

REVIEW

SARS-CoV-2 and natural infection in animals

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of the novel coronavirus disease (COVID-19) pandemic, which has caused serious challenges for public health systems worldwide. Due to the close relationship between animals and humans, confirmed transmission from humans to numerous animal species has been reported. Understanding the cross-species transmission of SARS-CoV-2 and the infection and transmission dynamics of SARS-CoV-2 in different animals is crucial to control COVID-19 and protect animal health. In this review, the possible animal origins of SARS-CoV-2 and animal species naturally susceptible to SARS-CoV-2 infection are discussed. Furthermore, this review categorizes the SARS-CoV-2 susceptible animals by families, so as to better understand the relationship between SARS-CoV-2 and animals.

KEYWORDS

animals, COVID-19, natural infection, SARS-CoV-2

1 | INTRODUCTION

Since the emergence of the novel coronavirus disease (COVID-19), it has spread rapidly throughout the world, causing serious health problems for human beings. According to the World Health Organization (WHO), as of June 10, 2022, more than 530 million COVID-19 cases and more than 6 million deaths have been confirmed worldwide.¹ It has been determined that the etiologic agent of the pandemic is a novel coronavirus, named by the International Committee on Taxonomy of Viruses (ICTV) as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This virus is highly infectious, spreads rapidly, and has a high rate of genome mutations. Since the beginning of the pandemic, the virus has continued to endanger human health. At the same time, SARS-CoV-2 also threatens the health of many animals. Many cases of natural infection of animals such as cats, dogs, tigers, and lions have been reported. As of April 31, 2022, more than 600 animal infections involving more than 20 species have been reported (Table 1) according to the World Organisation for Animal Health (OIE). This suggests that the host range of SARS-CoV-2 is gradually expanding.⁶ Cross-species transmission of SARS-CoV-2 may have led to further evolution in new hosts, leading to a new transmission, such as the mutation of SARS-CoV-2 in minks and transmission from minks to humans.^{32,33} In addition, SARS-CoV-2 infection and transmission

vary among different animals. For example, cats are susceptible to SARS-CoV-2, and SARS-CoV-2 can be transmitted from cat to cat. In contrast, dogs are less sensitive and are not currently known to transmit SARS-CoV-2.^{2,34-36} Minks, for example, are also vulnerable to SARS-CoV-2, which can be transferred between minks and zoonotic transmission has been identified.³² These animals are sensitive and transmissible to SARS-CoV-2 and may endanger both animal and human populations with which they interact. Understanding the cross-species transmission of SARS-CoV-2 and the infection and transmission of SARS-CoV-2 in different infected animal species is of great importance to animal health and disease control and prevention. To understand the relationship between SARS-CoV-2 and animals, the possible animal origin of SARS-CoV-2 and naturally infected animal species are introduced in this paper.

2 | POSSIBLE ORIGINS

Identifying the origins of a virus and its route of introduction to humans is an important piece of information to prevent its reintroduction to humans and animals, reduce its transmission and the risk of future pandemics, and may aid in treatment of the disease. At present, the origin of SARS-CoV-2 remains controversial. There are two hypotheses about the origins of SARS-CoV-2: a laboratory

TABLE 1 Overview of animals naturally infected with SARS-CoV-2

Order	Family	Species	Clinical signs	Susceptibility	Transmission	References
Primates	Hominidae	Western lowland gorilla	Mild signs	High	—	[2–4]
	Callitrichidae	Black-tailed marmoset	—	—	—	[5]
Pilosa	Myrmecophagidae	Giant anteater	—	—	—	[6]
Rodentia	Circetidae	Hamster ^a	No or mild signs	High	Yes, between hamsters	[7–9]
Carnivora	Felidae	Cat ^a	No or mild signs	High	Yes, between cats	[9]
		Tiger	Mild signs	High	Yes	[9]
		Lion	Mild signs	High	Yes	[9]
		Cougar	Mild signs	High	—	[10,11]
	Viverridae	Snow leopard	Mild signs	High	—	[2,11–13]
		Indian leopard	—	—	—	[14]
		Eurasian lynx	Mild signs	—	—	[15]
		Canada lynx	Mild signs	—	—	[16]
Canidae	Fishing cat	Mild signs	—	—	[17]	
	Binturong	No	—	—	[17]	
Hyaenidae	Spotted hyena	Mild signs	—	—	[18]	
Procyonidae	Coatimundi	No	—	—	[19,20]	
Mustelidae	Mink ^a	No or respiratory signs	High	Yes, between minks and suggested from mink to humans	[9,21,22]	
	Ferret ^a	No or mild signs	High	Yes, between ferrets	[9]	
	Asian small-clawed otter	Mild signs	—	—	[23]	
Sirenia	Trichechidae	Antillean manatee	No	—	[6,24]	
Artiodactyla	Cervidae	White-tailed deer ^a	No or mild signs	High	Yes, between white-tailed deer	[2,25–29]
		Mule deer	—	—	—	[30]
	Hippopotamidae	Hippo	Mild signs	—	—	[31]

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

^aClinical signs, susceptibility, and transmission status of animal infection are a combination of results from natural and experimental infections with SARS-CoV-2.

containment breach or natural evolution. In a joint study between the WHO and China on the origin of SARS-CoV-2, the collaborative team's assessment of the likelihood of each possible pathway was as follows: (1) introduction through a laboratory incident was considered to be an extremely unlikely pathway; (2) direct transmission to humans as a zoonosis was a possible pathway; (3) introduction through an intermediate host was considered to be very likely.³⁷

