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Transmission of severe acute respiratory syndrome coronavirus 2 from humans to animals: is there a risk of novel reservoirs?

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a zoonotic virus able to infect humans and multiple nonhuman animal species. Most natural infections in companion, captive zoo, livestock, and wildlife species have been related to a reverse transmission, raising concern about potential generation of animal reservoirs due to human–animal interactions. To date, American mink and white-tailed deer are the only species that led to extensive intraspecies transmission of SARS-CoV-2 after reverse zoonosis, leading to an efficient spread of the virus and subsequent animal-to-human transmission. Viral host adaptations increase the probability of new SARS-CoV-2 variants' emergence that could cause a major global health impact. Therefore, applying the One Health approach is crucial to prevent and overcome future threats for human, animal, and environmental fields.

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Introduction

Major viral outbreaks in the last two decades involved coronaviruses (CoVs) causing epidemics or pandemics: the severe acute respiratory syndrome (SARS, 2002–2003), the Middle East respiratory syndrome (MERS, 2012–present), and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2019–present) [1]. Although SARS-CoV-2 is not considered as virulent as SARS-CoV and MERS-CoV, its highly transmission capability has prompted a rapid spread through the world, triggering the ongoing Coronavirus disease 2019 (COVID-19) pandemic [1]. SARS-CoV-2 was reported for the first time in late 2019 in China and, as on August 24th, 2023, more than 769 million human infections and over 6.9 million deaths have been officially reported (World Health Organisation, URL: https://covid19.who.int/).

CoVs are a family of viruses that have constantly crossed the species barriers, expanding their host range. In fact, all human CoVs are zoonotic viruses that originated in other mammalian hosts such as bats, mice, or livestock [1]. As in the case of SARS-CoV and MERS-CoV, there are evidences pointing out to bats as the animal origin of SARS-CoV-2 since the highest genome sequence homology has been found in CoVs isolated from *Rhinolophus* spp. bats (96.1% for RATG13 and 96.8% for BANAL-52) [2,3]. The genetic divergence (≈4%) between the identified bat-CoVs and SARS-CoV-2 supports the potential contribution of an intermediate host into the spillover to human population, although no animal species has been found in such respect yet [4]. Importantly, the efforts to assess potential intermediate host and animal reservoirs have scaled up since SARS-CoV-2 has continuously exhibited its capability to infect a huge variety of animal species [4].

Animal (domestic and wildlife) and human interactions occur daily in many different scenarios, a fact that increases the possibility of zoonotic and reverse zoonotic (RZ) viral transmission [5]. In consequence, the spread of the virus has facilitated viral evolution and the appearance of new variants of SARS-CoV-2 [6]. To date, five major variants of concern (VOCs: Alpha [B.1.1.7], Beta [B.1.351], Gamma [P.1], Delta [B.1.617.2], and Omicron [B.1.1.529]) have been recognized for their higher capability of transmission, virulence, and/or increased immune escape compared with original ones. Currently, there are no SARS-CoV-2 variants considered as VOC (European Centre for Disease Prevention and

Control, URL: https://www.ecdc.europa.eu/en/covid-19/variants-concern).

Considering the significant role of animals in the origin, transmission, and as potential new reservoirs of SARS-CoV-2, the objective of this review is to present and discuss the complex framework of SARS-CoV-2 reverse zoonoses and their potential consequences.

