



(REVIEW ARTICLE)



Rodent species as possible SARS-CoV-2 spills

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Abstract

The current worldwide outbreak of COVID-19 is associated with a novel coronavirus, SARS-CoV-2. This outbreak has been tentatively associated with a seafood market in Wuhan, China, where the sale of wild animals may be the source of the zoonotic infection. When the epidemic, which began on December 12, 2019, had caused 2,794 laboratory-confirmed infections, including 80 deaths, as of January 26, 2020, whole-genome sequences were obtained from five patients early in the outbreak. The sequences were nearly identical and shared 79.6% sequence identity with SARS-CoV. In addition, SARS-CoV-2 has been shown to be 96% genome-wide identical to a bat coronavirus. Phylogenetic analysis of the virus spike proteins indicates that SARS-CoV-2 is classified into several small subclades, including a bat coronavirus RaTG13, suggesting that bats are a likely natural origin. Refined alignment of the spike proteins at NCBI showed that several sequences are conserved with high similarity within SARS-CoV-2 and/or SARS-CoV isolates from *Rattus norvegicus* and/or *Mus musculus*, suggesting that rodents may be intermediate reservoirs for SARS-CoV-2 and SARS-CoV.

Keywords: SARS-CoV; SARS-CoV-2; Coronavirus; Zoonoses; Rodents; Spills

1. Introduction

SARS-CoV-2 is the etiological agent responsible for the disease known as coronavirus 19 (COVID-19) associated with respiratory diseases; The most common symptoms associated with COVID-19 infection are fever, nasal congestion, and cough; however, the virus can develop severe cases of pneumonia in pediatric, elderly, and immunocompromised patients (Boban, 2021).

SARS-CoV-2 belongs to the Betacoronavirus genus of the Orthocoronavirinae subfamily of the Coronaviridae family and its first detections occurred in December 2019 when an outbreak of pneumonia of unknown origin occurred in Hubei province, in Wuhan, China (Huang *et al.*, 2020). Since the recognition of COVID-19, there has been an exponential increase in the number of cases around the world. As of June 20, 2022, the World Health Organization has reported more than 385,000,000 cases in more than 195 countries, areas, or territories (WHO, 2022). Reasons for the rapid spread include the high transmissibility of the virus, especially among asymptomatic or minimally symptomatic carriers; the apparent absence of any cross-protective immunity from related viral infections; and the delay in public health response measures, as well as the generation of new variants, due to high rates of mutation and recombination between circulating strains (Cheng *et al.*, 2020). Among the still unknown factors of SARS-CoV-2 are those related to its exact origin, since despite the fact that through a phylogenetic analysis of samples of patients with COVID-19 it has been suggested that bats could be the host origin of this virus because it has a 96% similarity to the bat coronavirus RaTG13

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(Zhou *et al.*, 2020). Despite this, the RaTG13 virus is not capable of infecting humans without first adapting to it, so an intermediate host is necessary to facilitate the transmission of the virus to humans (Lu, 2020). It is essential to identify the intermediate reservoirs of SARS-CoV-2 and discover how the virus is transmitted to humans. Among the possible intermediate hosts, those animals sold in the Wuhan seafood market have been considered, among which different mammals were investigated, the most studied being pangolins, snakes, minks, cats, and even common mice and rats (Lam *et al.*, 2020). Recent studies indicate that both SARS-CoV-2 and SARS-CoV have their natural origin in bats and could be transmitted to humans via rodents. This was demonstrated by performing a complete amino acid sequence analysis and comparing fragments of coding sequences of the new virus with all available mammalian sequences in the NCBI database (Huang *et al.*, 2021). If in addition to this, we consider that the house mouse (*Mus musculus*) and the Norway rat (*Rattus norvegicus*, also known as the brown rat) are the most widely distributed mammals and with the greatest success in adapting to various environments after man and that prefer habitats close to human populations, they are likely to be the intermediate hosts of the SARS-CoV-2 virus.