2.1 | Bats

No direct evidence supporting the natural origin of SARS-CoV-2 has been reported. Numerous studies suggest that bats are likely to be its

natural host. Bats are natural hosts of many coronaviruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), both of which have jumped species from bats. Many kinds of bat origin coronaviruses (Bat-CoV) similar to SARS-CoV-2 have been identified, such as Bat-CoV-RaTG13 (RaTG13), RpYN06, PrC31, RmYN02, Bat-SL-CoVZC45, and Bat-SL-CoVZXC21. The RTG13 found in the Chinese chrysanthemum-headed bat (*Rhinolophus sinicus*) shared 96.2%, 97.5%, and 89.2% identities with SARS-CoV-2 for nucleotide, and amino acid sequences of the spike (S) protein and the receptor-binding domain (RBD), respectively.^{38,39} The genome sequence identity between RpYN06 and SARS-CoV-2 was 94.48%, which was second only to RaTG13.⁴⁰ At the same time, other bat

coronaviruses and SARS-CoV-2 have relatively high genome sequence identities.^{40–44} The high identity between the SARS-CoV-2 and bat coronavirus genomes suggests that it probably originated in bats. He et al.⁴³ constructed a UPGMA phylogenetic tree based on the correlative coefficient feature vector method. The authors observed a close evolutionary relationship between bat-associated coronaviruses and SARS-CoV-2. This also suggested that SARS-CoV-2 might have originated from bats. In addition, Shan et al.⁴⁵ found that de novo mutations of the virus were highly dependent on the specific mutation mechanism in the host cell environment. Hence, the molecular spectrum of the virus gene evolution mainly reflected the cell environment in which the virus reproduced. The similarity between the mutation spectrum of SARS-CoV-2 and that of coronavirus RaTG13 suggested that SARS-CoV-2 may have evolved from RaTG13 in a bat-like host cell environment before spreading to humans. This study not only suggests that SARS-CoV-2 may have originated from bats but also supports the natural origin of SARS-CoV-2.⁴⁵ Although bats may be the natural host of the virus, they lack direct contact with humans, who are less likely to be directly infected with bat coronavirus. Therefore, during the emergence of SARS-CoV-2, it is highly likely that other mammalian species may have acted as an intermediate or amplifying host, such as the pangolin.^{46,47}

2.2 | Pangolins

Coronaviruses similar to SARS-CoV-2 have been detected in Pangolins. The Guangxi Pangolin-CoV (GX PCoV) and Guangdong Pangolin-CoV (GD PCoV) were isolated from Malayan pangolin (*Manis javanica*) located in Guangxi and Guangdong, China. These viruses shared high genomic sequence identities with SARS-CoV-2 (85.5%–92.4%).³⁹ The coronavirus of the pangolin is currently believed to be the second closest relative to SARS-CoV-2 after the bat coronavirus.³⁹ In addition, the S protein in SARS-CoV-2 is capable of binding the host cell receptor and mediating membrane fusion. The RBD of the S protein is the main factor in determining the host range of the virus.³⁹ The homology of the RBD amino acid sequence between GD PCoV and SARS-CoV-2 was 96.9%, which was higher than that of the amino acid sequence of RaTG13 and SARS-CoV-2 (89.2%). This implies that the RBD of GD PCoV could bind more easily to human Angiotensin-converting enzyme 2 (ACE2) than that of the bat RaTG13.³⁹ Therefore, pangolins may also have contributed to the evolution of SARS-CoV-2. The molecular and phylogenetic analysis of SARS-CoV-2, PCoV, and other coronaviruses from different species have shown that PCoV, SARS-CoV-2, and a group of bat coronaviruses were genetically related.^{48,49} However, based on the phylogenetic analysis of the SARS-CoV-2 S protein gene and the amino acid sequence, the hypothesis that SARS-CoV-2 was directly derived from PCoV was not supported. The S protein gene of PCoV may be a mosaic of fragments of bat-SL-CoVZC45 or bat-SL-CoVZXC21, and fragments of RaTG13.^{48,49} Additionally, the cleavage site between S1 and S2 in SARS-CoV-2 has multiple insertions (i.e.,

PRRA), compared with RaTG13 and PCoV.^{48,49} However, RmYN02 has similar insertions of multiple amino acids at the junction site of the S1 and S2 subunits of the SARS-CoV-2 S protein.^{48,49} In summary, one hypothesis for the possible origin of SARS-CoV-2 is proposed: SARS-CoV-2 originated from bats and then spread to pangolins or another wild animal, where SARS-CoV-2 recombined with viruses present in these animals to acquire the ability to spread to humans (Figure 1). Determining the origin of the virus is a possible key to cutting off SARS-CoV-2. So far, the origin of SARS-CoV-2 remains controversial, and further research is needed to provide more substantial evidence.

3 | NATURAL INFECTIONS IN ANIMALS

3.1 | Nonhuman primates

3.1.1 | Western lowland gorilla

Gorilla gorilla ssp. *gorilla* was first found to be infected with SARS-CoV-2 in the gorilla troop at the San Diego Zoo Safari Park in California, United States, which was the first time that nonhuman primates were apparently naturally infected with SARS-CoV-2.^{3,4,30} After two gorillas were observed to be coughing at the zoo, fecal samples were collected from all the gorillas. Diagnostic testing detected SARS-CoV-2 in some of the gorillas, who were presumably infected by an asymptomatic staff member. Some gorillas developed mild clinical signs after infection, such as cough, congestion, runny nose, and intermittent lethargy.^{3,4} The cases in the western lowland gorilla have only been reported in the United States as of the publication date of this manuscript.