Susceptibility of animals to severe acute respiratory syndrome coronavirus-2

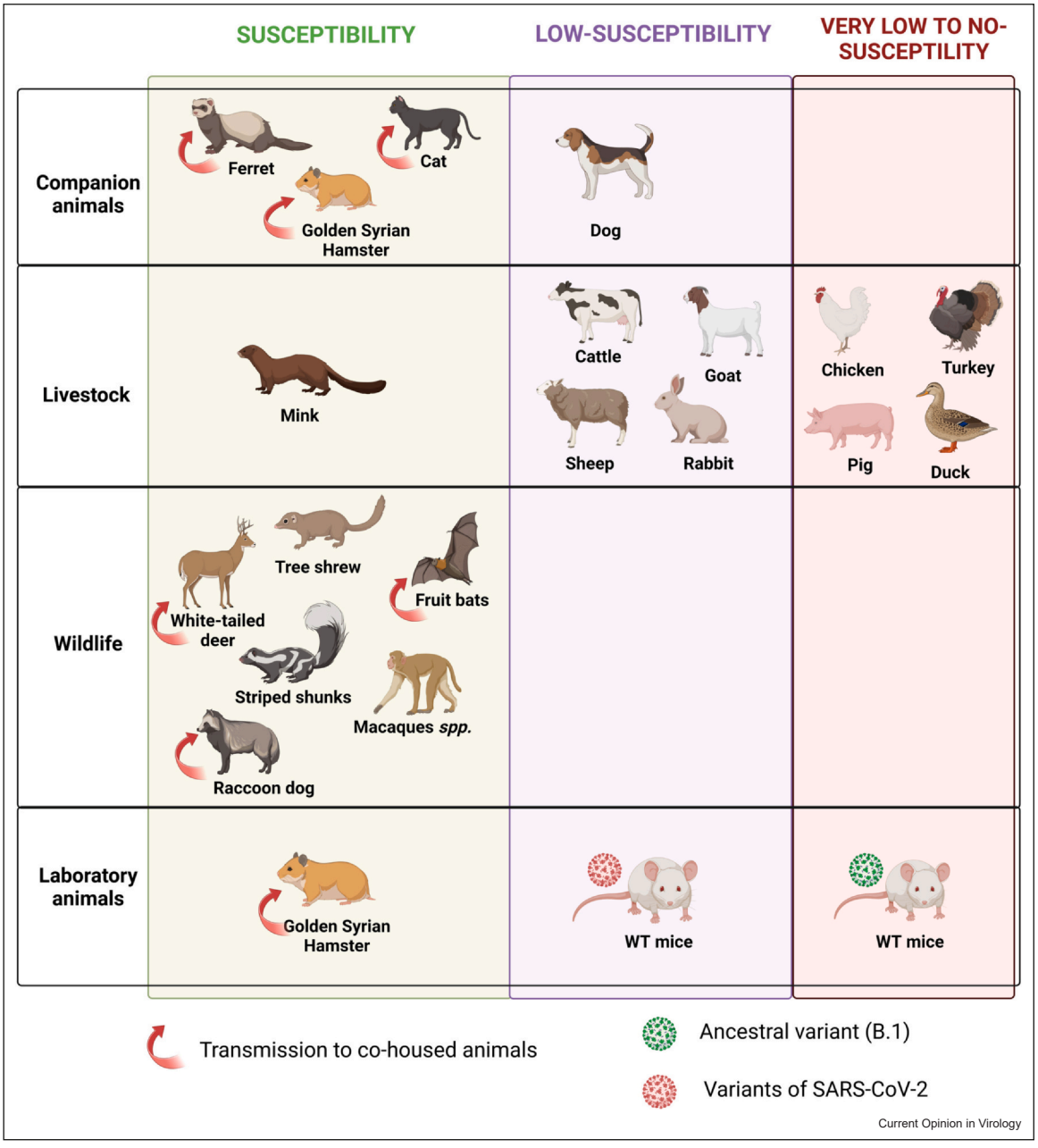
SARS-CoV-2 uses the receptor-binding domain (RBD) of its spike (S) protein to recognize the angiotensin-converting enzyme-2 (ACE2) host cell receptor to mediate viral infection [7]. Upon SARS-CoV-2 binding to the ACE2, the transmembrane serine protease 2 (TMPRSS2) cleaves the S protein allowing the fusion of viral and cellular membranes facilitating viral entry [7]. Previous studies demonstrated that presence, tropism, and expression levels of the ACE2 receptor determine the susceptibility and host range of SARS-CoV-2, while TMPRSS2 is not a limiting factor for viral entry and infection [8–10]. Comparative genomic analyses between the ACE2 receptor of humans and nonhuman animal species evidenced a highly conserved sequence among mammals, supporting a broad host range of SARS-CoV-2 [8,11]. Importantly, 25 amino acids of the ACE2 have been identified as critical determinants for SARS-CoV-2 binding, with six of those residues (Ser19, Lys26, Thr27, Asp30, Leu79, and Met82), being highly associated with viral host susceptibility [8].

Accordingly, several domestic and wildlife animal species confirmed SARS-CoV-2 susceptibility under experimental conditions (Figure 1), being of particular concern those species in close contact with humans, such as companion animals [12]. Cats, ferrets, and hamsters have exhibited high susceptibility to SARS-CoV-2, whereas dogs demonstrated low susceptibility after experimental challenge [13–16]. Likewise, a higher risk of infection in cats than in dogs was already predicted by previous *in silico* studies based on the comparison of the critical binding residues of their ACE2 sequences to those from the ACE2 of humans [17]. However, computational studies do not always agree with *in vivo* experiments; as an example, very low binding affinity was predicted between the ACE2 of ferrets and the SARS-CoV-2 RBD, considering them within the group of low risk of infection [17,18]. This apparent higher susceptibility of cats and ferrets could be partially explained by the higher ACE2 levels in the upper respiratory tract (RT) compared with the ACE2 low levels in dogs, which may be related with a reduced viral replication in the nasal turbinates of the latter species [10,19]. Regarding hamsters, although they exhibited low ACE2 levels in the RT, the high ACE2–RBD-binding affinity might explain the high SARS-CoV-2 susceptibility [10]. Altogether, it supports viral intraspecies transmissibility in cats, ferrets and hamsters, but not in dogs [15,16]. Even though none of these species showed significant clinical signs associated with the SARS-CoV-2 experimental inoculation, except for hamsters, which developed moderate–severe weight loss, which would be similar to the moderate–severe disease course of human COVID-19 patients [13,15,16]. In this matter, other members of the family *Mustelidae*, such as minks, develop severe respiratory disease, probably attributed to the presence of the ACE2 not only in the upper but also in the lower RT [10,20]. On the other hand, livestock species (cattle, sheep, and goat), which were predicted within the group of medium risk of infection, demonstrated very limited susceptibility to SARS-CoV-2 and its different VOCs [18,21–24]. Regarding pigs, several investigations demonstrated that they are not susceptible to SARS-CoV-2 consistent with predictive studies [16,17,25], although Pickering et al. [26] suggested a very low susceptibility to SARS-CoV-2. Last, several wild animal species also exhibited SARS-CoV-2 susceptibility such as the white-tailed deer (WTD), rhesus macaque, tree shrew, raccoon dog, and the fruit bat [27–30]; some of them were able to transmit the virus to the contact animals (Figure 1). Besides, the wild-type (WT) mice, which were not susceptible to SARS-CoV-2 ancestral variants, have exhibited certain susceptibility to Alpha, Beta, Gamma, and Omicron VOCs (Figure 1) [31]. In fact, some authors evidenced that the Omicron variant might not have originated from humans directly but may have been transmitted from murine species to humans [32,33].