2. SARS-CoV-2 spill events

SARS-CoV, MERS-CoV, and SARS-CoV-2 have emerged in recent decades and cause severe respiratory illnesses from different strains of coronaviruses. These viruses are believed to originate from bats and have been transmitted to humans via intermediate hosts. SARS-CoV has been identified in palm civets in wildlife markets and MERS-CoV in dromedaries (Cui, 2018), but the direct source of the causative agent of COVID-19, SARS-CoV-2, remains indeterminate. SARS-CoV-2 infections have been reported in animals and people working or living on 16 mink farms in the Netherlands. SARS-CoV-2 infections were detected in 66 of 97 (68%) of the owners, workers, and their close contacts. Some people became infected with viral strains, based on nucleotide sequences identified in animals, demonstrating that SARS-CoV-2 can spread between animals and humans within mink farms (Oude *et al.*, 2021). In addition to mink, multiple species of wild or domestic animals can carry SARS-CoV-2 or its related viruses. Experimental infections and binding affinity assays between the SARS-CoV-2 spike protein (a surface protein involved in host cell entry) and its receptor, angiotensin II converting enzyme (ACE2), have shown that SARS-CoV-2 has a wide host range (Wu, 2020). After the SARS-CoV-2 outbreak, several groups reported the presence of SARS-related coronaviruses in horseshoe bats in China and in pangolins smuggled from South Asian countries, but based on genome sequence comparison, none is directly the origin of SARS-CoV-2 (Tan, 2020). Domestic dogs and cats, as well as tigers in zoos, have also been found naturally infected with SARS-CoV-2 from humans, but there is no evidence that they can infect humans, so it is unlikely that they are the hosts. SARS source. -CoV-2 (Hu, 2021; McAloose, 2020).

To date, SARS-CoV-2 infections have been reported on mink farms in eight countries, the Netherlands, Denmark, Spain, France, Sweden, Italy, the United States and Greece (World Organization for Animal Health, 2020). In addition to animal-to-human transmission on farms, cold food supply chains are causing great concern. Several small-scale COVID-19 outbreaks caused by virus-contaminated seafood or raw pork from foreign countries have been documented in various cities in China. The viral genome sequences in these outbreaks were found to be different from viral strains present in China (Liu *et al.*, 2020) (Han, 2021). There is evidence that SARS-CoV-2 can survive up to 3 weeks in meat and on the surface of cold food packages without losing infectivity (Liu *et al.*, 2020) (Han, 2021). Therefore, meat from animals infected with SARS-CoV-2 or food packaging contaminated with SARS-CoV-2 could be a source of human infection.

This makes public health and the agri-food industry interested in the prevention and control of SARS-CoV-2. Most animals infected with SARS-CoV-2 do not show an obvious clinical syndrome and infections would not be recognized without routine diagnosis. Mass culling of infected mink on farms is an effective way to prevent transmission of the virus. However, it cannot be applied to all domestic animals (if other species are found to be hosts for SARS-CoV-2).

Therefore, as a precautionary measure, strict and extensive quarantine measures should be applied on all domestic farms with high density animal populations. Since the virus can jump between some animals (such as mink) and humans, similar strategies should be applied to people in key occupations that involve animal-human interfaces, such as ranchers, zookeepers, or slaughterhouse workers. In particular, there is little evidence of animal-to-human transmission of SARS-CoV-2, except in the case of mink. It should be investigated if other domestic animals are carriers of SARS-CoV-2, if they can transmit it to humans and the factors related to the infection.

It has been debated whether bats or pangolins, which carry the coronavirus and with identified sequences ~90 to 96% similar to human SARS-CoV-2 sequences, were the animal source of the first human outbreak (Hu, 2021). Evolutionary analyses of bat and pangolin viral genomes indicate that other adaptations occurred, either in animal hosts or in humans, before the virus caused the COVID-19 pandemic (Andersen, 2020). Therefore, an animal species that has a high population density is necessary to allow natural selection and a competent ACE2 protein for SARS-CoV-2. The mink, for example, would be a possible host of the direct progenitor of SARS-CoV-2.

Another debate concerns the origin of the SARS-CoV-2 that caused the COVID-19 outbreak in December 2019. Current data questions the animal origin of SARS-CoV-2 in the seafood market where the first cases were identified in Wuhan, China. Given the finding of SARS-CoV-2 on the surface of imported food packaging, contact with contaminated raw food could be an important source of SARS-CoV-2 transmission (Han, 2021). Recently, antibodies to SARS-CoV-2 were found in human serum samples taken outside of China before the COVID-19 outbreak was detected (Apolone, 2021) (Basavaraju, 2021), suggesting that SARS-CoV-2 existed for some time before the first cases were described in Wuhan. Retrospective investigations of pre-outbreak samples from mink or other susceptible animals, as well as from humans, should be conducted to identify the hosts of the original direct virus and to determine when the virus spread to humans. SARS-CoV genomes, which were under greater adaptive pressure in the early phase of the epidemic (palm civet to human) than in later phases (human to human) (Chinese SARS Molecular Epidemiology Consortium, 2004).

