clinical symptoms of thepathogen include fever, cough, fatigue, inability to breathe smoothly and loss of smell and taste[5]. Some of these symptoms may develop to Acute Respiratory Distress Syndrome (ARDS), blood clots etc.[6]. After exposure, the virus may take up five days but it might range from two to fourteen (2-14) days before it shows manifestation [7].

The most recent common ancestor of all coronaviruses is estimated to have existed as recently as 8000 BCE, implying long term coevolution with bat and avian species [8]. The most recent origin ofancestry of alpha-coronavirus line was placed to be around 2400 BCE, ofbeta-coronavirus line at 3300 BCE, of the gamma-coronavirus line at 2800 BCE, and of the delta-coronavirus line at about 3000 BCE. Bats and birds, as warm-blooded animals, are considered to be ideal natural reservoir for the coronavirus gene pool (with bats the reservoir for alpha coronaviruses and beta-coronavirus – and birds the reservoir for gamma-coronaviruses and delta-coronaviruses). The large number and global range of bat and avian species that host viruses has enabled extensive evolution and dissemination of coronaviruses.

The coronaviruses that infect humans were discovered in the 1960s. These viruses were isolated using two distinct techniques[9] by E.C. Kendall, Malcom Byone, and David Tyrrell working at the Common Cold Unit in 1960 isolated from a boy a novel common cold virus B814[10]. In 1965, Tyrrell and Byone successfully cultured the novel virus by passing it through organ culture of human embryonic trachea.The new culturing technique was introduced to the lab by BertilHoorn[11].The isolated virus when inoculated into volunteers showed symptoms of cold and was inactivated by ether which indicated it had a lipid envelope.

Coronaviruses (CoVs) are members of the Coronaviridae family, this familyis composed of a group of enveloped, positive-sensed, single-stranded RNA viruses[12]. The virus contains the largest genome of about 26 to 32 kilo-bases (kb) amongst RNA viruses, they were called"CoVs" because of their crown-like morphology under high power microscope [12].

On the Basis of the difference in their protein arrangement, CoVs can be grouped into four different genera (alpha-CoV, betaCoV, gamma-CoV and delta-CoV), whichalso include the beta-CoV genera that contains most Human Corona Viruses (HCoVs) . Phylogenetic results has shown that bats and rodents are the gene source of most alpha-CoVs and beta-CoVs, and birds are the main reservoir of gamma-CoVs and delta-CoVs[12]. For thousands of years, CoVs have constantly crossed species barriers and some have emerged as important human pathogens[13]. To date, seven human CoVs (HCoVs) are known.

Among them HCoV-229E and HCoV-NL63 are alpha-CoVs. The other five beta-CoVs include HCoV-OC43, HCoV HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 [14]. HCoV-229E, HCoV-OC43, HCoV-HKU1 and HCoV-NL63 usually cause moderate symptoms, such as common cold and/or diarrhea [15]. In contrast, SARS-CoV, MERS-CoV and the newly identified SARS-CoV-2 are very much pathogenic, causing serious lower respiratory tract infection in patients that have higher vulnerability to develop acute respiratory distress syndrome (ARDS) and extrapulmonary symptoms.

**Table I:** Animal coronaviruses: groups, target tissues and types of diseases

| | | | Disease/Infected tissue | | | |
|---|---|---|---|---|---|---|
| **Genetic group** | **Virus** | **Host** | **Respiratory** | **Enteric** | **Other** | |
| I | Human coronavirus-229E | Human | X[a] (Upper) | | | |
| Transmissible gastrointestinal virus | Pig | X (Upper) | x (SI) | | Viraemia | |
| Porcine respiratory coronavirus | Pig | X (Upper/Lower) | | | | |
| Porcine epidemic diarrhoea virus | Pig | | x (SI, Colon) | | | |
| Feline enteric coronavirus | Cat | | x | | | |
| Feline infectious peritonitis virus | Cat | X (Upper) | x (SI) | | Systemic | |
| Canine coronavirus | Dog | | x (SI) | | | |
| Rabbit coronavirus | Rabbit | | | | Systemic | |
| II | Human coronavirus-043 | Human | X (Upper) | | BCoV | |
| Mouse hepatitis virus Rat coronavirus | Mouse | | x | Liver,CNS | | |
| | Rat Coronavirus | Rat | x | | Eye,SLG | |
| (Sialodocryadenitis) | | | | | | |
| | Haemagglutinating Encephalitis | Pig | x | | CNS | |
| Virus | | | | | | |
| | Bovine Coronavirus | Cattle | x (Upper, lung) | | x (SI, colon) | |
| III | Infectious bronchitis virus | Chicken | x (Upper) | | x (no | |
| diarrhea) | Oviduct | | | | | |
| | Turkey coronavirus | Turkey | | | x (SI) | |
| IV | Severe acute respiratory syndrome | Human | x (Lung) | x? | Viraemia? | |
| Civet cat coronavirus | Palm Civet | x | x | Subclin? | | |
| Raccoon dog coronavirus | Raccon Dog | ? | x | Sub clin? | | |

