Experimental and natural infections of severe acute respiratory syndrome-related coronavirus 2 in pets and wild and farm animals

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Abstract

The severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has spread globally and has led to extremely high mortality rates. In addition to infecting humans, this virus also has infected animals. Experimental studies and natural infections showed that dogs have a low susceptibility to SARS-CoV-2 infection, whereas domesticated cats and other animals in the family Felidae, such as lions, tigers, snow leopards, and cougars, have a high susceptibility to viral infections. In addition, wild white-tailed deer, gorillas, and otters have been found to be infected by SARS-CoV-2. Furry farm animals, such as minks, have a high susceptibility to SARS-CoV-2 infection. The virus appears to spread among minks and generate several new mutations, resulting in increased viral virulence. Furthermore, livestock animals, such as cattle, sheep, and pigs, were found to have low susceptibility to the virus, whereas chicken, ducks, turkeys, quail, and geese did not show susceptibility to SARS-CoV-2 infection. This knowledge can provide insights for the development of SARS-CoV-2 mitigation strategies in animals and humans. Therefore, this review focuses on experimental (both replication and transmission) in vitro, ex vivo, and in vivo studies of SARS-CoV-2 infections in pets and in wild and farm animals, and to provide details on the mechanism associated with natural infection.

Keywords: animal disease, coronavirus disease 2019, infectious disease, pandemic, severe acute respiratory syndrome-related coronavirus 2.

Introduction

In December 2019, a new human infectious respiratory disease outbreak was documented in Wuhan, Hubei Province, China [1]. The disease spread rapidly through human transmission and became a global pandemic. The disease had a high health impact, amounting to 422,510,872 cases and 5894,569 deaths by February 19, 2022 [2]. The causative agent of the disease was identified as a new coronavirus strain [1]. As such, the disease was designated by the World Health Organization as the coronavirus disease 2019 (COVID-19), and the virus was named as the severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses [3]. The SARS-CoV-2 genome was 96.2% identical to the bat coronavirus RaTG13, Rhinolophus affinis, which was isolated at the Yunnan Province in China [4]. The increased genomic similarity and close phylogenetic tree prove that bats were the origin of SARS-CoV-2 [4]. The intermediate host appeared to be the Malayan pangolin (Manis javanica), whose genome Pangolin CoV is 91% identical to that of the SARS-CoV-2 and is 90.55% identical to that of the BatCoV RaTG13 [5]. Snakes and turtles can be considered as intermediate hosts, but this is still controversial and requires further investigation [6]. SARS-CoV-2 was transmitted to humans in Wuhan, China [1], and spread worldwide. The first cases of SARS-CoV-2 infections were identified in Australia on January 19, 2020 [7], in Europe on January 24, 2020 [8], in the Americas on February 29, 2020 [9], and in the African continent on March 5, 2020 [10].

SARS-CoV-2 belongs to the subgenus Sarbecovirus (genus Betacoronavirus) in the family Coronaviridae. It is an enveloped virus with a single-stranded, positive-sense ribonucleic acid (RNA) genome with a nucleotide size of ~30 kb [1,11]. The SARS-CoV-2 genome encodes four structural proteins: The nucleocapsid protein (N), membrane protein (M), envelope protein (E), and surface spike protein (S) [1,11]. The S-protein of SARS-CoV-2 is a glycosylated transmembrane protein that forms a homotrimer structure. It protrudes from the viral surface and mediates viral entry into host cells [12].

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S-protein of SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor as its binding receptor [13]. The sequence of the receptor-binding domain (RBD) of SARS-CoV-2, which includes the receptor-binding motif (RBM) of the S-protein, directly contacts the ACE2 receptor [13-15]. Human ACE2 is highly expressed in the lungs, heart, kidney, bladder, and gastrointestinal system [14,16]. ACE2 may also be present in mammalian cells. Analyses of the phylogenetic tree of animals that come into close contact with humans, such as pets and livestock, and ACE2 homology with the human ACE2 in various mammalian cells, showed a high degree of homology similarity [17-20]. In silico studies showed that ACE2 receptors from various domesticated animals, such as Felis catus (cat) and Canis lupus familiaris (dog), are highly homologous. F. catus and C. lupus familiaris have high degrees of similarity to human ACE2 of the orders of 85.2% and 83.4%, respectively [20]. Likewise, livestock, such as Bos taurus (cow), Ovis aries (sheep), and Sus scrofa domesticus (pig), exhibit high similarity [17-20]. The interactions between the ACE2 amino acids of the cat, dog, cow, sheep, and pig and the RBD and RBM of the SARS-CoV-2 S-protein were predicted to allow the binding of SARS-CoV-2 [17,18]. Analyses of changes in the binding energy (ΔG) of the SARS-CoV-2 S-protein and the ACE2 complexes from cats, dogs, cows, sheep, and pigs showed that these animals belong to the risk category of SARS-CoV-2 infections, as indicated by ΔG values ≤3.72 [21]. Consequently, these findings support the susceptibility of domesticated and livestock animals to SARS-CoV-2 infections.

In addition to infecting humans, SARS-CoV-2 has been reported to infect animals. Experimental infections of SARS-CoV-2 in animals have been reported in cats, dogs, ferrets, and poultry (March 2020) [22]. SARS-CoV-2 RNA has also been detected by the reverse transcription-polymerase chain reaction (RT-PCR) in pets from owners with confirmed COVID-19 infections. The first case was reported in Hong Kong (February 2020) [23], and in cats in Hong Kong (February-August 2020) [24], Belgium (March 2020) [25], and France (April 2020) [26]. The serological surveys found antibodies against SARS-CoV-2 in cats from Wuhan, China (during January-March 2020) [27] and in cats and dogs in Italy (May 2020) [28]. Furthermore, SARS-CoV-2 was detected in wild animals, such as lions, and tigers at the Bronx Zoo in New York City, United States of America (USA) in March 2020 [29,30]. Recently, antibodies to SARS-CoV-2 were also detected in wild whitetailed deer (Odocoileus virginianus) during January-March 2021 in four states in the USA [31]. SARS-CoV-2 RNA was detected in wastewater in Australia (published online on April 18, 2020) [32] and in the USA in January 2021 [33]. Both the SARS-CoV-2 RNA virus and antibodies against SARS-CoV-2 were also detected in farmed minks. The first case was also detected in the Netherlands during April and May 2020 [34]. Furthermore, SARS-CoV-2 was reported to be transmitted from humans to minks, which led to the development of zoonotic diseases that have been proved to be transmitted back to humans [35]. Many animals, including those with experimentally induced or natural infections, are not yet known for their susceptibility to SARS-CoV-2 infections and many cases of natural infection have not been reported.

Therefore, this review focuses on experimental studies of SARS-CoV-2 infections, including in vitro, ex vivo, and in vivo studies on viral replication and transmission capabilities in pets and wild and farm animals. This explains the evidence of natural cases of SARS-CoV-2 infections in domesticated animals, including cats, dogs, minks, and wild animals, such as big cats and wild deer, in all continents until October 2021. This knowledge can be used to determine policy strategies adopted to mitigate the spread of infectious diseases in both animals and humans.

### SARS-CoV-2 Infections in Pets

#### SARS-CoV-2 infections in cats

Some animals have been known to be experimentally infected with the SARS-CoV-2 virus. In addition, there has been evidence of natural infections in various animals from several countries, including China, which was the first country in which human infections were found, and in other countries in Asia, Europe, Australia, Africa, and the Americas. Some studies conducted to challenge animals against SARS-CoV-2 infection are presented in Table-1 [22,36-50], whereas natural infections in animals, including domestic animals, farm animals, and wild animals, are listed in Table-2 [23-29,31,34,35,51-66], and natural infections in the USA are listed in Table-3 [67-90]. Experimental infections and natural cases with the presumed sources of infection and their transmission are summarized in Figure-1 [4,5,23-29,31,34,35,40,41,43-66,91].

Experimental studies on SARS-CoV-2 replication and transmission have been observed in cats [22,36-39]. The viral replication was investigated in juvenile [22], sub-adult [22,36,38,39], and adult cats [37]. In juvenile cats, SARS-CoV-2 was efficiently replicated in the upper and lower respiratory tracts [22]. In young cats, viral RNA was replicated and detected in nasal or oropharyngeal swabs during the 1st week post-infection and peak viral shedding at 4-5 days post-infection [36,38,39]. In sub-adult cats, the virus replicated efficiently in the upper respiratory tract in the beginning of infection, but some replicated in the lower respiratory tract and in the small intestine [22]. Viral replication and shed viruses were also found orally and nasally up to days 5 post-infection in adult cats [37].