Natural infections and reverse zoonosis transmission

Natural infections of SARS-CoV-2 in domestic and wildlife animals have also been reported almost since the beginning of the COVID-19 pandemic. Indeed, according to the World Organization Animal Health (WOAH) (URL: https://www.woah.org/en/crossing-the-species-barriers-covid-19-an-example-of-reverse-zoonosis), the COVID-19 (understood basically as SARS-CoV-2 infection, not necessarily with a clinical outcome) was the 3rd most reported animal disease in 2021. This was probably due to the systematic efforts in detecting evidence of SARS-CoV-2 infection in animals. As per 24 August 2023, the WOAH has reported 775 SARS-CoV-2 outbreaks in animals, including 26 species in 36 countries [34]. Besides, an open-access database summarizing SARS-CoV-2 events in animals published by the Complexity Science Hub (Vienna, Austria) (URL: https://vis.csh.ac.at/sars-ani/) indicates at present a total of 887 outbreaks, including 34 species in 39 countries. Importantly, most of the SARS-CoV-2 animal infections have been associated with close contact with SARS-CoV-2-infected humans and, thus, pointing out to RZ transmission events (Figure 2).

Figure 1

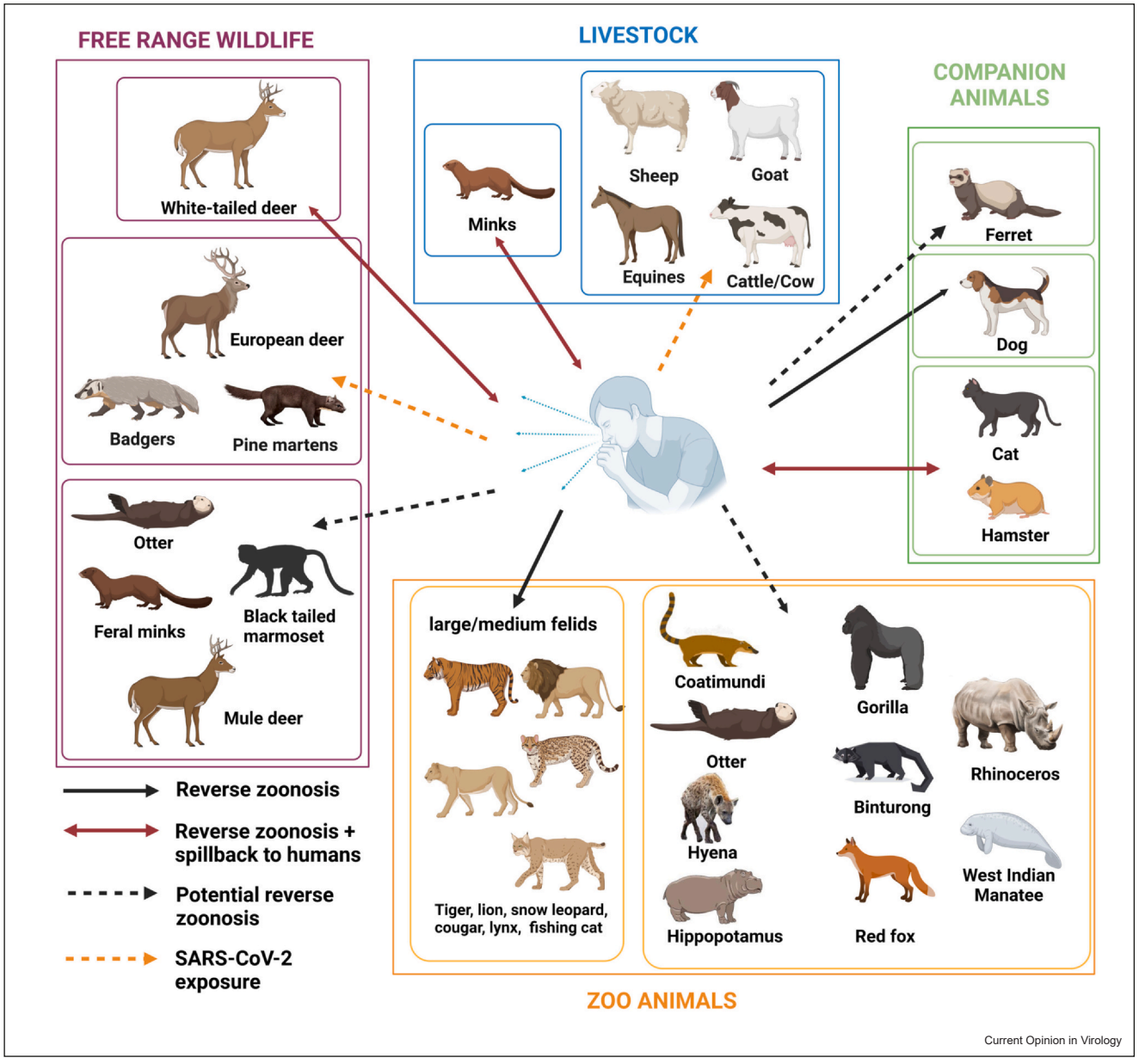


Susceptibility degree of companion animals, livestock, wildlife, and laboratory animals to SARS-CoV-2 under experimental conditions. Susceptible animals (green column), low-susceptible animals (purple column), and very-low or no susceptible animals (red column) are shown separately. WT mice, which are represented twice, are not susceptible to the ancestral variant (virus in green color) but to the Alpha, Beta, Gamma, and Omicron (virus in red color) ones. The red arrows indicate the animal species with the ability to transmit SARS-CoV-2 to cohoused animals. Figure is created with BioRender.com.

Companion animals

The first known SARS-CoV-2 infection in animals was described in Hong Kong on February 2020 in an asymptomatic dog from a COVID-19-positive household, and from which a RZ was evidenced by genetic sequencing and epidemiological analyses [35]. Thereafter, SARS-CoV-2 infections in companion animals, mainly cats and dogs but also ferrets and hamsters, have been constantly reported worldwide and mainly related to a human–animal contact [36–46]. Interestingly, large-scale studies performed in different countries (e.g. USA, China, Italy, Switzerland, Spain, and France) demonstrated a higher risk

Figure 2



