

COVID-19 Pandemic: Bat to Human?

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REVIEW ARTICLE

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ABSTRACT

Background: The human novel coronavirus disease-2019 is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoVs-2), which emerged in Wuhan, Hubei province, China in December 2019 and was named by the World Health Organization as COVID-19. Bats are known for their reservoirs of large number of zoonotic diseases, including coronaviruses (CoVs) that have caused disease outbreaks in human and livestock populations.

Aim: In this literature review efforts have been made to identify the potential intermediate and the exact transmission route from bat to human.

Methods: The related data on COVID-19 and bat were retrieved from electronic databases PubMed, Science Direct.com and Google Scholar.

Sources: The Genome sequence of SARS-CoVs-2 shares a high level of genetic similarity (96.3%) with the bat coronavirus RaTG13 and genetically more distinct from SARS-CoVs (with 79% sequence identity) and MERS-CoVs (with 50% sequence identity). Pangolin- CoVs is 91.02% and 90.55% identical to SARS-CoVs-2 and Bat CoVs RaTG13, respectively, at the whole genome level. Bat could be the key reservoir and pangolin could be the intermediate host for COVID-19. Environmental changes, Migration, Climate change, Human population growth, Deforestation and also Accidental process may be the reason for transmission of CoVs from bat to human.

Conclusion: The present review has highlighted that emergence of new zoonotic source of SARS-CoVs-2 is not confirmed; however, the sequence-based analysis suggests that bats are the key reservoir.

INTRODUCTION

Coronavirus (CoVs) is an animal virus from bats which infected human in Guangdong province, China [1,2]. Coronaviruses are single-stranded RNA viruses that can infect not only humans, but also a huge variety of animals as well [3]. All seven identified human coronaviruses (HCoVs) originated from animal reservoirs including domestic animals, bats or mice. While most human coronaviruses (HCoVs) cause mild illness, severe acute respiratory syndrome coronavirus (SARS-CoVs), Middle

East respiratory syndrome coronavirus (MERS-CoVs) and the novel SARS-CoVs-2 have been associated with severe lower respiratory tract infections, acute respiratory distress syndrome and death [4].

SARS-CoVs-2 is a member of the family Coronaviridae and order Nidovirales. The family consists of two subfamilies, Coronavirinae and Torovirinae and members of the subfamily Coronavirinae are subdivided into four genera: including alpha, beta, gamma and delta coronaviruses. Alpha and beta coronaviruses were originated from mammals, particularly from bats, gamma and delta coronaviruses originated from pigs and birds [5]. SARS-CoVs-2 has phylogenetic similarity to SARS-CoVs and MERS-CoVs. The virus was identified as a novel enveloped RNA beta coronavirus that has been named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoVs-2) [6]. The recent threatening COVID-19 outbreak in humans is associated with SARS-CoVs-2 which belongs to the species of SARS-CoVs together with SARS-CoVs from humans and SARS-CoVs from wild carnivores and horseshoe bats (*Rhinolophus*) [7-9].

Bats are one of the largest (> 1,3000 species) mammalian species, accounting for ~ 20% of all mammals [10]. They belong to the order Chiroptera. The Phylogenetic analysis classified bats into two large suborders, Yinpterochiroptera consisting of one Pteropodidae (megabat) and five Rhinolophoidea (microbat) families, and the Yangochiroptera comprising a total of thirteen microbat families [11,12]. Bats act as a host for many viruses [13] and in particular coronaviruses, which represent 31% of their virome [14]. Furthermore, bats display a remarkable resistance to viruses [15,16], which can be envisioned to be a risk factor in the emergence of a novel bat coronavirus disease. The Bats are key reservoirs for a large number of zoonotic viruses, including coronavirus that have caused disease outbreaks in human and livestock populations [17-19].

THE ORIGIN OF COVID-19

In the highly biodiverse southern region of China, interactions among humans, wildlife and livestock are likely to be common and so are the risks of emerging zoonotic infectious diseases [20,21]. The Human-animal interactions are associated with zoonotic disease emergence, in particular few studies have reported that the nature of this specific interaction that occur between animals (particularly wild animals) and humans lead to pathogen spill over [22].