3. Coronavirus taxonomy

The Coronaviridae family is divided into two subfamilies, the coronaviruses and the toroviruses. All identified coronaviruses are classified into four different genera: alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus, Figure 1. Coronaviruses that infect mammals, including humans, belong to alpha coronaviruses and beta coronaviruses and probably have originate from bats, while Gamma coronaviruses and Delta coronaviruses infect and originate from birds and fish.

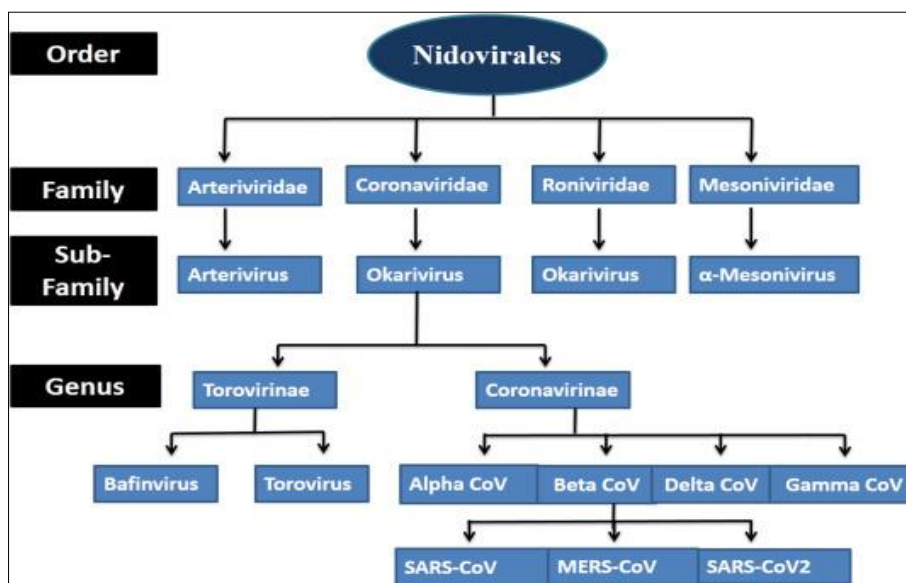


Figure 1 Classification of coronaviruses (Junejo *et al.*, 2020)

4. Virology of coronaviruses

Coronaviruses have a spike-shaped glycoprotein shell, made up of two subunits S1 and S2. S1 is involved in the adhesion of the virus to the host cell and S2 helps its fusion with the host cell membrane. Genetic modification of the glycoprotein coat could potentially affect the virulence of the virus (Shereen, 2020), as has been explored in pangolin coronaviruses, in which the S1/S2 furin-like cleavage sites of the S protein were deficient, what made it different and suggested a higher rate of human-to-human transmission (Lam, 2020). It also consists of structural proteins, integral membrane proteins, small membrane proteins (M and E proteins), and the nucleocapsid (N) protein. The genes that encode this protein (S, E, and N) can be identified by a diagnostic test based on nucleic acid amplification (Figure 2) (Pastrian Soto, 2020).

SARS-CoV2 has a phylogenetically distinct RNA-dependent RNA polymerase (RdRp) gene and proteins such as chymotrypsin-like protease, papain-like protease, and others that exert their virulent impact. Coronaviruses, in general, have a positive-sense single-stranded RNA envelope and have the largest genome of all RNA viruses, ranging from 26 to 32 kilobases. Two-thirds of the coronavirus genome at the 5' end encodes viral proteins involved in viral RNA transcription and replication, while one-third at the 3' end encodes group-specific structural and accessory viral proteins (Yadav, 2021).

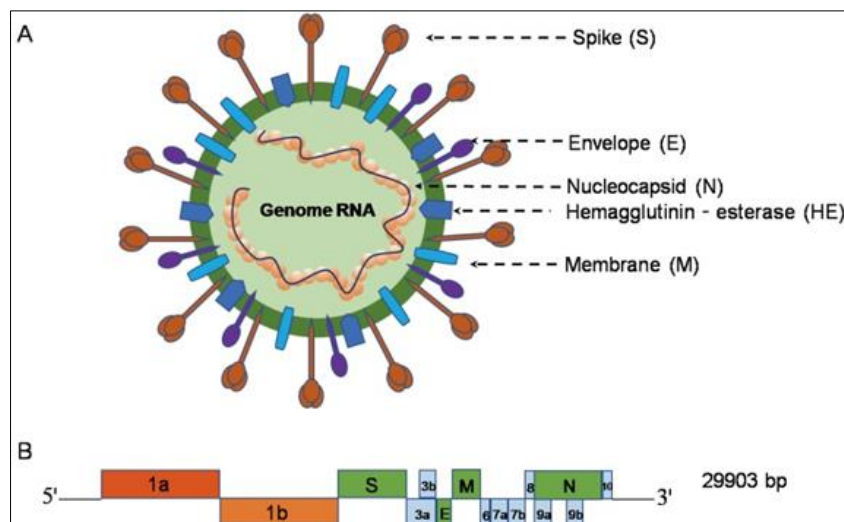


Figure 2 Particle and genome of beta-coronavirus, (Pastrian-Soto, 2020)