3.1.2 | Black-tailed marmoset

A case of SARS-CoV-2 infection in a wild black-tailed marmoset (*Mico melanurus*) was found in Mato Grosso, Brazil, which was the first reported case of natural infection with SARS-CoV-2 in Callithricidae.^{5,6} Infection of black-tailed marmoset has only been reported in Brazil, but clinical disease was not described due to death of the animal.⁵ In addition, the source of infection is unknown, although fomite exposure has been hypothesized.⁵

3.2 | Myrmecophagidae

3.2.1 | Giant anteater

Giant anteater (*Myrmecophaga tridactyla*) is the only reported natural infection of SARS-CoV-2 in Myrmecophagidae, and has only been reported in Brazil.⁶ A giant anteater was found to be infected with SARS-CoV-2 in Mato Grosso, Brazil, and the source of the infection and whether it has clinical signs have not yet been determined.⁶

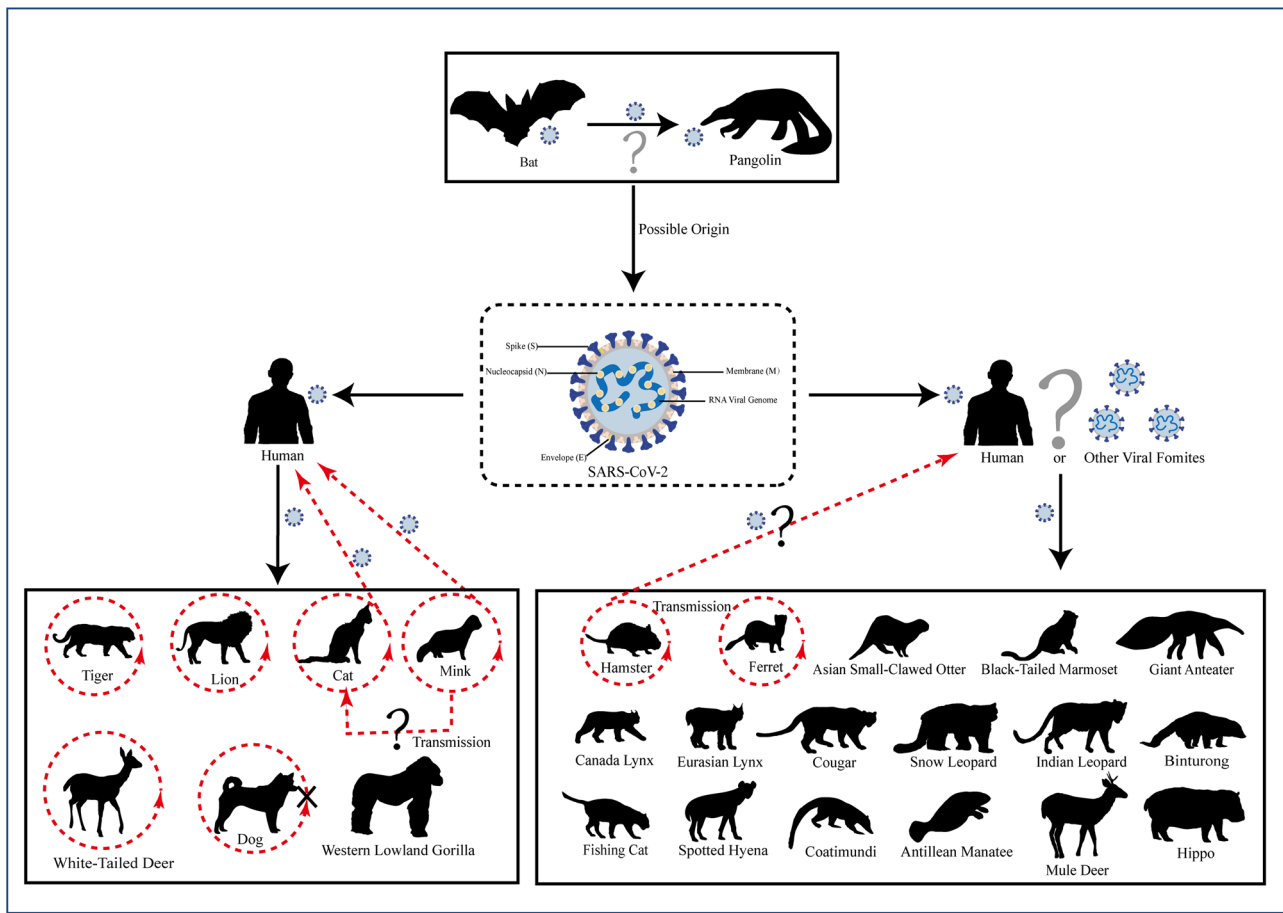


FIGURE 1 Transmission of SARS-CoV-2 in animals. Possible sources of SARS-CoV-2 and animal species naturally infected with SARS-CoV-2 are listed. Species in the left box can be infected with SARS-CoV-2 by positive human patients, and the origins of infection of the species in the right box are not yet clear. The solid black arrows indicate the transmission route of the virus. The red dash line circles indicate that the infected animals can transmit virus between members of the same species. A red dashed arrow indicates that cross-species transmission has been confirmed, or that there is research showing that cross-species transmission may occur but has not been confirmed. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

3.3 | Cricetidae

3.3.1 | Hamster

Several reports of natural SARS-CoV-2 infection in hamsters have been reported in Hong Kong, China, which was the first reported instance reported.⁵⁰ The origin of this case was associated with the SARS-CoV-2 δ variant AY.127 in Hong Kong, and an epidemiological investigation of these patients revealed that they were all associated with a local pet store.^{7,8,51} SARS-CoV-2-positive samples were found in environmental and hamster samples from pet stores as well as in the associated supply warehouses. However, the hamsters were not exhibiting clinical signs.^{7,8} Meanwhile, two different SARS-CoV-2 strains, B.1.258 and δ variants AY.127, were present in these positive hamster samples. The SARS-CoV-2 strain in three positive dwarf hamsters (*Phodopus* sp.) found in the warehouse was phylogenetically related to B.1.258.⁷ The human patient in this incident was infected with a strain of SARS-CoV-2 that shared high sequence homology to that found in the positive Syrian hamster (*Mesocricetus auratus*)

sample, both of which belonged to the AY.127 lineage.⁸ These results suggested that hamster infections were not likely a one-time event. In addition, the genetic and phylogenetic analysis of viral genomes in human patients and hamsters showed that SARS-CoV-2 could be transmitted between hamsters and likely to humans, leading to human-to-human transmission.^{7,8} So far, the source of the hamster infection has not been determined.