All young and sub-adult cats did not show clinical signs and symptoms of the disease [36,38,39]. However, the histopathological features of the respiratory tract showed lymphocytic inflammation.
| Species | Method | Age | Route and Dose | Virus Isolation | Clinical Sign | Replication virus | Antibody to SARS-CoV-2 | Transmission | Susceptibility | Reference |
|---------|--------|-----|----------------|-----------------|---------------|------------------|-----------------------|--------------|----------------|-----------|
| Cat (*Felis catus*) | In vivo | 70-100 days | Intranasal with 10^5 PFU of CTan-H | SARS-CoV-2/CTan/human/2020/Wuhan (CTan-H) | N/A | Yes, and shed virus | Yes | Yes | High | [22] |
| In vivo | 5-18-week-old | Intranasal, oral, intratracheal, ocular by 5.2×10^5 PFU | UT-NCGM02/Human/2020/Tokyo | No | Yes, and shed virus | Yes | Yes | High | [36] |
| In vivo | 6-9 months | Intranasal with 10^5 PFU of CTan-H | N/A | Yes, and shed virus | Yes | Yes | High | [22] |
| In vivo | 5-8 years | Nares (500 μL/nare) for a total volume of 1 mL (3.0×10^5 PFU) | SARS-CoV-2 virus strain WA1/2020WY96 | No | Yes, and shed virus | Yes | Yes | High | [37] |
| In vivo | 15-18-week-old | Intranasal, oral, intratracheal, ocular by 5.2×10^5 PFU | UT-NCGM02/Human/2020/Tokyo | No | Yes, and shed virus | Yes | Yes | High | [38] |
| In vivo | 4.5-5 months | Intranasal and oral with 1×10^6 TCID50/mL | SARS-CoV-2 USA-WA1/2020 strain | No | Yes, and shed virus | Yes | Yes | High | [39] |
| Dog (*Canis lupus*) | In vivo | 3 months | Intranasal with 10^5 PFU of CTan-H | SARS-CoV-2/CTan/human/2020/Wuhan (CTan-H) | N/A | Yes, but not shed virus | Yes | No | Low | [22] |
| In vivo | 5-6 years | Nares (500 μL/nare) for a total volume of 1 mL (1.4×10^5 PFU) | SARS-CoV-2 virus strain WA1/2020WY96 | No | Yes, but not shed virus | Yes | N/A | Low | [37] |
| Cattle (*Bos taurus*) | In vitro: bovine turbinate, *Bos taurus* trachea normal (EBTr (NBL-4)), cow pulmonary artery epithelial, primary fetal bovine lung, and fetal bovine kidney cells | N/A | Multiplicity of infection of 1 or 0.1 (MOI=1 or 0.1) | SARS-CoV-2 isolate TGR/NY/20 | N/A | Not replicate | N/A | N/A | N/A | [40] |

(Contd...)
| Species          | Method                        | Age     | Route and Dose                                                                                                                                                                                                 | Virus Isolation                                                                 | Clinical Sign     | Replication virus | Antibody to SARS-CoV-2 | Transmission | Susceptibility | Reference |
|------------------|-------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------|-------------------|------------------------|--------------|----------------|-----------|
| **Cattle (Bos taurus)** | *Ex vivo*: Respiratory ex vivo organ cultures | 18 months | Infected with $10^3$ TCID$_{50}$/mL                                                                                                                                  | SARS-CoV-2/INMI1-Isolate/2020/Italy (D614); SARS-CoV-2/IZSAM/46419(D614G)       | N/A               | Yes               | N/A                    | N/A          | N/A            | [41]      |
|                  | *In vivo*                                                                 | 6 weeks | Intratracheal or intravenous, 5 mL each respective route                                                                                                           | SARS-CoV-2 isolate TGR/NY/20                                                    | High temp and mild caught | Yes, but not shed virus | Yes                    | N/A          | Low            | [40]      |
|                  | *In vivo*                                                                 | <1 year | Intranasal with $1\times10^5$ 50% tissue culture infectious dose of SARS-CoV-2 Strain 2019\_nCoV Muc-IMB-1                                                 | N/A                                                                            | Yes, but not shed virus | Yes                | N/A                    | No           | Low            | [42]      |
| **Sheep (Ovis aries)** | *Ex vivo*: Respiratory ex vivo organ cultures                                 | 10 months | Infected with $10^3$ TCID$_{50}$/mL                                                                                                                                          | SARS-CoV-2/INMI1-Isolate/2020/Italy (D614); SARS-CoV-2/IZSAM/46419(D614G)       | N/A               | Yes               | N/A                    | N/A          | Low            | [41]      |
| **White tail deer (Odocoileus virginianus)** | *In vitro*: Deer lung cells                                                | N/A     | Inoculated multiplicities of infection of 0.1 and 1                                                                                                                  | SARS-CoV-2 lineage A WA1 strain                                                  | N/A               | Yes               | N/A                    | N/A          | N/A            | [43]      |
|                  | *In vitro*: lung cells isolated from white-tailed deer, mule deer and elk | N/A     | Infected at approximately 0.1 MOI                                                                                                                                   | SARS-CoV-2-2 isolate TGR/NY/20                                                   | N/A               | Yes               | N/A                    | N/A          | N/A            | [44]      |
|                  | *In vivo*                                                                 | 6 weeks | Intranasal with 5 mL (2.5 mL per nostril) of a virus suspension containing $10^{6.3}$ TCID$_{50}$/mL                                                                 | SARS-CoV-2 isolate TGR/NY/20                                                    | Subclinical viral infection | Yes, and shed virus | Yes                    | High         |                | [43]      |
|                  | *In vivo*                                                                 | 2 years | Intranasal and oral with 2 mL dose of $1\times10^6$ TCID$_{50}$/per animal                                                                                           | 1:1 titer ratio of lineage A WA1 and the alpha VOC B.1.1.7 strain               | Subclinical viral infection | Yes, and shed virus | Yes                    | Yes, and vertical | High         | [44]      |

(Contd...)
Table-1: (Continued).

| Species | Method | Age | Route and Dose | Virus Isolation | Clinical Sign | Replication virus | Antibody to SARS-CoV-2 | Transmission | Susceptibility | Reference |
|---------|--------|-----|----------------|-----------------|--------------|-------------------|------------------------|--------------|---------------|-----------|
| Pig (Sus scrofa domesticus) | In vitro: Porcine kidney-15, swine kidney -6, and swine testicle | N/A | Inoculated with 10^5 TCID_{50} SARS-CoV-2 | SARS-CoV-2 2019_nCoV Muc-IMB-1 | N/A | Yes, in SK-6 and ST | N/A | N/A | N/A | [45] |
| In vitro: ST and PK-15 cell lines | N/A | 0.05 MOI of passage 3 of the VeroE6-passaged SARS-CoV-2 | SARS-CoV-2 USA-WA1/2020 isolate | N/A | Yes, in ST and PK-15 | N/A | N/A | N/A | [46] |
| Ex vivo: Respiratory ex vivo organ cultures | 12 months | Infected with 10^3 TCID_{50}/mL | SARS-CoV-2/INMI1-Isolate/2020/Italy (D614); SARS-CoV-2/IZSAM/46419 (D614G) | N/A | Not detected | N/A | N/A | N/A | [41] |
| In vivo | 5 weeks | Oral, intranasal, intratracheal with 1x10^5 TCID_{50} of SARS-CoV-2 | SARS-CoV-2 USA-WA1/2020 isolate | No | Not detected | Not detected | No | No | [46] |
| In vivo | N/A | Intranasal with 10^0 PFU of CTan-H | SARS-CoV-2/CTan/human/2020/Wuhan (CTan-H) | N/A | Not detected | Not detected | No | No | [22] |
| In vivo | 9 weeks | Intranasal with 10^5 TCID_{50} SARS-CoV-2 isolate (GISAID ID EPI_ISL_510689) | No | Yes, but not shed virus | Yes, at IM, IV route | N/A | No | [45] |
| In vivo | 5-6 weeks | Intranasal, intratracheal, intramuscular and intravenous 10^5.8 TCID_{50} | SARS-CoV-2 isolate used in our study (TGR1/NY/20) | No | Yes, but not shed virus | No | Low | [47] |
| In vivo | 8 weeks | Intranasal and pharynx routes of 10^0 PFU/animal | SARS-CoV-2 isolate hCoV-19/Canada/ON-VIDO-01/2020 | No, but an animal yes | Yes, but not shed virus | No | Low | [48] |
| In vivo | 3 weeks | Intravenous, intratracheal, and intranasal 6.8x10^6 TCID_{50}/mL | SARS-CoV-2 isolate used in our study (TGR1/NY/20) | No | Yes, but not shed virus | No | Low | [49] |
| Species                  | Method                          | Age   | Route and Dose                          | Virus Isolation                                                                 | Clinical Sign | Replication virus | Antibody to SARS-CoV-2 | Transmission | Susceptibility | Reference |
|--------------------------|---------------------------------|-------|----------------------------------------|--------------------------------------------------------------------------------|---------------|------------------|------------------------|--------------|----------------|-----------|
| Chickens \((Gallus gallus domesticus)\) | In vivo: Embryonating chicken eggs | N/A   | Yolk sac, chorioallantoic sac, and chorioallantoic membrane | USA-WA1/2020 isolate of SARS-CoV-2 (BEI NR-58221) | N/A           | Not detected     | Not detected           | N/A          | No             | [50]      |
|                          | In vivo: ECE                    | N/A   | Inoculated SARS-CoV-2 in ECE           | SARS-CoV-2 2019_nCoV Muc-IMB-1                                                  | N/A           | Not detected     | N/A                    | N/A          | No             | [45]      |
|                          | In vivo                         | 5 weeks | Intranasal with 10⁵ TCID₅₀ SARS-CoV-2  | SARS-CoV-2 2019_nCoV Muc-IMB-1                                                  | No            | Not detected     | Not detected           | N/A          | No             | [45]      |
|                          | In vivo                         | N/A   | Challenged with SARS-CoV-2            | USA-WA1/2020 isolate of SARS-CoV-2 (BEI NR-58221) SARS-CoV-2/CTan/Human/2020/Wuhan (CTan-H) | No            | Not detected     | Not detected           | N/A          | No             | [50]      |
| Turkeys \((Meleagris gallopavo)\) | In vivo                         | N/A   | Challenged with SARS-CoV-2            | USA-WA1/2020 isolate of SARS-CoV-2 (BEI NR-58221) SARS-CoV-2/CTan/Human/2020/Wuhan (CTan-H) | No            | Not detected     | Not detected           | N/A          | No             | [50]      |
| Ducks \((Anas platyrhynchos domesticus)\) | In vivo                         | N/A   | Intranasal with 10⁵ PFU of CTan-H     | SARS-CoV-2/CTan/Human/2020/Wuhan (CTan-H)                                      | N/A           | Not detected     | Not detected           | No           | No             | [22]      |
|                          | In vivo                         | N/A   | Challenged with SARS-CoV-2            | USA-WA1/2020 isolate of SARS-CoV-2 (BEI NR-58221) SARS-CoV-2/CTan/Human/2020/Wuhan (CTan-H) | No            | Not detected     | Not detected           | N/A          | No             | [50]      |
| Quail \((Coturnix japonica)\) | In vivo                         | N/A   | Challenged with SARS-CoV-2            | USA-WA1/2020 isolate of SARS-CoV-2 (BEI NR-58221) SARS-CoV-2/CTan/Human/2020/Wuhan (CTan-H) | No            | Not detected     | Not detected           | N/A          | No             | [50]      |
| Geese \((Anser cygnoides)\) | In vivo                         | N/A   | Challenged with SARS-CoV-2            | USA-WA1/2020 isolate of SARS-CoV-2 (BEI NR-58221) SARS-CoV-2/CTan/Human/2020/Wuhan (CTan-H) | No            | Not detected     | Not detected           | N/A          | No             | [50]      |