4.1. History of the zoonotic origin of Coronaviruses

Coronaviruses (CoV) are a group of viruses that belong to the Coronaviridae family. These families of viruses infect both humans and vertebrate animals. Four types of coronaviruses, HKUI, NL63, OC43, and 229E, are known to cause mild respiratory illness, while SARS-CoV, MERS-CoV, and SARS-CoV-2 may be responsible for severe lung injury and respiratory disorders that can be fatal in humans. (Zhou, 2020) (Chen, 2020). All human coronaviruses can be zoonotic in origin, and bats are most likely the natural hosts for all currently known coronaviruses (Vijaykrishna, 2007).

During the SARS pandemic in 2002 and 2003, the first indications pointed to a zoonotic origin of SARS-CoV, with civets being the presumed natural source of human infection (Corman *et al.*, 2018). Subsequently, coronaviruses genetically similar to SARS-CoV were found in Chinese rhinolophia bats, implying that these bats are considered natural hosts for SARS-CoV. As for SARS-CoV-2, it showed high sequence identity with some bat coronaviruses such as RaTG13 (96% nt identity with SARS-CoV-2), indicating a probable origin of SARS-CoV-2 in bats, Figure 3 (Ge *et al.*, 2013).



Figure 3 Horseshoe bat (*Rhinolophus*). The *Rhinolophus* bat is considered one of the possible natural hosts of SARS-CoV-2 (Mallapaty, 2021)

Bat habitats are generally remote from areas of human activity, and the virus was likely transmitted to humans from another animal host. SARS-like coronaviruses from bats cannot directly infect humans unless they undergo mutation or recombination in animal hosts. However, the intermediate host for this virus is elusive, some reports have claimed that snakes or mink are the intermediate hosts. In addition, 99% genetic sequence similarity was found between pangolins and the current infectious human strain (Andersen, 2020). Based on this evidence, there is a high probability that pangolins are one of the intermediate hosts of COVID-19, Figure 4 (Lam, 2020). Another theory is that in some blocks of the Huanan Seafood Wholesale Market, animals are actively traded as delicacies, and their carcasses and viscera are displayed day and night, providing a food source for rats and mice. Therefore, viruses harbored by wild animals would

be carried by rodents, whereby the viruses would spread everywhere inside or even outside the market and then transfer to humans.

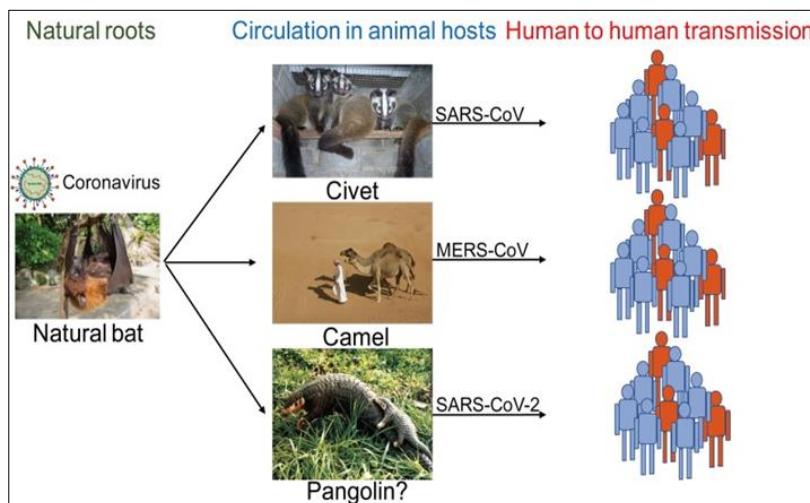


Figure 4 Ecology of the emerging coronaviruses SARS-CoV, MERS-CoV and SARS-CoV-2 are coronaviruses of bat origin, which cause infections in humans after circulating in animal hosts such as civets, camels and pangolins (Jin *et al.*, 2020)

In this sense, it is interesting that both SARS-CoV and SARS-CoV-2 have dozens of fragments derived from rodents (rats and/or mice), respectively. Two fragments (EAEVQID/NHTSPDV) shared by both viruses are more conserved than other virus-encoded proteins. This explains why the two viruses cross-react with the antibodies generated between them (Lv, 2020). It also strongly suggests that these rodents could be the intermediate hosts for both SARS-CoV and SARS-CoV-2 transferred to humans. This statement is corroborated by the following facts, among the samples of rats and mice captured in Guangzhou hospitals in 2003, 12.5% tested positive for SARS-CoV by anal swab tests, and in these positive samples, between 90% and 96% had sequence homology with SARS-CoV (Yi, 2004). In addition, in the vicinity of the Amoy Gardens housing complex in Hong Kong in 2003, traces of SARS-CoV were detected in four out of eight rat dropping samples and in swabs from the throat or rectum of at least one rat (K, 2004).