3.4 | Felidae

3.4.1 | Cats

There have been many reports of natural SARS-CoV-2 infection in domestic cats (*Felis catus*). The cases have been reported in at least 20 countries, including Argentina, Belgium, Brazil, Canada, Chile, the United States, France, Germany, and Greece.⁵² Cats accounted for the vast majority of naturally infected Felidae cases, and most were infected through close contact with SARS-CoV-2-infected humans. A

cat in Belgium that was naturally infected presented with clinical signs including anorexia, diarrhea, and vomiting. Genetic analysis of the cat isolate was consistent with the SARS-CoV-2 gene sequence isolated from the owner.⁵³ In a single household in Arizona, USA, a cat and a dog were both infected with SARS-CoV-2. Neither animal presented with overt clinical signs of infection; however, the owner was symptomatic.⁵⁴ Whole-genome sequencing of paired virus samples collected from animals and owners found that they were all the same B.1.575 variant strain.⁵⁴ In addition, studies reported that cats were also infected with lambda (C.37), AY.3, B.1.1.7, and B.1.1.39 variants, all of which were from households that had experienced COVID-19 infection.^{55–59} These data suggest that SARS-CoV-2 can achieve cross-species transmission from humans to cats. In addition to humans, the natural infection of cats with SARS-CoV-2 may also originate from other animals. For example, an outbreak of SARS-CoV-2 occurred in mink farms in the Netherlands, and feral cats near the farms were also infected. Because these cats were not in close contact with humans, they were likely infected by minks, not humans.⁶⁰ In addition, a case of cat-to-human transmission was reported in Songkhla Province, southern Thailand, which was the first confirmed case of cat-to-human transmission.^{61,62} A veterinarian from the Veterinary Hospital at Prince of Songkla University examined a cat belonging to two SARS-CoV-2 positive patients. The cat sneezed in front of the veterinarian who was performing a nasal swab. While the veterinarian wore a mask and gloves, no face shield or goggles were worn. The veterinarian subsequently tested positive for SARS-CoV-2. Genetic analysis of the viral genomes of the sick owners, cats, and the ill veterinarian showed that the genome sequences of the viruses they were infected with were identical. However, the veterinarian had not contacted with the cat's owner, which suggested that the veterinarian was infected by the cat.^{61,62}

3.4.2 | Tigers

The cases of natural infection of tigers (*Panthera tigris*) with SARS-CoV-2 have been reported in several countries, including the United States, Argentina, Denmark, Indonesia, Sweden, and the United Kingdom.⁵² At the Bronx Zoo in New York, USA, a Malayan tiger (*Panthera tigris jacksoni*) was first reported infection. Soon thereafter, another Malayan tiger, three Siberian tigers (*Panthera tigris altaica*), and three Kruger lions (*Panthera leo krugeri*) in the same park tested positive.^{63,64} This is the first confirmed case of natural SARS-CoV-2 infection in animals in the United States and the first case of SARS-CoV-2 infection in nondomestic Felidae in the world. The animals may have contracted SARS-CoV-2 from the breeders, who were SARS-CoV-2 positive. The presence of two distinct SARS-CoV-2 virus strains in tigers and lions were among the nine extracted from both animals and breeders. These findings suggest that tigers and lions were infected in unrelated events.^{63,64} Analysis of epidemiological and genomic data has shown that the virus strains isolated from the tigers and infected breeder were similar, which supported the

transmission between humans and tigers.⁶⁴ In addition, three Malayan tigers were also reported to be infected with the SARS-CoV-2 alpha variant (B.1.1.7) at a zoo in Virginia, USA, all of which showed clinical respiratory signs of SARS-CoV-2 infection.⁶⁵ These results indicate that cross-species transmission from humans to tigers, and among tigers is likely.⁹

3.4.3 | Lions

The cases of natural infection in lions (*Panthera leo*) with SARS-CoV-2 have been reported in the United States, India, Croatia, Colombia, Singapore, South Africa, and Spain.^{52,63,66,67} For example, in the case of Kruger lion (*Panthera leo krugeri*) infection was detected in the Bronx Zoo, New York, USA; a different strain was identified than what was isolated from the tigers at the same zoo.^{63,64} This suggests at least two separate transmission events, one in tigers and one in lions. The lion and tiger breeders were carrying different virus sequences, and the lions' breeders tested negative for viral RNA but had SARS-CoV-2 antibodies.^{63,64} Therefore, it was speculated that the virus infection of the lions may have occurred during the breeder's asymptomatic period, or the lions were infected by other asymptomatic staff.^{63,64} Nine Asian lions (*Panthera leo persica*) were infected with SARS-CoV-2 in an Indian zoo, presenting with loss of appetite, nasal discharge, and occasional cough.⁶⁶ Sequence and phylogenetic analysis showed that the infection was the δ variant (B.1.617.2), but the source of infection could not be determined. Still, they were presumed to have been indirectly infected by fomites.⁶⁶ In addition, four Angora lions (*Panthera leo bleyenberghi*) and three breeders were infected with SARS-CoV-2 at the Barcelona Zoo in Spain. Human-lion transmission of SARS-CoV-2 is indicated by the fact that a breeder had the same SARS-CoV-2 genetic sequence as the lions, the chronological sequence of events, and the viral kinetic analysis.⁶⁷