a) no specific information is provided in parentheses, the entire respiratory/gastrointestinal tract is affected or the specific site of infection is not known
b) bovina coronavirus-like coronavirus from a child (102)
SI Small intestine
? unknown or unreported

CNS: central nervous system

History of human corona virus

All the four different community-acquired HCoVsthat cause moderate symptoms show great adaptation to human beings. In other words, both the viruses could be resistant strains of the of ancient HCoV pandemics. HCoVs that cause higher rate of infections in humans and humans who developed severe HCoV diseases have been wiped out. For this to occur, HCoVs have to reproduce in humans to sufficient extent to allow the accumulation of adaptive mutations that counteract host restriction factors. In this sense, the longer the SARS-CoV-2 outbreak persists and the more people that it infects, the greater chance that it will fully adapt to humans. If it adapts well, its transmission in humans would be difficult to stop by quarantine or other infection control measures. For many years, the four community-acquired CoVs circulate in human populations, triggering common cold in immunocompetent subjects. These viruses do not need an animal reservoir. In contrast, highly pathogenic SARS-CoV and MERS-CoV have not adapted to humans well and their transmission within humans cannot be sustained. There is a need to maintain and extend in their zoonotic reservoirs and look for the chance to spillover to a more susceptible human targets, possibly through one or more intermediate hosts. The characteristic features of SARS CoV-2 and SARS-CoV/MERS-CoV are almost similar. It is highly transmissible just like other community-acquired HCoVs, at least for the time being. However,SARS-CoV-2 is more pathogenic than community-acquired HCoVs and less pathogenic than SARS-CoV or MERS-CoV. It remains to be seen whether it will adapt fully to humans and circulate within humans without a reservoir or intermediate animal host[16].

Before we discuss the zoonosis of HCoVs, it will good to talk about the definitions andfeatures of evolutionary, natural, reservoir, intermediate and amplifying hosts of HCoVs. An animal serves as the evolutionary host of an HCoV if it sustain a closely related ancestor sharing high genetic similarities at the level of nucleotide sequence. The ancestral virus is usually well adapted and nonpathogenic in this host. Likewise, a reservoir host housesHCoV continuously and for a very long term. In both cases, the hosts are naturally infected and are the natural hosts of HCoV or its parental virus. In contrast, if the HCoV is newly introduced to an intermediate host right before or around its introduction to humans, it is not well adapted to the new host and is often pathogenic. This intermediate host can serve as the zoonotic source of human infection and play the role of an amplifying host by allowing the virus to replicate transiently and then transmitting it to humans to amplify the scale of human infection. An HCoV can undergo a dead-end infection if it cannot sustain its transmission within the intermediate host. On the contrary, HCoVs can also adapt to the intermediate host and even establish long-term endemicity. In this case, the intermediate host becomes a natural reservoir host[16].

**History of SARS-CoV**

Epidemiological data revealed retrospectively that the index case of SARS had a contact history with conserved animals [17]. Subsequent investigations indicated that animal traders had a higher prevalence of anti-SARS CoVIgG compared with that of the general population [17]. Masked palm civets (*Pagumalarvata*) and a racoon dog in live animal markets were first identified to carry SARS-CoV-like viruses that are almost identical to SARS-CoV[18]. This was indirectly supported by the fact that after killing the civets no any further reported case of CoV. However, it has been reported that masked palm civets from the wild or farms without exposure to the live animal markets were largely negative for SARS-CoV[19], suggesting that masked palm civets might only serve as the intermediate amplifying host but not the natural reservoir of SARSCoV. It was noted that, since 80% of the different animals in the markets in Guangzhou have anti-SARS-CoVantibodies[20], the possibilities that multiple species of small mammals might also serve as intermediate amplifying hosts of SARS-CoV cannot be excluded.