PFU=Plaque-forming units, SARS-CoV-2=Severe acute respiratory syndrome-related coronavirus 2, N/A=Not available
### Table 2: Natural infections of SARS-CoV-2 in pet, wild and farm animals.

| Species         | Location          | Sample Sources                                                      | Total sample | Total Positive | Clinical Sign                                      | RNA Virus Detected | Antibody to SARS-CoV-2 | Reference |
|-----------------|-------------------|---------------------------------------------------------------------|--------------|----------------|---------------------------------------------------|--------------------|-------------------------|-----------|
| Cat (Felis catus) | Wuhan (China)     | Animal shelters, pet hospital, and Households confirmed COVID-19     | 102          | 15             | N/A                                               | Negative           | Positive                | [27]      |
|                  | Hong Kong (China) | Households confirmed COVID-19                                       | 7            | 0              | Asymptomatic                                      | Negative           | Negative                | [23]      |
|                  | Hong Kong (China) | Households confirmed COVID-19                                       | 50           | 6              | Asymptomatic                                      | Positive           | Positive                | [24]      |
| Spain            | Households confirmed COVID-19 |                                                              | 8            | 1              | Asymptomatic                                      | Positive           | N/A                     | [52]      |
| Spain            | Households confirmed COVID-19 |                                                              | 1            | 1              | Feline hypertrophic cardiomyopathy, but the animal was also infected by SARS-CoV-2 | Positive | Positive | [53] |
| Belgium          | Households confirmed COVID-19 |                                                              | 1            | 1              | Mild gastrointestinal and respiratory signs       | Positive           | Positive                | [25]      |
| France           | Households confirmed COVID-19 |                                                              | 22           | 1              | Mild respiratory and digestive signs.              | Positive           | Positive                | [26]      |
| Italy            | Households confirmed COVID-19 or living in geographic areas that were severely affected by COVID-19 | | 191 | 11 | Not clearly explained | Negative | Positive | [28] |
| Rio de Janeiro (Brazil) | Households confirmed or not confirmed COVID-19 and stray animals | | 49 | 1 | N/A | Negative | Positive | [54] |
| Rio de Janeiro (Brazil) | Households confirmed COVID-19 | | 10 | 4 | Unspecified, mild, reversible signs, respiratory or gastrointestinal signs | Positive | Positive | [55] |
| New York (USA)   | Households confirmed COVID-19 | | 2 | 2 | Sneezing, clear ocular discharge, and mild lethargy | Positive | N/A | [51] |
| Tiger (Panthera tigris) | New York (USA) | Bronx Zoo | 5 | 4 | Mild respiratory signs | Positive | N/A | [29] |
|                  | Jakarta (Indonesia) | Ragunan Jakarta Zoo | 2 | 2 | Mild respiratory signs and general symptoms | Positive | N/A | [65,66] |
| Lion (Panthera leo) | New York (USA) | Bronx Zoo | 3 | 3 | Mild respiratory signs | Positive | N/A | [29] |
| Catalonia (Spain) | Barcelone | Zoo Arignar Anna Zoological Park in Chennai | 12 | 3 | Mild respiratory signs | Positive | Positive | [64] |
| Tamil Nadu (India) | Arignar Anna Zoological Park in Chennai | | 11 | 9 | Mild respiratory signs and general symptoms | Positive | N/A | [62] |

(Contd...)
| Species | Location | Sample Sources | Total sample | Total Positive | Clinical Sign | RNA Virus Detected | Antibody to SARS-CoV-2 | Reference |
|---------|----------|----------------|--------------|----------------|---------------|---------------------|------------------------|-----------|
| Uttarakhand and Rajasthan (India) | Lion Safari Park, Etawah and Nahargarh Biological Park | 3 | 12 | Mild respiratory signs and general symptoms | Positive | Positive | [63] |
| Snow leopard (Panthera uncia) | Louisville Zoo | 3 | 3 | Mild respiratory signs | Positive | N/A | [61] |
| Cougar (Puma concolor) | San Diego Zoo | 1 | 1 | NOT A | Positive | N/A | [60] |
| Dog (Canis lupus familiaris) | Quarantine animal from households with confirmed COVID-19 | 15 | 2 | Asymptomatic | Positive | Positive | [23] |
| Spain | Households confirmed COVID-19 | 12 | 0 | Asymptomatic | Negative | N/A | [52] |
| France | Households confirmed COVID-19 | 11 | 0 | Mild respiratory and digestive signs | Negative | Negative | [26] |
| Italy | Households confirmed COVID-19 or living in geographic areas that were severely affected by COVID-19 | 451 | 15 | Not clearly explained | Negative | Positive | [28] |
| Rio de Janeiro (Brazil) | Households confirmed or not confirmed COVID-19 and stray animals | 47 | 1 | N/A | Negative | Positive | [54] |
| Rio de Janeiro (Brazil) | Households confirmed COVID-19 | 29 | 9 | Unspecified, mild, reversible signs, respiratory or gastrointestinal signs | Positive | Positive | [55] |
| White tail deer (Odocoileus virginianus) | Wild white-tailed deer population | 385 | 152 | N/A | N/A | Positive | [31] |
| Mink (Neovison vison) | Mink farms | 16 mink farms | N/A | Mild to severe respiratory distress | Positive | N/A | [34,35,56] |
| Denmark | Mink farms | 290 mink farms | N/A | Positive | N/A | [57] |
| Poland | Mink farms | 28 mink farms | N/A | Positive (70% sample) | Positive (30% sample) | [58] |
| Guinea pig (Cavia porcellus) | Households confirmed COVID-19 | 1 | 1 | Asymptomatic | Negative | N/A | [52] |
| Rabbit (Oryctolagus cuniculus) | Households confirmed COVID-19 | 1 | 2 | Asymptomatic | Negative | N/A | [52] |

SARS-CoV-2=Severe acute respiratory syndrome-related coronavirus 2, N/A=Not available
During early infection in combination with mixed inflammation during the peak infection period and decreased during the recovery period [38]. Moderate lesions were found in the lungs in the early infection stage [38,39] but tended to persist during the clearance of the virus, during which the lesions progressed to chronic histopathological features [38]. Adult cats exhibited no clinical signs of diseases, but histopathological features indicated subclinical pathological changes in the upper respiratory tract [37]. Juvenile cats exhibited massive lesions in the upper and lower respiratory tracts, suggesting that young cats are more susceptible to SARS-CoV-2 infections than adult cats [22]. Viral RNA obtained from nasal swabs was not detectable in re-infected animals. Microscopically, the lungs appeared with peribronchial fibrosis and thickening of the alveolar septa [38]. All these experiments revealed that cats were highly susceptible to SARS-CoV-2 infection. The virus can replicate efficiently in the respiratory tract and then shed nasally and orally, even though the cats did not exhibit any clinical symptoms [22,36-39].