3.4.4 | Cougars

The cases of natural SARS-CoV-2 infection in cougars (*Puma concolor*) have been reported in Argentina, South Africa, and the United States.⁵² A cougar was confirmed to have SARS-CoV-2 at a wild animal exhibitor in Texas, USA, accompanied by clinical signs such as coughing, and wheezing.⁶⁸ This was the first confirmed positive cougar in the United States, which possibly had been infected by an infected team member or volunteer.⁶⁸ In addition, a cougar infected with SARS-CoV-2 was also reported in a zoo in Johannesburg, South Africa, which exhibited mild clinical signs. The source of infection could not be determined as insufficient viral RNA was extracted from the cougar for sequencing.¹⁰

3.4.5 | Snow leopard and Indian leopard

Natural infection of SARS-CoV-2 in snow leopards (*Panthera uncia*) has only been found in the United States.⁵² Three snow leopards at

the Louisville Zoo in Kentucky tested positive after presenting with mild respiratory signs, occasional dry cough, or wheezing. The leopards were suspected to have been infected by asymptomatic staff.^{12,13} A wild Indian leopard (*Panthera pardus fusca*) infected with SARS-CoV-2 was found dead in India.¹⁴ Whole-genome sequence analysis confirmed that the Indian leopard had been infected with the SARS-CoV-2 δ variant, possibly from humans.¹⁴

3.4.6 | Eurasian lynx and Canada lynx

The lynx SARS-CoV-2 cases have been identified in Croatia and the United States.⁵² A Eurasian lynx (*Lynx lynx*) at the Zagreb Zoo Park in Croatia was infected and developed clinical respiratory signs.¹⁵ SARS-CoV-2 infection was also confirmed in a Canada lynx (*Lynx canadensis*) at a zoo in Pennsylvania, USA, with clinical signs including coughing and lethargy.¹⁶ Up to now, the source of infection in the two animals has not been identified.

3.5 | Viverridae

3.5.1 | Fishing cats and binturong

SARS-CoV-2 infection of a fishing cat (*Prionailurus viverrinus*) and a binturong (*Arctictis binturong*) were confirmed at a zoo in Illinois, USA.^{17,19} The fishing cat presented with lethargy and gastrointestinal signs, but the binturong was asymptomatic. Samples were collected when the first tiger infection case was identified in the park.^{17,19} Currently, the cases of SARS-CoV-2 infection in both of the two species have only been found in the United States, and the source of infection has not been identified.

3.6 | Canidae

3.6.1 | Dogs

Dogs (*Canis lupus familiaris*) infected with SARS-CoV-2 have been reported in Argentina, Brazil, Canada, Spain, China, Thailand, the United States, and the United Kingdom. Most dogs were infected through close contact with SARS-CoV-2-infected owners.⁵² Two asymptomatic SARS-CoV-2 positive dogs were found in Hong Kong, both from families with SARS-CoV-2-positive members.^{2,69} Whole-genome sequencing found that the viral gene sequences of the two domestic dogs were identical to those from the positive humans in their respective families.^{2,69} Meanwhile, While one dog within the household was infected, another dog in the household was not, suggesting challenges in dog-dog SARS-CoV-2 transmission.^{2,69} In an epidemiological survey of cats and dogs from infected households in Texas, USA, it was found that three cats and one dog were infected among 17 cats and 59 dogs from 39 infected families. These data suggest that cats were more susceptible to infection than dogs.⁷⁰ At

the same time, the sequence analysis of the SARS-CoV-2 genome extracted from the infected animals found that the virus came from local SARS-CoV-2-positive patients.⁷⁰ Studies also found cases of domestic dogs infected with SARS-CoV-2 variants B.1.575, B.1.1.7, AY.3, and AY.43, which were all from human households with a history of COVID-19.^{54,71-73} Most dogs showed asymptomatic or presented with mild clinical signs after infection, such as sneezing, dry cough, and digestive problems.^{54,71-73} These results indicate that SARS-CoV-2 can achieve cross-species transmission from humans to dogs.

3.7 | Hyaenidae

3.7.1 | Spotted hyenas

The spotted hyena (*Crocuta crocuta*) is the only animal within Hyaenidae reported to be naturally infected with SARS-CoV-2, and is only known to have occurred in the United States.⁵² Two cases in spotted hyenas were confirmed at the Denver Zoo in Colorado, USA. At the same time, lions and tigers at the zoo also tested positive.⁷⁴ Infected spotted hyenas exhibited mild clinical signs, such as mild lethargy, nasal discharge, and occasional cough.^{18,74} The source of infection in the two confirmed spotted hyenas is not yet clear.

3.8 | Procyonidae

3.8.1 | Coatimundis

The coatimundi (*Nasua olivacea*) is the only animal within Procyonidae reported to be naturally infected with SARS-CoV-2, and has only been detected in the United States.⁵² After a tiger showed signs of being infected at a zoo in Illinois, USA, the medical staff collected and tested samples from various species and found that a coatimundi was also infected with SARS-CoV-2, but showed no clinical signs.^{19,20} The source of infection is not yet clear.

3.9 | Mustelidae

3.9.1 | Mink

Minks (*Neovison vison*) infected with SARS-CoV-2 have been reported in the Netherlands, Denmark, Canada, France, Spain, the United States, Italy, and others.⁵² Natural infection of minks with SARS-CoV-2 was first detected on a mink farm in the province of North Brabant in the southern Netherlands. Subsequently, the SARS-CoV-2 epidemic emerged in several mink farms in the Netherlands. Disease in the infected minks ranged from asymptomatic to respiratory, characterized by nasal discharge and dyspnea, which led to death in severe cases.^{21,75,76} Through an in-depth investigation of the outbreak in mink farms in the Netherlands, it was concluded

that the infection was introduced by humans, and was subsequently transmitted between minks.^{21,22} The virus then mutated in the minks and formed a mink SARS-CoV-2 strain.^{21,22} Whole-genome sequencing revealed that some employees of mink farms were infected with the mink strain, suggesting that minks can also transmit SARS-CoV-2 to humans.^{21,22} Based on the high sensitivity of minks to SARS-CoV-2 and the virus' evolution minks, it is reasonable to predict that variants could be repeatedly disseminated from minks to humans or other mammals, which may lead to an expanded viral transmission.^{21,60} For example, SARS-CoV-2 infection has occurred in feral cats near the mink farms in the Netherlands, which were believed to be infected by the minks.^{21,60} In addition, two minks escaped from the farm during culling of the company, and throat swabs collected from the animals were SARS-CoV-2 positive.²¹ Infection in wild mink was also reported in Utah, USA.⁷⁷ These events may trigger spillover and further dissemination of SARS-CoV-2.