4.2. Relationship between SARS-CoV-2 and rodents

Rodents are known as mammals of the order Rodentia, among which rats and mice belong to the suborder Myomorpha. Members of the Muridae family are the dominant species in any region of the world due to their ability to adapt and exploit new situations. Within this family belong commensal rats and mice, that is, those that live at the expense of humans, invade their homes, eat their food, disturb their comfort and often transmit their diseases. Three species of commensals are the most widely distributed: the Norway rat, *Rattus norvegicus*; the roof rat, *Rattus rattus*; and the house mouse, *Mus musculus* (Figure 5). Pathogenesis and immune response mechanisms also include parasitism such as trichinosis (*Trichinella spiralis*); eosinophilic meningitis due to *Angiostrongylus cantonensis* and taeniasis due to *Hymenolepis nana* or *H. diminuta*.

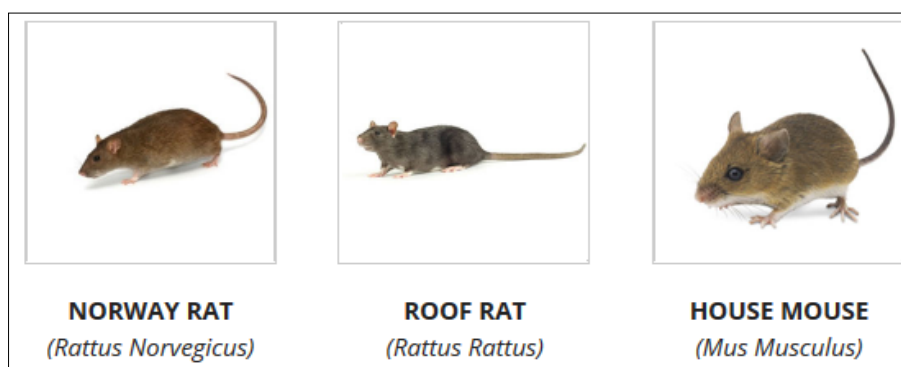


Figure 5 Classification of rodents of public health importance (WHO, 2022)

The transmission of these infections to humans is indirect. Some through infected urine or feces, others through fleas and lice, and others through mosquito bites. Urban areas are ground zero for the COVID-19 pandemic, with 90% of reported cases (WHO 2022). Rodents (order Rodentia), constituting the largest group of mammalian species, are widely distributed throughout the world and are known to be reservoirs of several zoonotic viruses. The prototype strain of murine hepatitis virus 1 (MHV-1) is a Beta coronavirus that was first identified and isolated in mice in 1949, and is one of the recognized animal models for multiple sclerosis. Although several viruses have recently been described in rodents from China, most research on CoVs from wildlife has focused on bat hosts due to their role as reservoirs for SARS-CoV, and likely MERS-CoV as well. CoV, SARS-CoV and SARS-CoV-2.

Although the natural host of SARS-CoV-2 remains unidentified, there is evidence pointing to the origin of SARS-CoV-2 in reservoirs of wild animals, such as pangolins and bats, with the possibility of introduction through contamination of imported cold products. String. HCoV OC43 and HKU1 and the Omicron variant of SARS-CoV-2 are believed to originate from rodent-associated viruses. Given the close contact between humans and rodents in nature around homes and workplaces and the relative paucity of research on rodent CoVs, we undertook a project to assess the presence of potentially zoonotic CoVs in rodents from urban and peri-urban areas in Mexico.

5. Conclusion

Based on the available studies, we consider the house mouse (*Mus musculus*) and the Norway rat (*Rattus norvegicus*, also known as the brown rat) to be one of the best possible candidates to be discovered as an intermediate host for SARS-CoV-2, since they share characteristics that make them susceptible to this disease and have enough interaction with humans and bats to be the contact bridge between both species. However, to confirm this theory it is necessary to carry out epidemiological studies to demonstrate the presence of the virus in rodent populations in urban and peri-urban areas and to demonstrate the ability of rodents to infect humans.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare not to have any interest conflicts.

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