The transmission of SARS-CoV-2 from inoculated cats to naive-contact cats was observed in...
**Table 3:** Natural infection of severe acute respiratory syndrome-related coronavirus 2 in USA reported by OIE.

| Species | No. of follow-up report | Location | Date of outbreak | Suspect | Case | Death | Clinical signs | Reference |
|---------|-------------------------|----------|------------------|---------|------|-------|----------------|-----------|
| Domestic cat (*Felis catus*) | No. 2 and 3 | Nassau County, Nassau, New York, NY | April 1, 2020 | 1 | 1 | - | Respiratory signs | [67,68] |
| | No. 2 and 3 | Orange County, Orange, New York | April 6, 2020 | 2 | 1 | - | Respiratory signs | [67,68] |
| | No. 5 | Carver County, Carver, Minnesota | May 20, 2020 | 1 | 1 | - | Respiratory signs | [75] |
| | No. 6 and 7 | Cook County, Cook, Illinois | May 19, 2020 | 1 | 1 | - | Respiratory signs | [76,77] |
| | No. 9 | Orange County, Orange, California | June 26, 2020 | 1 | 1 | | Respiratory and cardiac signs | [78] |
| | No. 9 | Orange County, Orange, California | June 27, 2020 | 1 | 1 | - | Asymptomatic | [78] |
| | No. 11 | Brazos County, Brazos, Texas | June 28, 2020 | 1 | 1 | - | Asymptomatic | [79] |
| | No. 11 | Maricopa County, Maricopa, Arizona | July 10, 2020 | 1 | - | - | N/A | [79] |
| | No. 12 | Brazos County, Brazos, Texas | July 17, 2020 | 1 | 1 | - | Asymptomatic | [80] |
| | No. 14 | Brazos County, Brazos, Texas | July 29, 2020 | 3 | 1 | - | Asymptomatic | [81] |
| | No. 16 | Coweta County, Coweta, Georgia | July 14, 2020 | 1 | 1 | - | Respiratory signs | [82] |
| | No. 16 | Hartford County, Hartford, Maryland | August 10, 2020 | 5 | 1 | - | Respiratory signs | [82] |
| | No. 16 | Contra Costa County, Contra Costa, California | August 13, 2020 | 1 | 1 | - | Respiratory signs | [82] |
| | No. 17 | Rapides Parish, Rapides, Louisiana | August 17, 2020 | 4 | 1 | - | Respiratory signs | [69] |
| | No. 18 | Brazos County, Brazos, Texas | August 11, 2020 | 1 | 1 | - | Asymptomatic | [70] |
| | No. 18 | Somervell County, Somervell, Texas | August 12, 2020 | 9 | 1 | - | Asymptomatic | [70] |
| | No. 18 | Brazos County, Brazos, Texas | August 21, 2020 | 1 | 1 | - | Asymptomatic | [70] |
| | No. 19 | Fayette County, Fayette, Kentucky | September 6, 2020 | 3 | 1 | - | Respiratory signs | [71] |

*(Contd…)*
Table 3: (Continued)

| Species | No. of follow-up report | Location | Date of outbreak | Suspect | Case | Death | Clinical signs | Reference |
|---------|------------------------|----------|------------------|---------|------|-------|----------------|----------|
| No. 20  | Brazos County, Brazos, Texas | September 11, 2020 | 1 | 1 | - | Asymptomatic | [72] |
| No. 21  | Lee County, Lee, Alabama | September 25, 2020 | 4 | 2 | 1 | Respiratory signs | [73] |
| No. 23  | Cumberland County, Cumberland, Pennsylvania | October 02, 2020 | 1 | 1 | - | Respiratory signs | [74] |
| Total of Domestic cat (Felis catus) | No. 4 | Richmond County, Richmond, New York | April 15, 2020 | 44 | 21 | 2 | Respiratory signs | [86] |
| Domestic dogs (Canis lupus familiaris) | No. 8 | Berrien County, Berrien, Georgia | June 22, 2020 | 3 | 1 | - | Neurological signs | [83] |
| No. 9  | Orange County, Orange, California | June 28, 2020 | 1 | 1 | - | Asymptomatic | [78] |
| No. 10 | Charleston County, Charleston, South Carolina | June 26, 2020 | 3 | 1 | - | Respiratory signs | [84] |
| No. 11 | Brazos County, Brazos, Texas | June 28, 2020 | 2 | - | - | Asymptomatic | [79] |
| No. 11 | Maricopa County, Maricopa, Arizona | July 10, 2020 | 3 | 1 | - | Respiratory signs | [79] |
| No. 12 | Brazos County, Brazos, Texas | July 17, 2020 | 2 | - | - | N/A | [80] |
| No. 13 | Livingston Parish, Livingston, Louisiana | July 22, 2020 | 2 | 1 | - | N/A | [85] |
| No. 14 | Brazos County, Brazos, Texas | July 28, 2020 | 1 | 1 | - | Asymptomatic | [81] |
| No. 14 | Moore County, Moore, North Carolina | August 4, 2020 | 2 | 1 | 1 | Respiratory signs and cardiac arrest | [81] |
| No. 16 | Hartford County, Hartford, Maryland | August 10, 2020 | 1 | - | - | N/A | [82] |
| No. 17 | Rapides Parish, Rapides, Louisiana | August 17, 2020 | 1 | - | - | N/A | [69] |
| No. 18 | Brazos County, Brazos, Texas | August 11, 2020 | 1 | 1 | - | Respiratory signs | [70] |
| No. 18 | Brazos County, Brazos, Texas | August 12, 2020 | 2 | 1 | - | Respiratory signs | [70] |
| No. 18 | Somervell County, Somervell, Texas | August 12, 2020 | 2 | - | - | Asymptomatic | [70] |

(Contd...)
juvenile, sub-adult, and adult cats [22,36-39]. In naive co-housed cats, viral RNA was detected in rectal swabs and in the upper respiratory tract tissues at days 1-3 post-exposure, persisted at days 5-9...
post-exposure, and the shed virus reached the peak at days 4-5 post-exposure [22,36,37,39]. Viral RNA in the naive co-housed cats was detected in the upper respiratory tract and esophagus but not in the lung or other organs on day 5 post-exposure [37]. The virus was optimally replicated and longer in the upper respiratory tract [36-39] than in the lower respiratory tract [39]. Subsequently, the virus was excreted and spread from the oral or nasal cavity [36,37,39] with respiratory droplets to the naive co-housed cats through the airborne route [22]. This suggested that cats allowed viral replication and the virus were then transmitted by direct contact (co-housed) to naive cats. It is proved the transmission of SARS-CoV-2 from infected cats to other cats [22,37,39].

In addition, re-challenges of SARS-CoV-2 infections in cats were observed at 21 days [39] and 28 days after the first infection [38]. A re-challenge at 21 days showed that the animals were asymptomatic, but viral RNA was found high in the upper respiratory tract and gastrointestinal tissue, and low in the lower respiratory tract, lymphatic tissues, heart, and olfactory bulb [39]. On the contrary, re-infection at 28 days showed no viral RNA detection in nasal, oral, and rectal swabs or in the respiratory tract, brain, liver, spleen, kidney, small and large intestines, heart, and eyelid tissues on day 3 after re-infection [38]. This may be related to the immunity to SARS-CoV-2. Immunoglobulin M bound to the RBD of SARS-CoV-2 was detected on day 7 and reached the peak on day 14, and decreased up to day 28, whereas immunoglobulin G was detected on day 7 post-infection and continued to increase up to day 28; it then reached a plateau on day 42 post-infection [37]. Immunity on day 28 after the first infection may have reached its peak to provide the protective effect on the second challenge infection [37].

In addition to the proof on experimentally induced SARS-CoV-2 infections, some studies reported natural infections in several animals, as summarized in Table-2. In Hong Kong, the natural infection with SARS-CoV-2 has been observed in 6 of 50 (12%) quarantined animals from households or animals with close contact with patients with COVID-19 [24]. A serological study in cats collected from animal shelters, pet hospitals, and households with COVID-19 in Wuhan, China, from January to March 2020 showed that 15 of 102 (14.7%) cats were positive for antibodies against SARS-CoV-2. However, all nasopharyngeal and anal swabs were negative for SARS-CoV-2 viral RNA [27]. In Thailand, a serological survey was conducted on cats from April to December 2020 and showed that 4 of 1112 sera antibodies were positive to antibodies against SARS-CoV-2 [92].

Natural SARS-CoV-2 infection was reported in Europe, including Belgium, Spain, France, and Italy. In Belgium, a cat from the owner with COVID-19 in March 2020 was positive for the SARS-CoV-2 viral RNA and developed neutralizing antibodies against SARS-CoV-2 [25]. In La Rioja, Northern Spain, a study on 23 asymptomatic animals in quarantine from April 8 to May 4, 2020, including eight cats from an owner with COVID-19, found that one of eight cats was positive for SARS-CoV-2 viral RNA based on RT-PCR [52]. Two cats of the owners who died from COVID-19 on March 18, 2020, in Spain, was reported seroconverted to SARS-CoV-2; however, viral RNA was detected in the first cat but not in the second cat [53]. In France, a cohort study conducted on 22 cats from owners who were infected, or suspected to be infected, showed that a cat was positive for viral RNA and antibodies. This cat had mild respiratory and digestive signs. Furthermore, the genomic analysis of SARS-CoV-2 from this cat revealed a genome resembling the SARS-CoV-2 genome in most French humans [26]. In addition, another study in France reported that seroprevalent antibodies against SARS-CoV-2 were increased in cats and dogs from the confirmed COVID-19 household cases by 21.3% and by 2.6% in no confirmed COVID-19 households [93]. In Italy, an epidemiological study involving 277 cats living in SARS-CoV-2-positive households or in the geographic areas severely affected by COVID-19 found that several animals developed neutralizing antibodies. In contrast, viral RNA was negative in all swab samples [28].