3.9.2 | Ferrets

Ferrets (*Mustela putorius furo*) infected with SARS-CoV-2 have been found in Slovenia, the United States, and Spain.^{52,78,79} A ferret was infected in a household experiencing an outbreak of COVID-19 in Slovenia. The animal exhibited several clinical signs, such as gastroenteritis, pneumonia, and dehydration.⁸⁰ Whole-genome sequencing of viruses from humans and ferrets revealed that the both genomes differed by only two nucleotides, and belonged to the B.1.258 lineage.⁸⁰ A ferret in Florida, USA, was also confirmed positive for SARS-CoV-2, and the ferret was suspected to have been infected by a positive human that had been sneezing and coughing.⁷⁸ Therefore, SARS-CoV-2 is likely to achieve cross-species transmission from humans to ferrets. In addition, 6 of 71 ferrets in Spain tested positive for SARS-CoV-2. These animals did not show any clinical signs, and resampling some of these ferrets after 2 months revealed no SARS-CoV-2-positive cases, including one ferret that tested positive for SARS-CoV-2 by oropharyngeal swab 2 months earlier.⁷⁹ This suggests that although ferrets are naturally infected with SARS-CoV-2, small ferret populations are less able to sustain virus transmission in the long term.⁷⁹

3.9.3 | Asian small-clawed otters

Asian small-clawed otter (*Aonyx cinereus*) was infected with SARS-CoV-2 in an aquarium in Georgia, USA, which was the first time that an otter infected with SARS-CoV-2 had been identified in the world.^{23,52} When the Asian small-clawed otter presented with mild clinical signs such as sneezing, nasal discharge, mild lethargy, and coughing, the medical staff collected samples and subsequently confirmed infection.²³ Currently, the infection in otters has only been found in the United States, and the source of infection is suspected to be from asymptomatic animal care staff.²³

3.10 | Trichechidae

3.10.1 | Antillean manatees

Two Antillean manatees (*Trichechus manatus manatus*) were infected with SARS-CoV-2 at the National Center for Research and Conservation of Aquatic Mammals in Brazil. However, the animals did not exhibit clinical signs.^{6,24} This is the first time that a marine mammal has been infected with SARS-CoV-2, and the case of infection in this species has only been reported in Brazil. The source of infection in the Antillean manatee is not yet clear, but it may have been infected by SARS-CoV-2-positive staff, by contact with contaminated fomites in the environment.²⁴

3.11 | Cervidae

3.11.1 | White-tailed deer

Cases of SARS-CoV-2-positive White-tailed deer (*Odocoileus virginianus*) have been reported in the United States and Canada.⁵² Several studies have shown that wild white-tailed deer are highly susceptible to natural infection with SARS-CoV-2.²⁵⁻²⁷ A survey of wild white-tailed deer populations in four states (Illinois, Michigan, New York, and Pennsylvania) found that although wild white-tailed deer could be infected with SARS-CoV-2, none of the animals presented with clinical signs.²⁸ Whole-genome sequencing of the white-tailed deer identified several variants, including B.1.2, B.1.311, B.1, B.1.596, and B.1.582.^{26,81} Phylogenetic analyses based on the whole-genome sequence supported a spillover event from humans to deer, and that SARS-CoV-2 could be efficiently transmitted between deer.^{26,81} A recently emerging variant of omicron (B.1.1.529) was also detected in wild white-tailed deer.⁸² Systematic analysis showed that the omicron sequences of deer were closely clustered with recently reported human omicron sequences, which also indicates that SARS-CoV-2 could achieve cross-species transmission from humans to deer.⁸² In addition, many genetic mutations in SARS-CoV-2 were observed in white-tailed deer, which occurred with low probability in humans, but might be amplified in new hosts with high infection rates.²⁶

3.11.2 | Mule deer

Odocoileus hemionus) infected with SARS-CoV-2 was captured in Utah, USA, which was the first mule deer reportedly infected with SARS-CoV-2.³⁰ This deer was suspected to be infected by a positive human, and it was unclear whether it showed clinical signs after infection.³⁰ So far, the infection of this species has only been found in the United States.

3.12 | Hippopotamidae

3.12.1 | Hippopotamus

Two hippopotami (*Hippopotamus amphibius*) were found to be infected with SARS-CoV-2 at the Antwerp Zoo in Belgium. These animals presented with only mild clinical signs (nasal discharge).³¹ This is the first report that hippo has been infected with SARS-CoV-2. So far, the infection of this species has only been detected in Belgium. The source of infection in the hippos is unclear, as their husbandry staff were not known to be infected.³¹

4 | DISCUSSION

4.1 | Animal susceptibility

Summarizing reports of animals naturally infected with SARS-CoV-2, it appears that 24 different species are susceptible. The susceptible species include Primates, Pilosa, Rodentia, Carnivora, Sirenia, and Artiodactyla. Of the 24 species, 16 are carnivores (Table 1). The critical step for a virus to infect an animal is its ability to enter the host cells. SARS-CoV-2 entry into cells first requires the S protein on the surface of the virus to bind the host cell receptor. The S protein is then activated by a cellular protease and exerts its activity. ACE2 is the primary host cell receptor for SARS-CoV-2. Many studies have predicted the susceptibility of vertebrates to SARS-CoV-2 by analyzing the similarity of the ACE2 gene or protein sequence to human ACE2. For example, Praharaj et al.⁸³ constructed a regression model based on the binding parameters of ACE2 and S protein to predict the possibility of SARS-CoV-2 entering the animal cells of different orders such as Artiodactyla, Perissodactyla, Chiroptera, Carnivora, Lagomorpha, Primates, and Lepidoptera. The results showed that most of the Carnivora, Artiodactyla, Perissodactyla, Lepidoptera, and Primates had a high probability of virus entry. Hamsters in Rodentia also had a high probability of virus entry, but the probabilities for mice and rats were low.⁸³ The distribution of naturally infected species in Carnivora, Artiodactyla, Primates, and Rodentia can support and supplement the results to some extent.