Natural infection and/or exposure to SARS-CoV-2 in free-range wildlife (purple square), livestock (blue square), companion animals (green square), and zoo (orange square) animals, which were associated with SARS-CoV-2-infected humans. Different arrows represent the route of transmission between animals and humans: black and red solid arrows indicate human-to-animal and animal-to-human transmission, respectively, evidenced by sequencing analysis; black dashed arrows indicate those cases in which human-to animal transmission was not evidenced by sequencing analysis but supported by epidemiological data; orange dashed arrows indicate the exposure of animal species probably by contact with infected humans. Figure is created with BioRender.com.

of infection in pets living with COVID-19-affected owners than in those in which evidence of contact with an infected human was not determined [47–54]. Similarly, de Souza Barbosa et al. [55] found a higher probability of dog infection when owners exhibited higher viral loads and/or related COVID-19 symptoms (e.g. cough, sneezing, and diarrhea). As expected, some authors confirmed human-to-pet transmission of the dominant SARS-CoV-2 VOC in human population at each pandemic wave [52,54,56,57]. On the other side, pet-to-human transmission has also been demonstrated in hamsters in a pet shop in Hong Kong, leading to onward human-to human transmission and in cats to veterinarians in Thailand [56,58,59].

Although similar infection and antibody prevalence have been usually observed when comparing cats and dogs, a higher risk of exposure in cats could be expected considering the higher susceptibility and pathology outcomes observed both *in silico* and experimentally [15,16]. Since higher titers of neutralizing antibodies (nAbs) have been already correlated with the severity of COVID-19 in humans [60], such scenario may also be occurring in animals. In a large-scale serological study in pets, higher titers of nAbs were found in cats than in dogs, even against almost all the VOCs [52]. Moreover, a positive correlation between the cases of SARS-CoV-2-infected humans and the proportion of seropositive pet cats, but not dogs, was described in provinces of Korea [61]. On the other hand, not only domestic cats but also stray and shelter cats have also been exposed to SARS-CoV-2 in different countries [46,52,62–64]. The most likely way of viral transmission to these cats would be by contact with infected humans, but the contact with polluted SARS-CoV-2 environments or even with other susceptible animal species such as wildlife cannot be ruled out [64,65]. Since cat-to-cat transmission is possible, and stray and shelter cats live in colonies and/or frequently in contact with other individuals, the probability of intraspecies transmission increases considerably, raising significant concerns about their potential role in the epidemiology of the COVID-19 as novel animal reservoirs [15,16,64]. However, a limited sustained cat-to-cat transmission has been suggested owing to a reduced SARS-CoV-2 transmissibility and pathogenic ability after serial passaging of the virus between cats [66].