All of these appear to be dead-end hosts of SARS-CoV. further search for the natural animal host of SARS-CoV unveiled a closely related bat CoV, termed SARS related RhinolophusbatCoV HKU3 (SARSr-RhBatCoV HKU3), which was found in Chinese horseshoe bats[21]. These bats are positive for anti-SARS-CoV antibodies and genome sequence of SARSr-RhBatCoV HKU3 [22]. This and other bat CoVs share 88-92% nucleotide sequence homology with SARS-CoV. These studies have laid the foundation for the new concept that bats host emerging human pathogens. Several SARS-like CoVs (SL-CoVs) have also been identified from bats, but none except for one designated WIV1 can be isolated as live virus [23]. Human angiotensin converting enzyme 2 (ACE2) is known to be the receptor of SARS-CoV.

Thus far, WIV1 represents the most closely related ancestor of SARS-CoV in bats[24], sharing 95% nucleotide sequence homology. Albeit the high homology between these two viruses, it is generally believed that WIV1 is not the immediate parental virus of SARSCoV and bats are not the immediate reservoir host of SARS-CoV.

**History of SARS-CoV-2**

SARS-CoV-2 has about 96.2% similar nucleotide arrangement with a bat CoV isolated from *Rhinolophusaffinis*bats[24]. As in the cases of SARS-CoV and MERS-CoV, the sequence divergence between SARSCoV-2 and bat CoV is too big to assign parental relationship. This shows that, bats might not necessarily be the immediate reservoir host(s) of SARS CoV-2 unless almost identical bat CoVs are found in future. Supposedly, the intermediate animal hosts of SARSCoV-2 should comefrom the wildlife species sold and killed at the Huanan Seafood Wholesale Market, with which many of the initial cases of COVID-19 were associated, this indicates an assumable animal-to-human transmission event [25]. Several recent studies based on metagenomic sequencing narrated that a group of endangered small mammals known as pangolins (*Manisjavanica*) could also be the host of ancestral beta-CoVs related to SARS-CoV-2[26]. The genomes of novel pangolin CoV share 85-92% nucleotide sequence homology with SARS CoV-2. However, they are equally closely related to RaTG13 that has about 90% identity at the level of nucleotide sequence. They are found in two sub-lineages of SARSCoV-2-like viruses in the phylogenetic tree, one of which has a more similar receptor binding domain (RBD) with SARS-CoV-2, with 97.4% amino acid sequence identity[26]. In stark contrast, the RBDs of SARS-CoV-2 and RaTG13 are more divergent, although a higher degree of sequence homology genome-wide. An earlier analysis on diseased pangolins also reported the detection of viral contigs from lung samples of the animal, which turn out to be similarly related to SARS-CoV-2[26]. The study adopted different assembly methods and manual healing to generate a partial genome sequence comprising about 86.3% of the full length viral genome [27]. The possibility of pangolin being the intermediate animal host of SARS-CoV-2 cannot be overlooked[26]. However, currently there is insufficient evidence which supports pangolin as the intermediatehost of SARS-CoV-2 due to the sequence divergence between SARS-CoV-2 and pangolin SARS-CoV-2-related beta-CoVs. In addition, the distance between SARS-CoV-2 shorter than that between SARSCoV-2 and pangolin SARS-CoV-2-related beta-CoVs.

The evolutionary pathway of SARS-CoV-2 in bats, pangolins and other mammals remains to be established. Whereas the highest sequence homology has been found in the RBDs between SARS-CoV-2 and pangolin, SARS CoV-2-related and beta-CoVs, SARSCoV-2 share the highest genome-wide sequence homology. It is highly speculative that the high degree of similarity between the RBDs of pangolin SARS-CoV-2-related beta-CoVs and SARS-CoV-2 is driven by selectivitymediated convergent evolution. A counter-proposal is in favor of a recombination between a pangolin SARS-CoV-2-related beta-CoV and RaTG13 in the third wild animal species. As a driving force in evolution, recombination is widespread among betaCoVs[28]. The jury is still out on the immediate zoonotic origin of SARS-CoV-2.