The outbreak of the novel coronavirus infection, COVID-19 was first recorded in December 2019, in Wuhan City, Hubei Province, China [23,24] but the origin of the SARS-CoVs-2 is unknown. However, the viral genome of the bat species, *Rhinolophus affinis* was close to the SARS-CoVs-2 [25]. The 60% of emerging transferable diseases originate from animals and 70% of these are supposed to originate in wild animals. So, the unrestricted wildlife trade might enhance the risks factor in the emerging new viruses. Many scientists have urged different countries to permanently ban the wildlife markets and trades [26]. The source of origination and transmission of COVID-19 from wild animals to human are important to be resolute in order to develop preventive strategies for zoonotic disease. In this literature review, we have collected information from past epidemiology studies on bat coronaviruses.

METHODS

We searched COVID-19 and bat related data for review in previously reported literature and retrieved from electronic databases (PubMed, Science Direct.com and Google Scholar) using the key words "Bat and COVID-19 or Coronavirus disease 2019, or SARS-CoVs-2 or Coronavirus, Bat and Coronavirus and Origin and transmission and Host and Genomic analysis, Bat and Coronavirus and Migration or Climate change or Overpopulation or Deforestation or Anthropization or Accidental". A total of 22 articles were retrieved from these databases. The important additional sources from 2000 to 2020 April were included from these articles. Overall, 80 articles were included in reference section. All reports of COVID-19 origin and transmission from bat to human (directly and indirectly) were included. We excluded duplication in review. Unrelated information to COVID-19 and bat were excluded. We included editorial guidelines.

LINKING BAT TO CORONAVIRUS

These viruses were first studied by Tyrell and Bynoe in 1966 who cultured them from patients with common cold. Due to their spherical virion's morphology along with a shell and surface projections like a solar corona, these viruses were named coronaviruses. The first evidence of a bat CoVs was published in 2005 [27]. Historically, only two human CoVs had been known before the emergence of SARS namely, HCoV-229E, an alpha coronavirus originated in bats and transmitted to humans through alpacas and HCoV-OC43, a beta corona virus which had transmitted from rodents to humans through cattle [17,28]. After 2002-03 SARS epidemic, the renovated interest in HCoVs allowed the discovery of two additional viruses, the alpha coronavirus HCoV-NL63 and the beta coronavirus HCoV-HKU1 that were derived from bats and rodents, respectively [29].

The animal to human transmission of viruses has already occurred in the past, but its frequency has increased in the last few decades, involving in a short span of time not only coronavirus (CoVs), but also other genetically and biologically different viruses with zoonotic potential, such as Ebola, Influenza, flaviviruses, Nipah and Hendra viruses [30]. SARS-CoVs,

causative agent of the SARS outbreak affecting 32 countries in 2002-03, infecting 8096 people and causing 774 deaths [31] and MERS-CoVs, which has caused 823 deaths from 2,374 human cases in 27 countries by the end of February 2019, and is thought to have originally spilled over from bats into camels [32-34]. SARS-CoVs which emerged in the pig population of China and caused the deaths of more than 20,000 piglets in 2017-18 [19]. As we are writing these lines, the COVID-19 pandemic affects more than 200 countries and territories, infecting more than 6,535, 354 people and the cause of 387,155 deaths according to the WHO statistics. Based on the past study, Coronavirus from most of the viral families can be found in bat species.

SIMILARITY EVIDENCE BETWEEN BAT AND HUMAN GENOME

Phylogenetic tree analysis of the novel coronavirus shows that SARS-CoV-2 (clade I, cluster IIa) belongs to SARS-CoVs (clade I, cluster IIb) while Bat SARS-like coronavirus belongs to different clade i.e. MERS-CoVs (clade II), which are more phylogenetically related to Bat SARS-like coronaviruses (isolated in China from horseshoe bats between 2015-18) than to SARS-CoVs [35-40]. Genomic comparison between SARS-CoVs-2 and SARS showed that there are only 380 amino acid substitutions between SARS-like coronaviruses and SARS-CoVs-2 mostly concentrated in the non-structural protein genes, while 27 mutations have been found in genes encoding the viral spike protein S responsible for receptor binding and cell entry [37]. These mutations might explain the apparent lower pathogenicity of SARS-CoVs-2 compared with SARS-CoVs, but further studies are required [38]. SARS-CoVs-2 possesses a genomic structure which is typical of other beta coronaviruses. Like other coronaviruses, its genome contains 14 open reading frames (ORFs) encoding 27 proteins. The ORF1 and ORF2 at the 50-terminal region of the genome encoded 15 non-structural proteins important for virus replication. The 30-terminal region of the genome encoded four structural proteins, including spike protein (S), envelope protein (E), membrane protein (M) and nucleocapsid (N) proteins [37,39]. The virus genome and its spike glycoprotein showed 96.11% and 92.86% similarities to the *Rhinolophus affinis* bat coronavirus [40]. The genome sequencing of COVID-19 from nine patients showed 99.98% sequence identity [41] and another study in five patients showed 99.8–99.9% nucleotide identity and sequencing studies revealed the presence of a new beta-CoVs strain [42].