Livestock

Farm animals may also be exposed to SARS-CoV-2, mainly by contact with potential infected farmers and animal caretakers (Figure 2). Although natural acute infection in common livestock species (e.g. cattle, goat, sheep, and horses) has not been evidenced, even after contact with COVID-19-positive humans [67], serological analyses confirmed SARS-CoV-2 past exposure in cattle [68], cows [69], equines [70], and sheep and goats [71]. Regarding equines, Pusterla et al. [72] suggested a potential transmission from a COVID-19- affected human to an adult horse. However, the most relevant SARS-CoV-2 event in farm animals has been related to the SARS-CoV-2 outbreaks in farm minks (*Neovison vison*). On April 2020, The Netherlands reported increased mortality in two mink farms, which was subsequently associated with severe interstitial pneumonia caused by the SARS-CoV-2 [73]. Until November 2020, SARS-CoV-2 was spread and detected in 68 out of 126 mink farms from the whole country [74]. On June 2020, SARS-CoV-2 infections in hundreds of Danish mink farms were also documented [75,76]. In both countries, genetic analysis of viral sequences from the animals and from associated SARS-CoV-2 human cases together with epidemiological data, confirmed the introduction of different viral strains in minks, being humans the primary source [76,77]. Animal-to-animal contact was confirmed within farm, facilitating viral host adaptation and the appearance of new SARS-CoV-2 strains that were subsequently detected in humans in the Netherlands and Denmark, respectively [76,77]. Zoonotic mink-to-human transmission and evidence of human-to-human transmission of viral strains acquired from animals led the governments from Netherlands and Denmark to order the culling of millions of minks by mid-June 2020 [75,77]. Worriedly, the Y453F mutation located in the RBD of SARS-CoV-2 in minks has shown a higher ability of viral immune escape in humans, raising concern about the efficacy of both current vaccines and acquired humoral response from previous infections [78]. In addition, many other countries, including the United States (US), Canada, France, Greece, Italy, Spain, Sweden, Poland, and Lithuania also reported SARS-CoV-2 outbreaks in mink farms [79–82]. Whereas the Y453F mutation was typically and exclusively found in European mink farms, N501T, F486L, and G142D mutations were also found in mink-derived sequences from the US [73,83]. Importantly, all these mutations support the adaptation of SARS-CoV-2 to minks and cross-transmission between minks and humans [83,84]. Accordingly, a recent experimental infection in these animals confirmed a rapid within-host evolution of SARS-CoV-2 since an enrichment of the L260F mutation appeared in lung tissue and oral swabs after challenge [20]. The same mutation was also repeatedly identified in mink outbreaks from the Netherlands, Latvia, and US [20]. This supports that L260F mutation also confers a positive selection in mink and confirms viral adaptation in this host [20].

Wildlife animals

Wild captive animals

Natural SARS-CoV-2 infections have also been reported in large felid species (e.g. lions, tigers, pumas, snow leopards, and lynxes) living in captivity in zoological parks worldwide [85–94]. Most infections caused by both classical and VOCs (e.g. Delta) induced mild-to-moderate upper respiratory clinical signs, loss of appetite, and anorexia, in contrast to the subclinical infections mostly frequently reported in domestic cats [64]. In this context, RZ has also played a key role, which is entirely reasonable since zoo animals are in frequent contact with humans, especially with their keepers [86–89,92]. Also, considering that large felids developed prolonged fecal shedding and that infectious virus has been found repeatedly in their feces, the risk of transmission between animals and from animals to keepers cannot be dismissed [85,90,93]. Other reported infections in zoos include nonhuman primates, otters, binturong, coatimundi, fishing cat, hyenas, red fox, hippopotamuses, and manatees (Figure 2), which have also been

linked to animal contact with COVID-19-affected humans [34,93,95,96]. Recently, the presence of SARS-CoV-2 in a fecal sample of a white rhinoceros from the Bandia reserve in Senegal was also confirmed, although direct contact with an infected human was not proven [97].

Free-range wildlife animals

Taking into account that direct contact between human and free wild animals seems to be infrequent, the risk of SARS-CoV-2 infection could easily be considered lower than in domestic animals. However, some authors demonstrated that wild species have already been infected and/or exposed to SARS-CoV-2, despite the major challenge of monitoring SARS-CoV-2 infection and to detect acute infection in this group of animals.