SARS-CoV-2 infections in cats were reported in Rio de Janeiro, Brazil. Data were collected from June to August 2020 from cats living in a household with owners with confirmed COVID-19 and stray animals. Interestingly, serum from a stray cat tested positive for antibodies to SARS-CoV-2, even though the tests were negative for viral RNA [54]. Another study in the same city showed that cats from households with owners positive for COVID-19 showed positive results for viral RNA (3 of 10 household cats) and developed a neutralizing antibody to SARS-CoV-2 (two of four cats) [55].

The first infection with SARS-CoV-2 in cats in the USA was reported in April 2020 [67,68]. The other cases were reported by the World Organization for Animal Health (OIE) in the follow-up reports, with numbers of 2, 3, 5, 6, 7, 9, 11, 12, 14, 16, 17, 18, 19, 20, 21, and 23 [67-82], as listed in Table-3. SARS-CoV-2 infections were confirmed by RT-PCR in a total of 44 suspected cats and 21 cats [67-82]. In the first case, two cats had clinical signs of respiratory illness from owners with COVID-19. Both cats were positive for SARS-CoV-2 RNA and developed antibodies against SARS-CoV-2 [51,67]. Recently, in Texas, USA, infection with SARS-CoV-2 was reported in cats of the COVID-19 household, which showed 17.6% of the cats were positive for SARS-CoV-2, and 43.8% of the cats were found to have neutralizing antibodies against SARS-CoV-2 [94].

The susceptibility of animals to SARS-CoV-2 infection was predicted by comparing ACE2 of animals and humans [17,18,95]. ACE2 is the receptor
that interacts with the spike protein of SARS-CoV-2 that allows viral entry to host cells [17,18,95]. Cats ACE2 presented four amino acid changes related to Gln24Leu, Asp30Glu, Asp38Glu, and Met82Thr [95]. The residue Asp30 in ACE2 was negatively charged and formed a salt bridge with Lys417 (positively charged) in the S-protein of SARS-CoV-2. This stable bridge is located in the middle of the surface interaction [95]. The Asp30 to Glu mutation residue formed more stable bridges than Asp30 residue [95]. His34, located in the center of surface interaction, and the N-glycosylation site at residue Asn90 were similar to those of human ACE2 [17,18,95]. This predicted that cat ACE2 was suitable as the attachment site of the S-protein of SARS-CoV-2 [17,18,95]. The findings of these in silico studies were consistent with experimental studies [22,36-39] and with naturally infected cases of SARS-CoV-2 in cats [24,25,52,53,94]. This may also explain the susceptibility of cats to SARS-CoV-2 infection [24,25,52,53,94], and the ability of the virus to replicate and transmit between cats [22,36,37].

SARS-CoV-2 infections in in vivo studies [22,36-39], and mainly in naturally infected cases, did not result in clinical symptoms [96]. Although asymptomatic, thickening of the alveolar septa was found histopathologically, which indicated chronic lung inflammation [38]. Recently, an unusual clinical manifestation has been documented, which included severe myocarditis and impaired general health in cats infected by the B.1.1.7 variant of SARS-CoV-2 [97]. It was also reported previously in human patients that symptoms of acute myocarditis developed in more than 25% of critical cases because of SARS-CoV-2 infections [14]. A systematic review reported that cats developed variable mild to severe respiratory signs, with predominant presentations of sneezing and coughing, gastroenteritis (vomit and diarrhea), diminishing general health status (fever, lethargy, and lack of appetite), cardiovascular signs (cardiomyopathy, congestive heart failure, and ventricular arrhythmia), and neurological signs [96]. The unusual signs may relate to the accumulation of mutations in the SARS-CoV-2 genome, which led to changes in the virulence of the virus and result in unusual outcomes [97]. Therefore, further research is needed on SARS-CoV-2 mutations in humans and cats to increase awareness and suspicion in natural cases of SARS-CoV-2 infection, especially in asymptomatic cats.

**SARS-CoV-2 infections in dogs**

Experimental studies in dogs found that SARS-CoV-2 replicated in the respiratory tract of dogs, but animals may not transmit the virus to other dogs [22,37]. Several inoculated dogs were positive for viral RNA, thus indicating the presence of viral replication, but dogs did not shed the infectious virus [22,37]. In addition, antibodies against SARS-CoV-2 were detected in inoculated dogs but were undetectable in naive co-housed dogs [22,37].

The natural infection of SARS-CoV-2 in dogs was reported in Hong Kong for the first time from a household infected with COVID-19. The dogs were found to be positive for viral RNA and seroconverted to SARS-CoV-2 [23]. Interestingly, the SARS-CoV-2 genomes from both dogs were identical to the viral genome from a related human case [23]. In addition, a serological study in dogs during the Wuhan outbreak showed that 1.69% of the dogs’ sera were positive for SARS-CoV-2 antibodies. The positive sera were collected from the owners with COVID-19, pet hospitals, and stray animals [98]. The same result in Thailand showed that 1.66% of the sera collected from dogs during the outbreak were positive to SARS-CoV-2 antibodies [92].

In Italy, an epidemiological survey on SARS-CoV-2 infection in dogs reported that viral RNA was not detected, but several dogs with COVID-19 positive or negative owner found positive for SARS-CoV-2 neutralizing antibodies [28]. In France and Croatia, the seroprevalence of SARS-CoV-2 in dogs with COVID-19 positive owners was 15.4% [93] and 43.9% [99] respectively, whereas in the United Kingdom from the unknown owner status, the seroprevalence was 1.4% [100].

Several cases of SARS-CoV-2 infection in dogs were also reported in Rio de Janeiro, Brazil, from a household with a confirmed COVID-19 infection [55] and from a stray dog [54]. As many as 31% of dogs from households with patients with positive COVID-19 were positively infected with SARS-CoV-2, and some showed positive outcomes for antibodies to SARS-CoV-2 [55].

The first confirmed case of SARS-CoV-2 in a dog in the USA was announced on June 2, 2020. A German shepherd dog, which lived with another dog and the owner who was COVID-19 positive, developed the symptoms of respiratory illness and tested positive for viral RNA and neutralizing antibodies to SARS-CoV-2 [86,101]. In addition, several SARS-CoV-2 infection cases were reported by the OIE in follow-up reports with the numbers of 4, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 20, and 23 [59-61,69-72,74,78-86,89,102-107]. In Texas was found that 1.7% of dogs from infected COVID-19 households were positive for the viral RNA, and 11.9% were positive for neutralizing antibodies to SARS-CoV-2 [94]. A serological study in Minnesota, USA, from April to June 2020 showed that 0.98% of dogs were seropositive for the N-protein SARS-CoV-2 [102].

The S-protein of SARS-CoV-2 interacted with the ACE2 of dogs. The analysis of canine ACE2 compared with human ACE2 contained five amino acid changes. These same amino acid changes also occurred in pig ACE2. These included the residues Gln24Leu, Asp30Glu, His34Tyr, Met82Thr, and Asp38Glu [95]. Changes in Gln24Leu and His34Tyr resulted in failure of hydrogen bond formation and in the weakening of the stability of the interaction between ACE2 and
the S-protein of SARS-CoV-2 [103]. In contrast, the replacement of Asn90 residues with Asp resulted in a lack of N-glycosylation at position 90 [17,18,95]. In silico studies found the low susceptibility of dogs to SARS-CoV-2 infections [17,18,95]. In addition, no viral transmission was documented from inoculated animals to naive, close contact animals [22,23]. In the cases of natural infections, there was no confirmed evidence of COVID-19 transmission among dogs [23]. This suggests that dogs may be infected with SARS-CoV-2, but they have low susceptibility and have not transmitted the virus to other dogs [22,23].

**SARS-CoV-2 Infections in Wild Animals**

**SARS-CoV-2 infections in big cats**

Natural infections of SARS-CoV-2 in big cats have been reported in the tiger (Panthera tigris) [29,30,89,104-106], lion (Panthera leo) [29,30,104,105], snow leopard (Panthera uncia) [86,106], and cougar (Puma concolor) [61]. The first confirmed SARS-CoV-2 case was reported in the Bronx Zoo, New York City, USA, in tigers on April 4, 2020, and in lions on April 15, 2020 [104,105]. Tigers and lions showed clinical signs, such as dry cough and some wheezing, but no respiratory distress. All animals with clinical signs improved and recovered. The sources of infection were assumed to be transmissions from the zookeepers who had no clinical signs (asymptomatic) [104,105]. Epidemiologic and genomic data from the tiger and lion showed a different genotype of SARS-CoV-2, which indicated human-to-animal transmission from two different sources [29,30]. Furthermore, viral RNA shedding was found in feces and respiratory secretions of infected animals and persisted in the feces for more than 4 weeks [29,30]. Based on the infection timeline, it was assumed that the virus was transmitted from zookeepers to animals and subsequently to other animals in the same cage [29,30].

Another case in Tennessee, USA, found that three Malayan tigers (P. tigris tigris) exhibited clinical signs, including mild coughing, lethargy, and inappetence; all tigers were confirmed positive for SARS-CoV-2. It seems that the tigers were infected by the transmission of SARS-CoV-2 from an infected human. All tigers recovered [89,106]. In addition, other natural infection cases of SARS-CoV-2 in big cats and in the snow leopard at the Louisville Zoo, USA, were detected in December 2020 [61] and at the San Diego Zoo, USA, in July 2021 [60]; additionally, there was a cougar case in Texas, USA, in February 2021 [59]. In mid-September 2021, three tigers and six lions at the Smithsonian National Zoo, USA, were presumed positive for SARS-CoV-2 after they presented mild respiratory symptoms, such as coughing and sneezing, lethargy, and decreased appetite [107].