SARS-CoVs-2 genome indicates that the virus is closely related to two bat-derived SARS-like coronaviruses which are bat-SL-CoVsZC45 (with 88% sequence similarity) and bat-SL-CoVsZXC21 (with 87.2% sequence similarity) and genetically more distinct from SARS-CoVs (with 79% sequence identity) and MERS-CoVs (with 50% sequence identity) [35,43]. The Genome sequence of SARS-CoVs-2 shares a high level of genetic similarity (96.3%) with the bat coronavirus RaTG13, which was previously detected in *Rhinolophus affinis* in Yunnan Province in 2013 [44,45]. Genomic and evolutionary evidence of the occurrence of a SARS-CoVs-2-like CoVs (named Pangolin-CoVs) can be found in dead Malayan pangolins. The Pangolin-CoVs is 91.02% and 90.55% identical to SARS-CoV-2 and Bat CoVs RaTG13, respectively, at the whole genome level [46].

In a fluorescent study, it was confirmed that SARS-CoV-2 also uses the same ACE2 (angiotensin-converting enzyme 2) cell receptor and mechanism for entering into the host cell which was previously used by the SARS-CoVs, while MERS-CoVs uses dipeptidyl peptidase 4 (DPP4) to enter into host cells [47-49]. The single N501T mutation in SARS-CoVs-2's Spike protein may have significantly enhanced its binding affinity for ACE2 [9]. According to the literature published, results have shown 96% genome sequence similarity between bat coronavirus and the novel human coronavirus-2019. So, bats might be the most likely natural reservoir for this novel coronavirus.

KEY RESERVOIRS AND INTERMEDIATE HOSTS OF SARS-CoVs, MERS-CoVs AND SARS-CoVs-2

Bats have been recognized as a natural reservoir and vector for a variety of coronaviruses, and these viruses have crossed species barriers (different kinds of animals) to infect humans. Few studies have suggested that, most of the human coronaviruses; including SARS-CoVs, MERS-CoVs, HCoV-229E, and HCoV-NL63 have originated from bats [50,51]. The researchers initially focused on palm civets and raccoon dogs as a key reservoir for infection of SARS-CoVs. However, the samples isolated from civets showed positive results for viral RNA detection, suggesting that the civet palm might be intermediate host of SARS-CoVs [52]. In Another study, MERS-coronavirus was detected in *Perimyotis* and *Pipistrellus* bats [53], which act as key host and transmitting medium of the virus [54,55]. However, the evidence suggests that camels play an important role as an intermediate host that transmits MERS - CoVs directly to humans [32,34]. The SARS-CoVs-2 most likely originated from bats, which play an essential role in the sustainability and spreading of virus into the environment. A group of researchers initially suggested snakes could be the possible host. However, after genomic sequence similarity findings of novel human coronavirus disease-2019 with SARS like bat viruses it was confirmed that snakes might not be the intermediate host but only bats could be the key reservoirs [35,36]. These results suggest that bats are the main ancestor of this virus. In a recent study, it was reported that Pangolin could be one of the potential intermediate hosts of SARS-CoVs-2 [56]. According to past literature, the evidence suggests that SARS-CoVs-2 may transmit directly (close contact with live animals or consumption as food) from bats to humans or indirectly through another animal playing the role of an intermediate host (Figure 1).

The transmission of virus from human to the human occurs mainly from close contact with an infected person, exposed to coughing, sneezing, respiratory droplets or aerosols and these aerosols can penetrate the human body (lungs) via inhalation through the nose or mouth [57-59].