White-tailed deer

The most concerning SARS-CoV-2 spillover event from humans to wildlife is related to the free-ranging WTD (*Odocoileus virginianus*) [98]. SARS-CoV-2 exposure and/or acute infection in WTD have been described in multiple US (e.g. Illinois, Michigan, New York, Pennsylvania, Texas, Ohio, and Iowa) [99–103]. In agreement with experimental and predictive *in silico* studies, Hale et al. [101] found high viral load and infectious virus in nasal swabs in WTD from Ohio (USA), providing evidence of viral shedding and high susceptibility of WTD naturally. Moreover, the authors confirmed up to six separate events of human-to-deer transmission, since WTD samples collected six weeks after the peak of Ohio's epidemic of COVID-19 in humans contained highly similar viral genetic sequences (lineage B.1) to human samples [101]. Additionally, RZ transmission in WTD was also confirmed in Iowa [102]. In cases of WTD infection in both Ohio and Iowa, several mutations were repeatedly found in viral sequences from deer but not in human-derived sequences, supporting deer-to-deer transmission, as already demonstrated experimentally [101,104]. Subsequently, multiple spillover events of the Alpha and Delta SARS-CoV-2 VOCs from humans to WTD in Pennsylvania were evidenced, as well as persistence and spread of the Alpha variant in deer [103]. Rarely, SARS-CoV-2 Delta variant was detected in mule deer (*Odocoileus hemionus*) in Utah (USA) [34]. In addition, a divergent lineage of SARS-CoV-2, designated as lineage B.1.641, was identified in WTD in Ontario (Canada) and considered as a result of viral host evolution and adaptation [105]. A recent common ancestor of lineage B.1.641 was found in mink- and human-derived sequences from Michigan, which suggested a potential spillover from humans to deer, or even with minks as intermediate host [105]. In this study, the authors also suspected of a human spillback of the B.1.641, although recurrent deer-to-human transmission or human-to-human transmission of B.1.641 was not evidenced [105]. As a matter of fact, the B.1.641 variant was efficiently neutralized by sera from vaccinated or convalescent human individuals, suggesting a nonsignificant impact on immune evasion capacity of SARS-CoV-2 in humans [105]. The RZ in WTD is not a very surprising event since it is one of the most abundant wild ruminants in the USA that live near urban population centers. The precise route of transmission from human to deer is unknown, but several potential ways are considered, including deer hunting or captive operations, conservation work, wildlife tourism, wildlife rehabilitation, or public feeding [99,101]. Additionally, indirect contact between humans and WTD, as, for example, through wastewater or other contaminated sources, may be also considered as another opportunity for deer to be infected. Besides, SARS-CoV-2 exposure has been described recently in free-ranging fallow deer (*Dama dama*) and red deer (*Cervus elaphus)* in suburban and urban areas from Spain [106]. This is the first serological investigation finding seropositivity in European deer, as other survey studies conducted in Germany, Austria, UK, and Belgium yielded negative results [106].

Other free-range wildlife

Other wildlife animals, included mainly within the family *Mustelidae*, have also been infected and/or exposed to SARS-CoV-2. Aguiló-Gisbert et al. [107] detected two positive free-ranging minks caught in the wild in the Valencian Community (Eastern Spain): those animals did not appear to have escaped from any nearby mink farm. A generalized outbreak of a COVID-19-like condition among mink populations in that geographic area was highly unlikely since the remaining 11 out of 13 trapped minks of the study tested negative [107]. Also, in the Valencian Community, SARS-CoV-2 was found in a wild Eurasian otter (*Lutra lutra*) living far away from the locations where infected minks were found [108]. Other species within the family *Mustelidae* have also been exposed to SARS-CoV-2, including pine martens (*Martes martes*) and European badgers (*Meles meles*) from Brittany (France) (Figure 2) [109]. A suggested route of viral exposure to wildlife species is through contact with SARS-CoV-2- contaminated environment, including household wastes, wastewaters, or rivers with feces and other excreta from SARS-CoV-2-infected humans [108,109]. The presence of SARS-CoV-2 RNA in wastewaters and sewage has been demonstrated continuously worldwide; however, it has not been found an infectious virus in these residual waters, which reduces the probability as a route of transmission [110]. The absence of infectious virus could be given by the environmental conditions of wastewater, such as the temperature, pH, and presence of antagonistic bacteria or chemicals, that could interfere with the viability of CoVs and inactivate them [110]. However, it is very likely that the amount of virus is low enough in these residual products to prevent effective infection of any species in contact with them [110].