Natural cases of SARS-CoV-2 in Katanga lions (P. leo bleyenberghi) were reported in the Barcelona Zoo (Catalonia, Spain) from November to December 2020 [64]. These four lions had respiratory symptoms, such as sneezing, coughing, and nasal discharge, and developed antibodies against SARS-CoV-2 [64].

Recently, two Sumatran tigers (P. tigris sumatrae) at Ragunan Zoo, Jakarta, Indonesia, were confirmed positive for SARS-CoV-2 by RT-PCR, on July 15, 2021. These big cats presented with mild respiratory symptoms, such as lethargy, sneezing, shortness of breath, mucus secretion from the nose, and decreased appetite [65,66]. In India, nine lions [62] and three [63] Asiatic lions (P. leo persica) were reported to be positive to SARS-CoV-2 Delta variant in the B.1.617.2 lineage during May-June 2021 [62,63].

The susceptibility of the tiger, lion, leopard, and puma was analyzed by in silico studies by comparing the ACE2 of these animals with the human ACE2. ACE2 receptors from the tiger, cougar, and leopard (Panthera pardus) identified four amino acids changes, which were Gln24Leu, Asp30Glu, Asp38Glu, and Met82Thr and had His34 and N-glycosylated Asp90, the same as those for humans and cats [95,103,108]. By contrast, in lions, apart from having the same four amino differences as cats, a mutation of Asn90 to Asp resulted in the loss of N-glycosylation at site 90 [98]. Furthermore, a mutation was reported in His34 to Ser was also reported [95]. The His34 residue was considered a critical residue associated with the susceptibility of lions and tigers to SARS-CoV-2 infections [103]. The His34 to Ser mutation was predicted to decrease the binding stability between ACE2 and the SARS-CoV-2 S-protein [103]. This suggested that animals with His34Ser mutations had a lower susceptibility than animals with His34 [103].

Almost all animals had respiratory tract symptoms, with or without general symptoms of disease, such as lethargy or loss of appetite [29,30,59-61,65,66,89,104-106]. In addition, up to 96.5% of animals had a cough and 79% of animals had sneezing symptoms [96]. The appearance of the clinical signs may be explained by the ACE2 expressions in the ciliated bronchial epithelium cells from tigers and lions and in the endothelial blood vessels within the alveolar septa in tigers [109]. In view of the expressions of ACE2 in the respiratory tracts of big cats [109], the increasing number of natural infections of SARS-CoV-2 in these animals and the transmission of the virus from asymptomatic carriers [29,30,59-61,65,66,89,104-107], a SARS-CoV-2 vaccination program should be implemented in these big cats. There should be more concern about SARS-CoV-2 surveillance in wild animals to minimize the spread of SARS-CoV-2 within the animal population.

**SARS-CoV-2 infections in deer**

The susceptibility of deer to the virus was investigatet in studies in vitro and in vivo, as well as in silico. An in vitro study was performed in deer lung cells infected with SARS-CoV-2 isolate TGR/NY/20 [43] and human/USA/WA1/2020 [44]. It was found that
SARS-CoV-2 replicated in white-tailed deer (O. virginianus) and mule deer (Odocoileus hemionus) lung cells [43,44], whereas the virus did not replicate in elk (Cervus canadensis) lungs cells [44].

Furthermore, in an in vivo study, SARS-CoV-2 was replicated in white-tailed deer fawns [43] and adult deer [44] and both groups of animals experienced subclinical viral infections [43,44]. Viral RNA was detected in nasal secretions and feces in fawns for longer periods than those in adult deer [43,44], in fawns during days 1-21 post-infection [43], and in adults during days 1-10 post-infection [44]. The virus replicated in the upper respiratory and gastrointestinal tracts and was shed from nasal, oral, and rectal swabs [44].

Viral transmission occurred from inoculated animals to indirect contact animals [43,44]. Viral RNA was detected in nasal, oral, or rectal swabs of co-housed animals [44]. Infectious viruses were detected in nasal secretions and feces from indirect contact animals at days 2-7 post-infection [43]. Both inoculated and non-inoculated deer developed neutralizing antibodies [43]. Furthermore, despite the horizontal transmission between inoculated animals and indirect contact animals, the vertical transmission from the adult female deer to the fetus was also reported [44].

In vitro and in vivo studies showed a high susceptibility of deer to SARS-CoV-2 infections [43,44]. Recently, a serological survey during January-March 2021 in the USA (Michigan, Pennsylvania, Illinois, and New York states) has found SARS-CoV-2 antibodies in 40% of the wild white-tailed deer population [31]. In addition, antibodies against SARS-CoV-2 were detected in one and three sera samples in 2019 and 2020, respectively; however, these samples showed low percent inhibition values [31]. At present, the first confirmation of SARS-CoV-2 in the wild white-tailed deer was announced in Ohio, USA, on August 27, 2021 [110].

White-tailed deer, reindeer (Rangifer tarandus), and Père David’S deer (Elaphurus davidianus) were predicted to have a high susceptibility to SARS-CoV-2 infections [108]. Homology analyses of deer ACE2 revealed high similarities to humans ACE2 [108]. It showed four different amino acid residues (Asp30Glu, Leu79Met, Met82Thr, and Asn322His) and a Lys31Asn residue for Père David’S deer [108]. In addition, analyses of the interaction between ACE2 of these three species of deer and RBD of SARS-CoV-2 exhibited a high-binding score and indicated high susceptibility to viral infection [108]. Considering these in silico studies [108], the high susceptibility and transmissibility to SARS-CoV-2 infection [43,44], the high seroprevalence of SARS-CoV-2 in the wild white-tailed deer population [31], and the confirmed SARS-CoV-2 infection case in wild white-tailed deer in the world, it is necessary to monitor the deer, its predators, and other wildlife populations [31].

SARS-CoV-2 Infections in Farm Animals

SARS-CoV-2 infections in cattle and sheep

In cattle (B. taurus), an in vitro study was performed in the bovine cell line, including turbinate, trachea normal, pulmonary artery, fetal bovine lung, and fetal bovine kidney cells. Cell lines were infected with SARS-CoV-2 isolate TGR/NY/20. This indicated that SARS-CoV-2 did not replicate [40]. However, another ex vivo study in organ cultures of respiratory tract cells demonstrated that SARS-CoV-2 replicated in lung and trachea cells. The respiratory tract was also shown immunoreactive to the polyclonal antibody of ACE2 [41].

An in vivo study of SARS-CoV-2 infection in cattle showed that the virus replicated but was not transmitted [40,41]. Six-week-old calves exhibited mild symptoms, such as a high temperature and mild cough. The virus replicated, but viral shedding was not found. The calves developed neutralizing antibodies against SARS-CoV-2, but this antibody titer did not persist for more than 21 days [40]. Another study in older calves revealed that the virus replicated, but the calves did not shed the virus and there were no clinical signs [42].

Homogenetic analyses of ACE2 of the family Bovidae, including cattle (B. taurus), water buffalo (Bubalus bubalis), wild goat (Capra aegagrus), goat (Capra hircus), and sheep (O. aries), with human ACE2 exhibited high similarity. This analysis identified four amino acid residues different from those of human ACE2: Asp30Glu, Leu79Met, Met82Thr, and Asn322Tyr. Furthermore, the evaluation of the binding contact between ACE2 of those animals with RBD in the S-protein of SARS-CoV-2 predicted medium susceptibility to SARS-CoV-2 infection, at the same level as documented in the cat [108]. In addition, ACE2 receptors were expressed in the bronchiole epithelia of cattle and sheep but not in the nasal mucosa and alveoli [109]. By contrast, ACE2 receptors in cats were expressed in alveoli and Type I pneumocytes [109]. However, an in vivo study found that the infectious virus was not detected in cattle. This may indicate that cattle had low susceptibility to SARS-CoV-2 infections [40,42].

The susceptibility of sheep to SARS-CoV-2 infection was investigated in ex vivo organ cultures of respiratory tract cells infected with SARS-CoV-2 with D614 and SARS-CoV-2 with D614G. The results demonstrated that sheep lung and trachea cells exhibited ACE2 receptors and thus supported the replication of both SARS-CoV-2 variants [41]. This indicates that SARS-CoV-2 can infect sheep, but further in vivo studies are needed to confirm the susceptibility of sheep to SARS-CoV-2 infection. Likewise, research on the susceptibility of other ruminant groups to SARS-CoV-2 infections still requires further in vitro and in vivo research studies.
SARS-CoV-2 infections in pigs

The susceptibility of pigs to SARS-CoV-2 infections was investigated in vitro using swine cell lines. Swine testicular and kidney cells (SK-6 and PK-15) [45,46] supported SARS-CoV-2 replication. In contrast, SARS-CoV-2 did not replicate in ex vivo respiratory organ cultures from pigs [41].