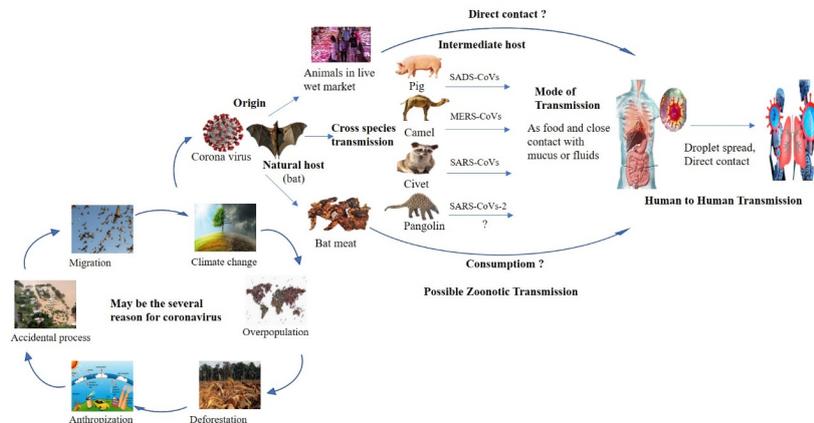


Figure 1. Origin and transmission route of Coronavirus from bat to Human.

SEVERAL REASONS FOR COVID-19 TRANSMISSION FROM BAT TO HUMAN

The changes in environment have a great impact on animal and human health and these changes may be the reason for coronavirus jumping from bat to human (Figure 1).

Bat-borne virus transmission

Before transmission of MERS-CoVs and SARS-CoVs emerged in humans, the four known human coronaviruses namely, HCoV-HKU1, HCoV-229E, HCoV-NL63 and HCoV-OC43 were reported as endemic causing mild to moderate respiratory tract diseases existing more than three decades. Evidence indicates that alpha CoVs from the bat *Hipposideros scaber* share common ancestors with human HCoV-229E [60] and that of related virus infected captive alpaca (*Vicugna pacos*) and related virus infected camel [61]. Furthermore, HCoV-NL63, found in 9.3% of samples from people hospitalized for respiratory disease displays genome sequence similarities with the bat (*Perimyotis subflavus*) CoVArCoVs, whereas HCoV-NL63 can replicate in cell lines derived from the lungs of tricolored bats [54].

Bat-borne viruses have the ability to infect livestock animals like camels, goats, pigs, buffaloes through contact with bat's saliva, urine or fecal matter and spill over to animals [22]. Bats were found roosting in people's homes and spotted eating fruits meant for human consumption. Under these circumstances, even vegetarian people stand a high chance of getting infected by the virus if they consume fruits contaminated with bat's saliva or the people can get exposed indirectly to these pathogens if they slaughter/consume livestock animals like lambs and buffaloes, which are already infected by consuming the virus contaminated food. In addition, the bat-borne viruses can be transmitted by rural communities which live close to forest areas [62], this shows the complex dynamics of CoVs circulation between bats and wild or domestic (bovine, pigs) animals prior to crossing to humans [63]. The anthropized environments effect on bats is a major risk factor in the emergence of bat-borne diseases in both humans and animals.

Migration

Bats can carry and transmit coronavirus into local bat populations via migration even though little is known about the migratory patterns of these animals [64]. Flight provided the selection procedure for coexistence with viruses, while the migratory ability of bats has particular relevance in the context of disease transmission [65]. Indeed, bats were linked to a few highly pathogenic human diseases, supporting this hypothesis. Some of these well characterized bat viruses, including bat lyssaviruses (Rabies virus), henipaviruses (Nipah virus and Hendra virus), CoVs (SARS-CoVs, MERS-CoVs, and SADS-CoVs), and filoviruses (Marburg virus, Ebola virus, and Mengla virus), pose a great threat to human health [66,67].

Migration pattern of horseshoe bats in China, SARSr-Rh-BatCoVs was found among 9.4% and 6.3% of alimentary specimens from horseshoe bats from Hong Kong and Guangdong respectively, with some bats coinfecting with a group 1 coronavirus, Rh-BatCoV HKU2. Mating and feeding activity soon after hibernation in spring may have facilitated the spread of the virus within the same roost and from roost to roost [68]. Migration of species is one of the reason possible for transmission of coronavirus from bat to human.