Additionally, mink farms are also a potential source of infection of other susceptible animal species, such as free-ranging animals that could have access to the farms and have direct contact with infected minks or their feces, feed, or bedding. This is why Sikkema et al. [111] assessed SARS-CoV-2 infection in wild carnivores near mink farms in The Netherlands, although reverse transcription quantitative real-time polymerase chain reaction (RT-qPCR)-positive animals were not detected [111]. However, Van Aart et al. [65] found positive feral cats in infected mink farms in the same country and strongly suspected mink-to-cat transmission by genome sequencing analyses [65]. They also found infected stray dogs, although whether mink or humans that infected them remained inconclusive [65]. Also, escapees of domestic minks to the wild could lead to cross-species transmission. Shriner et al. [112] already described SARS-CoV-2 exposure in 11 free wild American minks in Utah (US), that presumed to be domestic escapees from a fur farm where outbreaks of SARS-CoV-2 occurred previously. Also, 3 out of the 11 antibody-positive minks tested positive by RT-qPCR [112].

Last, SARS-CoV-2 infection was described in a free-ranging feline species (*Panthera pardus fusca*) in India [113] and in a free-ranging nonhuman primate in a black-tailed marmoset (*Mico melanurus)* from an urban area in Mid-West Brazil on March 2022 [114].

Conclusions and future perspectives

From the beginning of the COVID-19 pandemic, the promiscuity of SARS-CoV-2 for dozens of mammalian species has been translated into different natural scenarios, including domestic and wildlife (Figure 2). Natural SARS-CoV-2 infections reported worldwide in animals have been mainly related to a direct or indirect RZ transmission, raising concern about the frequent human and animal interaction. The regular acquisition of companion animals, the livestock industry, the existence of zoos and conservation centers, tourism, and hunting or deforestation, are everyday situations that highly increase the chances of cross-species transmission of SARS-CoV-2 (as well as other pathogens).

To date, American mink and the WTD are the only species that led an extensive intraspecies transmission of SARS-CoV-2 after a RZ [6], leading to an efficient spread of the virus and subsequent animal-to-human transmission. Viral host adaptation events subsequently increase the possibility of the establishment of animal reservoirs that, in the worst case, could give rise to the emergence of new variants with a huge global health impact. In this regard, the WTD could already be considered as a host reservoir since it is permissive to SARS-CoV-2 infection without suffering from a severe disease and with a vast immune tolerance. In contrast, a proportion of infected minks show certain degree of respiratory disease, including mortality in some cases [73], which may prevent the sustaining of the virus for a long time; anyway, an important role as intermediate host may be considered.

Interactions between human and free-ranging wild animals are more limited than in the case of domestic animals. However, many human activities with direct or indirect contact may pose a significant risk of animal exposure. Since monitoring wildlife animals is extremely challenging, it is advisable to use the current available information to prioritize the surveillance of some species groups with potential susceptibility such as mustelids or felids. Additionally, to promote monitoring of other species such as the racoon dog or palm civets may not be dismissed, considering their role in the previous SARS-CoV epidemic [115]. Bats may also be considered since a wide variety of CoVs have been found in these species over time, which may facilitate the recombination of SARS-CoV-2 with other CoVs [116]. However, to date, SARS-CoV-2 has not been found yet in bat species.

In light of the notable exposure to SARS-CoV-2 mainly to companion animals, it is appropriate to prevent close contact with them, at least by infected patients. Although the effectiveness of COVID-19 vaccines for preventing viral transmission is still debatable, considering that current vaccines are able to reduce viral replication, infectivity, and symptomatology, the capacity of the virus for host-to-host transmission might be also reduced in vaccinated humans [117]. Relevantly, dogs that usually are the closest pet to humans, do not efficiently transmit the virus as cats, ferrets, or hamsters, suggesting a lowest risk of spillback events and being far to be considered a potential animal reservoir. However, since pet-to-human transmission has already occurred in case of cats and hamsters (Figure 2), promoting additional measures such as vaccination of companion animals is currently being further considered and in development [118]. Other populations such as stray cats or shelter cats, which live in groups, need also to be controlled to prevent intraspecies transmission and the sustainment of SARS-CoV-2 and new emerging variants, or even to avoid the risk of transmission to other free-ranging animals as well as humans.

The current COVID-19 pandemic situation truly requires the One Health perspective, in which experts in human, animal, and environmental health coordinate together to design useful strategies to prevent and overcome potential new threats into global health. The One Health approach may include monitoring the emergence of new potential variants of SARS-CoV-2 since the range of animal susceptibility may increase and it would be paramount to avoid the risk of establishment of new animal reservoirs.

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Data Availability

This is a review paper using published results.

Declaration of Competing Interest

The authors declare no conflict of interest.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Ye Z-W, Yuan S, Yuen KS, Fung SY, Chan CP, Jin DY: **Zoonotic origins of human coronaviruses**. *Int J Biol Sci* 2020, **16**:1686-1697.

2. Temmam S, Vongphayloth K, Baquero E, Munier S, Bonomi M, Regnault B, Douangboubpha B, Karami Y, Chrétien D, Sanamxay D, *et al.*: **Bat coronaviruses related to SARS-CoV-2 and infectious for human cells**. *Nature* 2022, **604**:330-336.