Predicting the probability of virus entry into animals through the binding energy of SARS-CoV-2 to the host can reflect the susceptibility of animals to a certain extent, and its essence lies in the binding energy of SARS-CoV-2 to the host receptor. The binding energies between different animal receptors and the SARS-CoV-2 S protein differ. Intrinsic factors influencing these differences are a function of the S protein. The S protein consists of two subunits: S1 and S2. The S1 subunit is responsible for binding to cellular receptors, and its RBD recognizes and directly contacts host receptors (mainly ACE2) through the receptor binding motif (RBM) to form the RBD-ACE2 complex.^{84,85} The interaction between the RBD and the amino acid residues on ACE2 affects the binding ability of the virus to the host. Logically, the ACE2 receptor amino acid sequence varies with species resulting in differing RBD-ACE2 binding kinetics. This

ultimately impacts the susceptibility of the host to the virus.⁸⁶ For example, compared with the human ACE2, some key amino acid residues in the ACE2 of the rat and mouse are changed to uncharged polar amino acids. This change alters the surface properties of ACE2, and also eliminates several hydrogen keys,⁸⁶ which significantly interferes with the RBD-ACE2 interactions in the mice and rats, reducing the likelihood of these animals becoming infected with SARS-CoV-2.⁸⁶ Binding affinity between SARS-CoV-2 and the receptor is not the only factor responsible for the differences in animal susceptibility. For example, the ACE2 in dogs also has a high binding affinity and a high probability of virus entry, but dogs are less susceptible to SARS-CoV-2.^{86,87} This may be due to the presence of multiple ACE2 isoforms in dogs, one of which exists in the form of soluble ACE2.^{86,87} This ACE2 isoform may competitively inhibit the binding of the canonical ACE2 to RBD, resulting in lower susceptibility.^{86,87} In addition, the expression level of ACE2 also affects susceptibility. The difference in the binding energy between SARS-CoV-2 and the receptor, and the expression level of ACE2 actually affect the first step of SARS-CoV-2 entering the cell: the binding of the cellular receptor and the viral S protein. After the virus binds to the receptor, membrane fusion is also required. The membrane fusion process is also mediated by the S protein. Two cleavage events are involved, causing a conformational shift in the S protein to expose the fusion peptide (FP) in the S2 subunit, which facilitates the fusion of the viral envelope with the cytoplasmic or endosomal membrane.⁸⁸ Two cleavage events are located at the junction of the S1 and S2 subunits, and at the S2' cleavage site in the S2 subunit. This process mainly involves two proteases, Furin and TMPRSS2.⁸⁹ The Furin cleaves the Furin cleavage site at the S1/S2 boundary to separate the S1 and S2 subunits.⁸⁹ Subsequently, the TMPRSS2 cleaves the S2' site to further expose the internal FP for membrane fusion.⁸⁹ Therefore, proteases such as Furin and TMPRSS2 are also important triggers for the entry of SARS-CoV-2 into cells.^{89,90} The cellular expression levels of Furin and TMPRSS2 may affect the infectivity of SARS-CoV-2.⁹⁰ In addition, cells with high levels of Furin, TMPRSS2, and ACE2 co-expression may also be more susceptible to infection by SARS-CoV-2.^{90,91}

4.2 | Potential risk from animal infections

Reverse zoonotic transmission of SARS-CoV-2 has been reported in multiple animal species. Infections in most animal species were caused by humans or suspected human cross-species transmission, suggesting a high likelihood of reverse zoonotic transmission of SARS-CoV-2 from humans to animals. At the same time, the low number of secondary zoonotic events from animals to humans suggested that their likelihood of occurrence may be low. It has only been confirmed in cats, minks, and hamsters (Figure 1). Therefore, it is speculated that most animals are at less risk of SARS-CoV-2 zoonotic and reverse zoonotic cycles, and are believed to be dead-end hosts. There may be a higher risk of SARS-CoV-2 zoonotic and reverse zoonotic cycles in cats, minks, and hamsters, especially minks.

SARS-CoV-2 has also been mutated in mink populations, including a mutation Y453F on the RBD.⁹² The Y453F mutation acts as an adaptive mutation that increases the interaction of the virus with the mink ACE2 receptor, resulting in the mutant virus strain having an adaptive advantage in the mink population.⁹² At the same time, this mutation does not affect its utilization of the human ACE2 receptor, and the mink mutant virus strain can be introduced into humans.⁹² Although the mutation of SARS-CoV-2 in minks has not posed an additional risk to human infection, future SARS-CoV-2 mutations may occur in these animal hosts, possibly resulting in the production of a more contagious virus strain. These mutant strains may create new infection risks in humans. Therefore, monitoring of viral mutations in animal hosts is necessary to stay ahead of potential zoonotic events.

4.3 | The best natural animal model for COVID-19 study

Appropriate animal models are of great importance for clinical research and drug development of SARS-CoV-2. Currently, many species of animals have been naturally infected with SARS-CoV-2, and may be exploited as models for SARS-CoV-2 research. Currently, the leading natural animal models of SARS-CoV-2 include nonhuman primates (rhesus monkeys, macaques, common marmosets, and baboons), mice, Syrian hamsters, ferrets, minks, cats, and dogs.