Climate change

The increased changes in climate in this first quarter of 21st century acts as a leverage for the spread of vector-borne diseases, exploring of vectors and predisposing their occupation of new ecological niches. The emergence of vector-borne diseases caused by viruses in temperate climate areas such as Europe was considered exotic until a few years ago (West Nile virus, Usutu virus, Chikungunya virus) accounts for a progressive geographic expansion to tropical diseases of tropicalisation [30]. The Zoonotic agents like coronavirus jumps to host species and gets adapted to it as there is close connection between human beings and different wild animals. The two most severe zoonotic disease in the last two decades (highly pathogenic H5N1 avian influenza and SARS) emerged in the same Chinese province of Guangdong where the contact between humans and wild animals is closer [23]. The Increased rate of extreme weather, rising average temperature and ocean levels affect not only the global land and ecosystem, but also human health [69]. Climate change affects the habitat of both humans and animals. These changes in the climate pattern increases the chance of contact between wildlife and livestock or human and possibly become a reason for the spread of virus from bat to human.

Overpopulation

The ever-growing human population needs proper food, shelter and other natural resources in order to survive and live but which is directly and indirectly linked to deforestation. [70,71] As the population grows so will be the needs of eating variety of foods including different types of animals such as bats, snakes, birds, frogs [72] and which ultimately results in unhygienic and dense living conditions [70,71]. This demographic growth generates pressure on land use, agricultural land and deforestation, with the most common activities being farming, hunting, and logging. Owing to evolving land use, bat populations are setting up in areas closer to human dwellings [73] and this kind of habitat infringement increases the likelihood of disease spill over from bats and other animals to humans [70,71]. Over population leads to increased wild animals eating which in turn affects the bats habitat. So, When the bats move close to human population the chances of getting infected with virus becomes high. According to past literature, human overpopulation is the world's worst environmental problem and control of human population growth is very essential in this regard.

Deforestation

According to World Wildlife Fund, forests cover more than 30% of the Earth's land surface. The overpopulation lead to deforestation for resources, industries and land for agriculture or grazing [69]. Deforestation is linked to different types of disease due to the birds and bat-borne viral outbreaks [63,74]. Deforestation and anthropization will lead to the disappearance of species and anthropized environments can provide habitat for a large range of bat species, generating thus a higher diversity of bats and in turn of bat-borne viruses next to human dwellings [63,75]. Deforestation and urbanization are other major factors that facilitate the spill over of zoonotic agents to humans by reducing the habitat of wildlife and increasing the chances of contacts between wild animals like bats, rodents, birds and human beings [23,76].

Anthropization

Anthropized rural environments are characterized by a wide diversity of landscapes comprising houses, barns, fields, orchards and woods of differing density. Anthropization generates a highly diverse environment in the vicinity of human populations, characterized by differing forest densities. Unlike natural environments which are highly selective, these altered landscapes are acceptable by a wide range of bat species, usually not encountered together. They can find their anthropized environmental niches compatible with their roosting and hunting needs [63,77]. Furthermore, house lights attract a large number of insects at night, offering easy prey for insectivorous bats. Houses and barns offer shelter for cave dwelling bats while orchards and fields attract frugivorous bats. This attractive effect of anthropized environments on bats with differing biological needs results in a higher concentration and biodiversity of bat-borne viruses [63,73,75,77-79]. This increases the risk of transmission of viruses through direct contact, domestic animal infection or contamination by urine or feces. CoVs being primarily agents of veterinary diseases, the risk of emergence of disease is as much on domestic animals as is on human beings.

Accidental process

The emergence of infectious diseases and the exact time and nature of the disease in the accidental process is impossible to predict. Hendra virus in Australia (1994) is one such example where Pteropus bat-borne virus was transmitted to horses and from horses to humans, most likely via aerosols [80]. Natural environmental changes, such as climate or weather anomalies may be the reason for virus transmission from bat to human and the cause of new emerging infectious diseases in the population, or already existing ones that are rapidly increasing in incidence or geographic range.

CONCLUSION

The present review has highlighted that the emergence of new zoonotic disease SARS-CoVs-2 and their geographical spread is complex in nature and that the multiple factors involved at multiple levels, play a critical role in its emergence, which includes the pathogen, environment, animals and humans. The zoonotic source of SARS-CoVs-2 is not yet confirmed; however, the sequence-based genome analysis suggests that bats are the key reservoir. Also, there are still conflicting assumptions regarding the coronavirus from the animal and some studies link the virus to bat, but a decisive intermediate host has not been identified so far. Any Contact with these animal fluids or tissues should be avoided. Environmental changes may be the reason for coronavirus spill over from bat to human. Therefore, considering the national security, public health and biosafety, it is essential to globally prevent deforestation and respect wildlife habitats and globally ban wildlife markets and trade. These actions will go a long way in protecting human lives from future COVID- 19 pandemic.

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