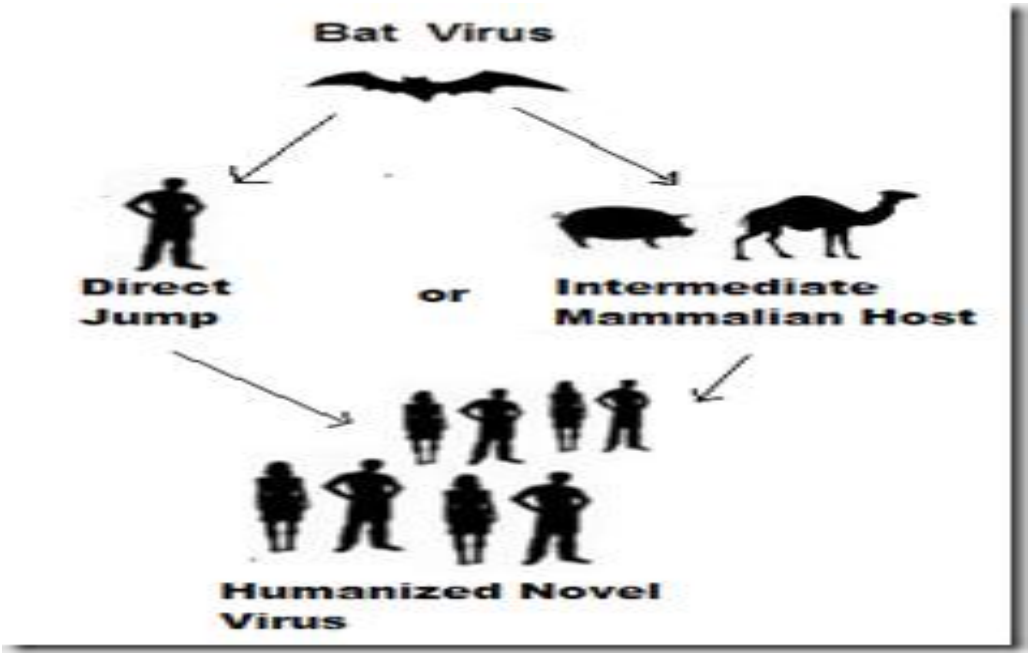
**Wildlife reservoirs**

Close to 75% of emerging infectious diseases are of zoonotic origin [1]. Epidemiological and genetic resultshave been presented suggesting that SARS evolved from aswild animal host, but no definitive evidence yet exists to prove this hypothesis. Epidemiological observations supporting the theory include the following: the index patient in Guangxi Province was a wild animal trader, two of seven index patients were restaurant chefs, food handlers were over-represented in early-onset cases with no contact history and early-onset patients were more likely to live near agricultural live animal markets [29]. This temporal and spatial clustering of index cases is consistent with the classical emergence of new agents from animal reservoirs. Based on genetic analysis, CoVs isolated from two clinically normal wild animal species (Himalayan palm civets, also referred to as masked palm civets or civet cats [*Pagumalarvata*] and a raccoon dog (*Neyctereutesprocyonoides*) from wild animal markets in Shenzen, the People's Republic of China, have been assigned as members of the new SARS CoVgroup [18]. All the animal SARS CoV isolates possessed a 29 nucleotide sequence not found in most human isolates. Furthermore, the highest IgG antibody titres to SARS CoV were observed in traders of masked palm civets (72.7%) compared to traders of all live animals (13%) and healthy controls (1.2%) [30]. However, the reservoir for SARS is still unknown and whether civet cats transmitted SARS CoV to humans or vice versa is undefined. Nevertheless, these data show that live animal markets (wet markets), which not only exist in the People's Republic of China but throughout the world, are likely to have played a vital role in the emergence of SARS CoV. These live markets are acknowledged as breeding grounds for influenza virus outbreaks such as that which occurred in Hong Kong in February 2003. The unsanitary crowded conditions, co-mingling of or close contact among different species of animals and between animals and humans, the carryover of animals and the introduction of new animals and animalslaughter on the premises, with the dispersion of bloodand secretions or offal, all foster an environment conducive to the emergence of new zoonotic diseases. In addition, unless more stringent, but cumbersome virus neutralization tests are conducted to confirm antibody sero-prevalence in humans and animals, the results using intact SARS CoV or nucleocapsid (N) protein may be suspect. This is because of the documented antigenic cross-reactivity (enzyme linked immunosorbent assay [ELISA], Western (blots, immunofluorescence) observed between SARSCoV and animal group I CoVs[31]attributed to the N protein. These issues hinder definitive analysis of animal reservoirs for SARS. Between December 2003 and January 2004, several new cases of SARS were re-established in humans in Guangdong Province, the People's