The Syrian hamster can be used as a natural animal model of SARS-CoV-2, which is highly susceptible to SARS-CoV-2. Through related experimental infection studies, it was found that the Syrian hamsters showed mild to moderate clinical signs after infection, such as weight loss, respiratory distress, lethargy, and hunchback. The animals also exhibited lung lesions similar to those of human COVID-19, such as macrophage and neutrophil infiltration in the alveoli and bronchi, pulmonary edema, inflammation, and severe alveolar hemorrhage.⁹³ In addition, SARS-CoV-2 replication was mainly observed in the upper and lower respiratory tracts. Syrian hamsters can mimic the clinical, virological, and histopathological features of human mild to moderate COVID-19.^{94,95} Infection of Syrian hamsters varies by the sex and age, with the males showing more severe clinical signs than females, and older hamsters also exhibit more severe clinical signs than younger hamsters.⁹⁴ This infection phenomenon in hamsters reflects the gender and age differences in human COVID-19 cases.⁹⁴ SARS-CoV-2 can be transmitted among Syrian hamster populations, suggesting that hamsters can be used to study SARS-CoV-2 transmission.⁹⁴ Therefore, the Syrian hamster is an important natural animal model to study the pathogenesis, transmission, and treatment of SARS-CoV-2.

Ferrets are also highly susceptible to SARS-CoV-2 and can also be used as natural animal models. Ferrets did not exhibit or only mild clinical signs after infection, such as increased body temperature, decreased activity, and decreased appetite, and the lungs showed edema and inflammation.^{94,95} Viral replication was observed in the respiratory and gastrointestinal tracts of ferrets, but mainly in the upper respiratory tract.^{94,95} Ferrets can serve as subclinical or mild

COVID-19 models. Additionally, SARS-CoV-2 can be efficiently transmitted among ferret populations, which enables their use as a human transmission model. Replication of the SARS-CoV-2 is mainly restricted to the upper respiratory tract of ferrets, so it can be used to study prevention of upper respiratory tract infections.

Minks, which belong to the Mustelidae family, are highly susceptible to SARS-CoV-2. Weight loss and moderate respiratory signs, such as dyspnea, may occur following infection.^{94,96} In related experiments, severe lesions in the lungs of minks were observed after infection, such as severe diffuse interstitial pneumonia and pulmonary edema, which were highly similar to the lung lesions observed in human cases of COVID-19.⁹⁶ Furthermore, SARS-CoV-2 can efficiently replicate in the upper and lower respiratory tracts of minks.⁹⁶ Therefore, minks have the potential to serve as a model for moderate or severe COVID-19. In addition, SARS-CoV-2 can be widely spread in mink populations, with secondary zoonotic infection from mink to humans. Minks can be used as a model to study transmission of SARS-CoV-2.⁹⁷

Cats are highly susceptible to SARS-CoV-2, but most present with subclinical or mild disease after infection. Interstitial pneumonia, pulmonary edema, and efficient replication of the virus in the upper and lower respiratory tracts have been reported in cats after experimental infection.^{93,94,98} Therefore, cats may also serve as a model for asymptomatic or mild COVID-19. In addition, SARS-CoV-2 can be transmitted among cats and from cats to humans. Cats may serve as a model for studying the transmission of SARS-CoV-2 between humans and animals. Dogs have low susceptibility to SARS-CoV-2, and their usefulness as a natural animal model for SARS-CoV-2 is somewhat limited.^{94,97}

The usefulness of these natural animal models varies. Like any model system, they are a tool to be used to answer specific questions. For example, the ferret model can be used to study the pathogenesis of asymptomatic or mild COVID-19, Syrian hamsters for the study of mild to moderate COVID-19 pathogenesis, and mink to study the pathogenesis of moderate or severe COVID-19 in humans. Therefore, the best animal model must be selected according to the research direction when choosing an animal model. In addition, the usefulness of these natural animal models differs from other animal models. For example, SARS-CoV-2 transmission studies may not be possible to use hACE2-transgenic mice, and more natural animal models, such as hamsters and ferrets, should be used. This is because the transmission efficiency of SARS-CoV-2 among the hACE2-transgenic mice is limited.⁹⁵ However, hACE2-transgenic mice were used in the simulation of neurological infection in human COVID-19 patients, which also develops in hACE2-transgenic mice.⁹⁹

5 | SUMMARY

Of the reported cases of natural SARS-CoV-2 infection of animals, most of the infected animals were in captivity. However, some cases have also been reported in wild animals, such as black-tailed marmoset, Indian leopards, mink, white-tailed deer, and mule deer,

which increases the risk of virus spread. So far, the susceptibility and transmissibility of SARS-CoV-2 in more naturally infected species remain unclear, which are undoubtedly potential challenges for epidemic prevention and control, and animal health protection. Further research is needed to determine the susceptibility and transmissibility, and assess the risk of infection in animals to provide direction for epidemic prevention, control, and surveillance. In addition, infections in black-tailed marmoset, Indian Asian lion, manatee, or other undetermined source animals may be the result of indirect transmission via fomites, which suggest environmental monitoring to assess the risk of indirect transmission.

In conclusion, the possible animal origins of SARS-CoV-2 and the natural infection of SARS-CoV-2 are summarized in this paper, to deepen the understanding of the relationship between SARS-COV-2 and animals.

AUTHOR CONTRIBUTIONS

Ailong Sha conceived and planned the overall structure of the review. Xinyu Qiu collected the references and wrote the manuscript. The revision of the manuscript was collaboratively finished by Xinyu Qiu and Yi Liu and finally approved by Ailong Sha. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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