In vivo studies in domesticated pigs (S. scrofa domesticus) found no viral replication and transmission of SARS-CoV-2 from inoculated animals to contact-naive animals [22,45-47]. Viral RNA was not detectable in oropharyngeal and rectal swabs from pigs inoculated with $10^6$ PFU of CTan-H or naive animals at all-time points, and there were no antibodies to SARS-CoV-2 [22]. Pigs infected with $10^6$ TCID$_{50}$ of 2019-nCoV Muc-IMB-1 yielded the same results [45]. Inoculated and naive-contact animals had no clinical signs. Viral RNA, antibodies, and organ lesions after necropsy were also not detected [45]. Both those studies challenged pigs intra-nasally [22,45]. Another study that carried out the challenge through the intranasal, oral, and intratracheal routes simultaneously obtained the same results, despite the higher dose (dose $10^6$ TCID$_{50}$ of SARS-CoV-2) [46]. Meanwhile, pigs inoculated with $10^6$ TCID$_{50}$ of SARS-CoV-2 intravenously and intramuscularly were shown to have low levels of anti-SARS-CoV-2 antibodies, despite the fact that they did not show clinical signs, and viral RNA was not detected in nasal or rectal swabs [47].

Although the previous studies that challenged pigs with SARS-CoV-2 through intranasal, intratracheal, oral, intramuscular, and intravenous routes showed that pigs were not susceptible to SARS-CoV-2 infections [22,45-47], there were two research groups reported different results [48,49]. First, pigs aged 8 weeks were challenged with $10^6$ PFU/animal of SARS-CoV-2 isolate hCoV-19/Canada/ON-VIDO-01/2020 via the nasal and pharynx routes. It was the first study that detected low-level viral RNA in nasal washing and oral fluids after inoculation. However, it was not detectable in other swab samples (oral, nasal, and rectal swabs). The study found neutralizing antibodies against SARS-CoV-2 at low levels in two pigs. One pig presented cough and mild depression symptoms from day 1 to 4 post-infection. The infectious virus was detected in this pig in the submandibular lymph node at day 13 post-infection [48]. A second study on pigs involved infections with $6.8 \times 10^6$ TCID$_{50}$ of the SARS-CoV-2 isolate TGR/NY/20 through the intratracheal, intranasal, and intravenous routes. Viral RNA in nasal/oral and rectal swabs and neutralizing antibodies against SARS-CoV-2 from all groups of administration routes were detectable but transient. Furthermore, some tissues (tonsils, mandibular lymph node, and tracheobronchial lymph node) from inoculated animals showed weak positivity for viral RNA, but the infectious viruses were not isolated successfully. That study proved that inoculation of the virus through these routes could not produce the infectious virus, and there were no viral transmissions from inoculated animals to naive-contact animals [49].

Several studies predicted the susceptibility of pigs to SARS-CoV-2 infections based on comparisons of pig ACE2 with human ACE2 [95,108]. These studies found five amino acid changes in pig ACE2, as in dogs [95,108]. There are mutations of Gln24Leu, Asp30Glu, and Met82Thr in pigs and dogs [95,108], His34 to Leu in pigs and Tyr in dogs, and Asn90 to Thr in pigs and Asp in dogs [95,108]. Mutations of Gln24 to Leu and His34 to Leu or Tyr led to the failure of hydrogen bond formation between the SARS-CoV-2 S-protein and porcine ACE2 receptors [95,108]. In addition, mutations of Asn90 to Thr or Asp led to a lack of glycosylation site at position 90 [95,108]. Based on these in silico studies, pigs and dogs exhibited low susceptibility to SARS-CoV-2 [95,108], but dogs have been shown infected with SARS-CoV-2 naturally [24,54,55,86,93,101].

Ex vivo [41] and in vivo studies [22,45-47] in swine respiratory tract cells found no SARS-CoV-2 replication. On the contrary, infection with higher doses showed weak positive viral RNA in swabs [48,49], and SARS-CoV-2 RNA and protein of inoculated animals were undetectable in respiratory tract cells [41,46,48]. The distribution of ACE2 protein on the tissues showed no expression in the upper and lower respiratory tract cells [41,109], but the mRNA type was found to be weakly expressed [49]. However, it was overexpressed in the small intestine [109] and kidney [41,49]. This may explain the fact that SARS-CoV-2 replicated in kidney cells [45,46] but not in the respiratory tract cells of pigs [41,45,46,49]. Those experimental studies were consistent with in silico predictions and indicated that pigs have a low susceptibility to SARS-CoV-2 infections [108].

SARS-CoV-2 infections in minks

The first case of natural infection of SARS-CoV-2 in minks (Neovison vison) was reported in two farms in the Netherlands in April 2020 [34]. These animals revealed severe respiratory diseases and increased mortality. The clinical signs included breathing difficulties and nasal exudate. SARS-CoV-2 viral RNA and viral antigen were detected in the upper and lower respiratory tracts [34]. Histopathological features included the thickening and degeneration of alveolar septa, which indicated acute severe interstitial pneumonia or diffuse alveolar damage [34,56]. Before the SARS-CoV-2 outbreak occurred in the mink farm, a worker in the farm tested positive for SARS-CoV-2, indicating the probable transmission from the human to mink [34].

In addition, SARS-CoV-2 infected minks were reported in Denmark around June 2020 [111]. Similar findings were reported in several countries in Europe, which included Spain in July 2020 [112,113].
Italy in August 2020 [112,113], Sweden in October 2020, Greece, France, Poland, and Lithuania in November 2020, the second infection in a mink farm in Poland on 30 January 2021, and in Latvia in April 2021 [58,112,113]. In the Netherlands and Denmark, the virus spread rapidly among minks, resulting in respiratory diseases and increased mortality [35,111].

The first case was reported in August 2020 in two commercial mink farms in the USA. The clinical findings included respiratory signs and sudden death. It was assumed that a mink was infected from SARS-CoV-2 infected people who contacted the mink and the virus spread it among minks in these farms [87]. A total of 177,357 suspected minks and the deaths of 16,130 minks due to SARS-CoV-2 infections were reported in mink farms in Utah, Michigan, Wisconsin, and Oregon, USA, from June to October 2020, as OIE reported in the follow-up reports No. 15, 16, 19, 20, 21, 22, 25, and 26 [71-73,82,87-90].

The SARS-CoV-2 genome in the mink farm in the Netherlands had a high diversity [35]. There were five clusters, among which three clusters (A, C, and E) contained the mutation of aspartate 614 to glycine (D614G) that was found in general human populations and in cases related to minks [35]. In Denmark, mutations that occurred in the ORF1b gene were mutations of threonine 730 to isoleucine (T730I) and proline 314 to leucine (P314L). In contrast, in the ORF3a gene, there was a mutation of histidine 182 to tyrosine (H182Y). Finally, in the nucleoprotein gene, there were mutations of arginine 203 to lysine and glycine 204 to arginine [111]. In addition, D614G and Y453F mutations occurred in the spike gene [111]. The SARS-CoV-2 variant T730I was found in humans and in the mink population in Jutland, Denmark, and in human from New Zealand [111]. A H182Y mutation within ORF3a gene appeared in all minks in Denmark and in human cases related to the mink. Even if it was a rare mutation, it was also found in a mink farm in the Netherlands [111].

Recently, the new variant of SARS-CoV-2 that contained the deletions of histidine 69 (H69) and valine 70 (V70) has been reported. Some mutations developed in mink farms and in 12 humans with COVID-19 who lived around the mink farms in Jutland included Y453F, D614G, isoleucine 692 to valine (I692V), and methionine 1229 to isoleucine (M1229I) [57]. The deletion of H69 and V70 within the spike gene occurred in mink farms probably as an adaptation of the virus to increase its binding ability to the receptor [114]. The same finding was revealed in Poland [115]. Mutations occurred in the spike gene, which resulted in alterations of the amino acids glycine 75 to valine, methionine 177 to threonine, cysteine 1247 to phenylalanine, and contained the amino acid mutation Y453F [115], as previously reported in the mink farm in Denmark [57,111].

D614G and Y453F are two interesting mutations in the S-protein of SARS-CoV-2. These are specific mutations found in the mink and are related to the mutations found in humans on the mink farm [35,111]. Mutations of D614G in S-protein were found predominantly in the human population, in the mink farm in Denmark and the Netherlands [35,111]. Furthermore, Y453F mutation was found in mink farms in the Netherlands and was related to human cases in mink farms in Denmark [111]. The change of aspartate residue at position site 614 to glycine and the tyrosine residue at position site 453 to phenylalanine were a form of virus adaptation to allow the virus to enter host cells; this efficiently increased ACE2 binding in minks and humans [116]. In addition, the mutation of Y453F reduced the efficiency of antibody therapy and convalescent serum/plasma therapy from patients with COVID-19, thus reducing the success of therapy and increasing the risk of death in patients [116].

The SARS-CoV-2 genome obtained from the mink samples was highly similar to humans associated with mink farms in the Netherlands and Denmark [35,111], indicating viral transmissions from the mink workers to the animals [35]. Subsequently, the spreading of the virus among minks in the farms occurred by inhalation of spray droplets from sneezing and coughing or inhalation of aerosol microparticles (<5 μm) that contained infectious viruses [117,118]. This has been proven by finding viral RNA in dust samples collected using stationary air sampling (over 5-6 h periods) in the mink farm during the outbreak [34]. Furthermore, based on genomic and epidemiological studies, it appeared that SARS-CoV-2 was transmitted from humans to minks and spread among minks following the appearance of several new mutations; it was then transmitted back to humans, as was also observed in the Netherlands and Denmark [35,111], making it possible to transfer the virus to other sites [112].