Republic of China [32]. In most of these cases there was no link to known risk factors such as civet cats. Other postulated reservoirs including rats and cats were tested, but no final conclusions were drawn concerning the origin of this re-emergent case. However, based on sequence data suggesting that the re-emerged SARS strains were most similar to the civet cat isolates [32], the Government of the country ordered the destruction of large numbers of civet cats in the wildlife markets in the People's Republic of China [33].

Further toMetropole Hotel outbreak, a second major outbreak of SARS occurred in 2003 in another location in Hong Kong at the Amoy Gardens apartments where over 321 people were ultimately infected [34]. This outbreak was clinically more severe and associated with more cases of diarrhoea (73%), higher intensive care unit admissions (32%) and mortality rates (13%) than the Metropole Hotel outbreak. Environmental factors (faulty sewage system) were postulated to have contributed to virus spread in the Amoy Gardens via aerosolized faecal material. However, an alternative hypothesis proposed was that an animal vector, such as roof rats, infected by the index patient, rapidly spread the disease among the 150 affected households [35]. The authors further speculated that dual infections of rats with a rat CoV and SARS CoV may have been required to cause a productive SARS CoV infection in other rats. Indeed, CoV was detected in rodent droppings from the apartment complex, but since the rodents showed no disease, they were postulated to be mechanical viral vectors [36]. It is also interesting to note that the virus were detected from throat or rectal swabs of five domestic cats, one of which had antibodies reactive with SARS CoV[35]. These data are consistent with SARS animal transmission studies which revealed that the respiratory tract of both mice and cats can be experimentally infected with SARS CoV, although infections in both species remained sub-clinical. Moreover, both experimentally-infected cats and ferrets (*Mustelofuro*) transmitted virus to their contact-exposed cage mates[37]. In the experimental animal transmission studies performed to date, only cynomologus macaques (*Macacacynomologus*) and ferrets have been reported to develop variable disease expression after infection by SARS CoV, with SARS CoV shedding detected from nasal or pharyngeal swabs [37]. However, in neither species do the clinical signs completely mirror those of human SARS cases, which include the delayed onset of clinical disease and frequent diarrhea with CoV shedding in stools [31]. Attempts have been made to experimentally transmit SARS CoV to domestic livestock and poultry. [38]reported failure to transmit SARS CoV to six-week-old pigs that were seropositive for antibodies to porcine respiratory CoV (PRCV) (a group I animal CoV). However, the authors detected SARS CoV ribonucleic acid (RNA) in the blood by reverse transcriptase-polymerase chain reaction (RT PCR) and noted that the pigs seroconverted with neutralizing antibodies to SARS CoV. This study should be repeated in pigs seronegative for PRCV or other CoV antibodies because several investigators have noted that antibodies to PRCV and other animal group I CoVs cross-react with SARS CoV[12]. Whether such preexistingantibodies to group I CoV interfere with SARS CoVinfection is unclear. Both [38] and [39] also reported lack of SARS CoV transmission to specific pathogen-free chickens, turkeys, ducks or quail, although again some RT-PCR positive samples were detected among the exposed poultry.

**Picture 1**




**Evolution SARS-CoV**

The emergence of SARS in healthy adults surprised the medical community, but veterinary coronavirologists have long recognized the potential of CoVs to produce lethal infections in young animals. Coronaviruses cause a broad range of diseases in domestic and wild animals, poultry and rodents ranging from mild to severe enteric, respiratory or systemic disease, as well as minor colds in humans[40]. In livestock and poultry, CoVs cause mainly localize denteric or respiratory infections, although infectious bronchitis virus (IBV) of poultry causes both upper respiratory and systemic infections targeting the kidney (interstitial nephritis) and oviduct (decreased egg production). Coronaviruses are enveloped and possess four major proteins, i.e. the nucleocapsid (N) protein surrounding the RNA genome and three membrane proteins: the surface spike (S) glycoprotein, the membrane (M) glycoprotein and the envelope (E) protein [41]. In addition, some group II CoVs can be distinguished from other CoVs by a surface haemagglutinin (HE), apparent as a shorter layer of projections on the virion surface compared to the longer S projections. The S protein appears to be a critical determinant for viral attachment and fusion, cell tropism, species specificity, pathogenicity and induction of neutralizing antibodies [42]. The CoV genome consists of linear, single-stranded RNA of positive polarity and ranges from 28 kb-32 kb in length [43]. For CoVs, the large size of the RNA genome, the replication strategy (nested set of sub-genomic RNAs) and the lack of proof-reading enzymes for RNA replication (analogous to other RNA viruses), all contribute to the recognized propensity of CoVs to recombine or mutate and for new strains to emerge. Numerous examples illustrate the emergence of new animal CoV strains or the mutation of existing strains to produce natural variants or host range mutants. In the late 1970s and into the 1980s, a new group I porcine CoV, the porcine epidemic diarrhea CoV (PEDV), appeared in Europe and rapidly spread to Asia [44]. The disease resembled TGEV of swine and caused severe diarrhea with major losses of piglets, before becoming enzootic in swine.

In addition, animalCoVs may acquire new genes via recombination, as demonstrated by the acquisition of an influenza C-like HE by BCoVor an ancestralCoV[45]. Recombination among CoVs may also generate new strains with altered tissue or host tropisms. Experimental targetedrecombination between feline and mouse S protein genesenablesFCoV to infect mice. Recent phylogenetic analysis suggests that SARS CoV may have evolved from a distant past recombination event between mammalian-like and avian-like parent strains, with the S gene representing a mammalian (group I)-avian (group III) origin mosaic [46]. This recognition that CoVs can further evolve in a host population to acquire new tissue tropisms or virulence via mutations or recombination suggests that similar events may occur if SARS CoV infections persist in humans.

**Interspecies transmission of Human Corona Virus**

A study in the phylogenetic relation between the CoVs has provided evidence for interspecies transmission events of HCoVs in the history. When HCoV-OC43 crossed species to infect humans from domestic livestock around 1890, a pandemic of respiratory infection was recorded [47]. There are no sufficient explanation to discuss the interspecies transmission of HCoV-229E. Bat alpha-CoVsclosely related to HCoV-229E have been found. Between them there is an alpaca alpha-CoV. Several lines of evidence support the transmission of virus from bats to humans directly. First, humans but not alpacas might have contact with bats in a shared ecological niche. Instead, humans have close contact with alpacas. Second, HCoV229E-related bat alpha-CoVs are diverse and non-pathogenic in bats, whereas alpaca alpha-CoV caused an outbreak of respiratory disease in infected animals [49]. Finally, alpaca alpha-CoV has not been found in feral animals. Thus, the possibility cannot be excluded that alpacas obtain the HCoV-229E-related alpha-CoV from humans. In fact, bats are the direct source of human pathogenic viruses including rabies virus, Ebola virus, Nipahvirus and Hendra virus [48]. It is therefore not too surprising that bats might transmit HCoV-229E to humans directly. Alternatively, whereas bat alpha-CoVs serve as the gene pool of HCoV-229E, alpacas and dromedary camels might serve as intermediate hosts that transmit viruses to humans, exactly as in the case of MERS-CoV ([48].

## II. Conclusion

SARS-CoV-2 is a zoonotic disease that infects human and it is believed to have emerged from two different viruses that almost the same nucleotide sequence with it, these viruses are Severe Acute Respiratory Syndrome Corona virus(SARS-CoV) and Middle East Respiratory Syndrome (MERS) which infect cats, there are several hypothesis which postulate that SARS-CoV-2 has a bush meat reservoir host.

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