The spread of SARS-CoV-2 from the mink to the surrounding environment or to other animals that live at the farms is also possible [112,119]. This is based on the finding of viral RNA in airborne dust collected at locations 2-3 m from farms, in fur and straw from infected farms, and in the feet of seagulls that often forage on mink farms in Denmark, thus making it possible to transfer the virus to other sites [112]. The dogs and cats on the farm were also positive for viral RNA, and some dogs and cats had antibodies to SARS-CoV-2 [112]. A study from the Netherlands [119] reported that viral RNA was identified in stray cats that lived near farm sites and cats and dogs that lived on the farm [119]. The authors presumed that the stray cats were infected by the minks, but the source of viral infections in dogs has not been determined [119].

SARS-CoV-2 transmission from humans to minks, minks to minks, and minks to humans or other animals was found [35,111,112,119]. In addition, indirect transmission through dust or objects around the mink farm contains the active virus [58,119]. There was evidence of the possibility of the emergence of new strains because of new mutations or
accumulations of mutations in the viral genome in the mink group, which were faster and more virulent [57,111,115,116]. Hence, it is necessary to consider mitigation strategies to manage outbreaks in animals, humans globally, especially those related to transmission cases among animals, from animals to humans, and humans to animals. It is also crucial to protect stray animals and wild animals around mink farms.

SARS-CoV-2 infections in poultries
To evaluate susceptibility of poultries to SARS-CoV-2 infection, several experimental studies have been conducted, including in chickens (Gallus gallus domesticus), turkeys (Meleagris gallopavo), pekin ducks (Anas platyrhynchos domesticus), Japanese quails (Coturnix japonica), and in white Chinese geese (Anser cygnoides) [22,45,50]. These domesticated fowl were infected intra-nasally or oculo-oronasally and later introduced to naive animals. All studies reported that viral RNA was not detected in any oropharyngeal and cloacal swabs collected from inoculated animals or naive animals. In addition, all these birds were seronegative for SARS-CoV-2 [22,45,50]. All animals showed no clinical signs during the study, and any lesion was detected at necropsy [45,50]. Similarly, embryonated chicken eggs (CEEs) were usually used for isolation, and the laboratory host system in the vaccine production exhibited no viral replication in CEEs [45,50]. All these studies on poultry and CEEs showed that the viral RNA cannot be replicated and transmitted among birds [22,45,50].

Despite experimental studies, it was found that chickens that had indirect contact with the mink farm outbreak were negative for SARS-CoV-2 viral RNA [112,119]. It was also reported that wild birds trapped in the mink farms affected, including hundreds of seagulls with other birds, including one hooded crow (Corvus cornix), a jackdaw (Corvus monedula), and a common kestrel (Falco tinnunculus), were found negative for SARS-CoV-2 RNA [112]. This was in accordance with the predictions of in silico studies [95]. The class Aves, including chickens and ducks, had ACE2 receptors that did not match the S-protein of SARS-CoV-2 [95]. Analyses conducted to compare the chicken and duck ACE2 receptors with human ACE2 receptors showed that the receptors of these avian species contained ten amino acids changes and lacked the N-glycosylation at position site 90 [95]. These changes affected the amino acid residue involved in the binding of ACE2 to the SARS-CoV-2 S-protein, in chicken including Gln24Glu, His34Val, Leu79Asn and Met82Arg, and Gly354Asn, and in ducks was His34Val, Leu79Asn, Met82Asn, and Gly354Asn [95]. This change also occurred in Tyr83Phe, which resulted in the failure of hydrogen bond formation, and in Asp30Ala, which resulted in the lack of salt bridge formation [95]. Therefore, these findings may explain the inability of ACE2 receptors in the bird group to bind to the S-protein of the SARS-CoV-2. These findings suggest that poultry are not susceptible to SARS-CoV-2 infections [22,45,50].

SARS-CoV-2 infections in other animals
SARS-CoV-2 infection has been reported in several animals. Gorillas (Gorilla gorilla) at the San Diego Zoo, USA, were found positive for SARS-CoV-2 on January 11, 2021. Despite appearing to have a mild cough, stuffy nose, and lethargy symptoms, they recovered [91]. Confirmation of COVID-19 was reported in Asian small-clawed otters (Aonyx cinereus) in Georgia, USA, in April 2021 [120]. These otters, which includes in the family Mustelidae that the same family with minks, showed clinical signs, such as sneezing, runny noses, mild lethargy, and coughing [120]. Recently, several animals have been reported to be infected with SARS-CoV-2, including animals at a zoo in Illinois, USA, that was a binturong (Arctictis binturong) and a fishing cat (Prionailurus viverrinus) on October 5, 2021, [121] and a South American coati (or coatimundi, Nasua nasua) on October 14, 2021 [122]. Furthermore, two hyenas at Denver Zoo in Colorado, USA [123] were tested positive for SARS-CoV-2 with other animals in the zoo, including lions and tigers, on November 5, 2021 [123]. The two hippos at a zoo in Antwerp, Belgium were positive for SARS-CoV-2 infections on December 6, 2021 [124].

Animals from infected mink farms, such as chickens, rabbits, and horses, tested negative for SARS-CoV-2 [112]. PCR-negative outcomes for SARS-CoV-2 were also found in a group of wild animals collected in the areas around the infected mink farms from October to November 2020 in Denmark, including red foxes (Vulpes vulpes), badgers (Meles meles), least weasel (Mustela nivalis), polecats (Mustela putorius), otter (Lutra lutra), beech martens (Martes foina), and raccoon dogs (Nyctereutes procyonoides), as well as in feral mink (N. vison) [112]. SARS-CoV-2 infections have not been reported in other wild animals, pets, and farm animals that have close contact with humans, such as horses, goats, camels, and buffaloes, have not been reported. This requires further investigation in terms of both the detection of viral RNA and serological surveys.

Recently, there have been many reported cases of COVID-19 in animals. To prevent SARS-CoV-2 infections in various animals, both pets and wild and farm animals, vaccines have been developed, including a vaccine from Zoetis company, Carnivac-Cov, and the LinearDNA™ COVID-19 vaccine [125-127]. Zoetis has developed a subunit recombinant vaccine for the SARS-CoV-2 S-protein for wild animals. It has been used to vaccine some species of wild animals in several zoos and sanctuaries in the USA and Canada, including orangutans, bonobos, hyenas, chimpanzees, and lions [125,126]. Thus, Russia has developed Carnivac-Cov, an inactivated vaccine, and has been on clinical trials in dogs, cats, foxes, and
minks [125]. The Linear DNA™ COVID-19 vaccine has been developed by Applied DNA Sciences (USA) and EvviVax (Italy) for use in domestic felines [127]. The safety and immunogenicity of this vaccine in cats showed to be well tolerated and induced high titers of SARS-CoV-2 neutralizing antibodies [127], while the safety and immunogenicity in minks are currently in progress of research [128]. Furthermore, successful immunization of animals could protect animals from SARS-CoV-2 infections and prevent virus transmission among animals and cross-species. Therefore, it reduces the risk of the emergence of new mutations of SARS-CoV-2 [125,129].

Conclusion

The susceptibility of animals to SARS-CoV-2 is very different depending on the family. Felines, including domestic cats and big cats, are susceptible species where virus transmission between animals has also been detected. Other wild animals that were found to be infected as natural infections in the zoos were gorillas, otters, a binturong, a fishing cat, a coati-mundis, hyenas, and hippos. Livestock, such as cattle, sheep, and pigs, have a low susceptibility to SARS-CoV-2 infections, whereas poultry have been shown to be less susceptible to SARS-CoV-2 infection.

In most cases, infection of SARS-CoV-2 in animals was through close contact with humans, including in domesticated animals, big cats, and other wild animals in zoos. This also occurred in white-tailed deer and minks. In white-tailed deer, the virus can transmit to other deer that are in close contact or to its fetus experimentally. Furthermore, it is suspected that SARS-CoV-2 may have spread to the white-tailed deer population naturally with the finding that the seroprevalence of SARS-CoV-2 in the deer population was quite high. In minks, the virus infections were being transmitted from humans and be spread among minks and then undergone adaptation and spread back to humans. Presumably, the virus in minks and white-tailed deer were also possible to be transmitted to other animals because of the large number of infected animals and the high seroprevalence rate in these two animal species.

When infecting humans or animals, viruses generate several mutations and accumulate; then the mutation will be transmitted to other humans or animals. Some mutations increase the level of viral virulence, and some cause resistance to antibodies or convalescent plasma therapy. Therefore, it is necessary to increase the awareness of rapidly mutating viruses and prepare various forms of appropriate therapies and treatments. Not only do vaccines need to be developed, but also research related to the development of antivirals and therapeutic management, as well as comprehensive strategies for mitigating infectious and dangerous diseases are also necessary. This knowledge may contribute to the management of the SARS-CoV-2 pandemic in humans and animals.

Authors’ Contributions

GM: Conception of idea and drafted and revised the manuscript. GM, AR, and RI: Literature search. AR and RI: Editing of the manuscript. IR and IdB: Conception of idea, literature search, and reviewing the manuscript. All authors read and approved the final manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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