3. Zhou P, Yang XLou, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, *et al.*: **A pneumonia outbreak associated with a new coronavirus of probable bat origin**. *Nature* 2020, **579**:270-273.

4. Frazzini S, Amadori M, Turin L, Riva F: **SARS CoV-2 infections in animals, two years into the pandemic**. *Arch Virol* 2022, **167**:2503-2517.

5. Goraichuk IV, Arefiev V, Stegniy BT, Gerilovych AP: **Zoonotic and reverse zoonotic transmissibility of SARS-CoV-2**. *Virus Res* 2021, **302**:198473.

6. Tan CCS, Lam SD, Richard D, Owen CJ, Berchtold D, Orengo C, Nair MS, Kuchipudi SV, Kapur V, van Dorp L, *et al.*: **Transmission of SARS-CoV-2 from humans to animals and potential host adaptation**. *Nat Commun* 2022, **13**:1-13.

7. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, *et al.*: **SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor**. *Cell* 2020, **181**:271-280.

8. •• Huang C, Jiang Y, Yan J: **Comparative analyses of ACE2 and TMPRSS2 gene: Implications for the risk to which vertebrate animals are susceptible to SARS-CoV-2**. *J Med Virol* 2021, **93**:5487-5504.
The authors found that ACE2 is crucial for SARS-CoV-2 susceptibility and host range whereas TMPRSS2 is not a limiting factor for viral infection. They also found 6 critical aminoacids of the ACE2 for SARS-CoV-2 binding.

9. Conceicao C, Thakur N, Human S, Kelly JT, Logan L, Bialy D, Bhat S, Stevenson-Leggett P, Zagrajek AK, Hollinghurst P, *et al.*: **The SARS-CoV-2 Spike protein has a broad tropism for mammalian ACE2 proteins**. *PLoS Biol* 2020, **18**:e3001016.

10. •• Lean FZX, Núñez A, Spiro S, Priestnall SL, Vreman S, Bailey D, James J, Wrigglesworth E, Suarez-Bonnet A, Conceicao C, *et al.*: **Differential susceptibility of SARS-CoV-2 in animals: Evidence of ACE2 host receptor distribution in companion animals, livestock and wildlife by immunohistochemical characterisation**. *Transbound Emerg Dis* 2022, **69**:2275-2286.
The authors described the distribution of ACE2 using immunohistochemistry (IHC) on tissues in a variety of vertebrates, giving new insights to further understand host suceptibility and pathology outcomes of SARS-CoV-2 infection in animals.

11. Veljkovic V, Vergara-Alert J, Segalés J, Paessler S: **Use of the informational spectrum methodology for rapid biological analysis of the novel coronavirus 2019-nCoV: prediction of potential receptor, natural reservoir, tropism and therapeutic/ vaccine target**. *F1000Research* 2020, **9**:52.

12. Mastutik G, Rohman A, I'tishom R, Ruiz-Arrondo I, De Blas I: **Experimental and natural infections of severe acute respiratory syndrome-related coronavirus 2 in pets and wild and farm animals**. *Vet World* 2022, **15**:565-589.

13. Chan JFW, Zhang AJ, Yuan S, Poon VKM, Chan CCS, Lee ACY, Chan WM, Fan Z, Tsoi HW, Wen L, *et al.*: **Simulation of the clinical and pathological manifestations of coronavirus disease 2019 (COVID-19) in a Golden Syrian Hamster Model: implications for disease pathogenesis and transmissibility**. *Clin Infect Dis* 2020, **71**:2428-2446.

14. Kim YII, Kim SG, Kim SM, Kim EH, Park SJ, Yu KM, Chang JH, Kim EJ, Lee S, Casel MAB, *et al.*: **Infection and rapid transmission of SARS-CoV-2 in ferrets**. *Cell Host Microbe* 2020, **27**:704-709 e2..

15. Bosco-Lauth AM, Hartwig AE, Porter SM, Gordy PW, Nehring M, Byas AD, VandeWoude S, Ragan IK, Maison RM, Bowen RA: **Experimental infection of domestic dogs and cats with SARS-CoV-2: pathogenesis, transmission, and response to reexposure in cats**. *Proc Natl Acad Sci USA* 2020, **117**:26382-26388.

16. Shi J, Wen Z, Zhong G, Yang H, Wang C, Huang B, Liu R, He X, Shuai L, Sun Z, *et al.*: **Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2**. *Science* 2020, **368**:1016-1020.

17. Damas J, Hughes GM, Keough KC, Painter CA, Persky NS, Corbo M, Hiller M, Koepfli K-P, Pfenning K [illegible] AR, Zhao H, *et al.*: **Broad host range of SARS-CoV-2 predicted by comparative and structural analysis of ACE2 in vertebrates**. *PNAS* 2020, **117**:22311-22322.

18. Liu Y, Hu G, Wang Y, Ren W, Zhao X, Ji F, Zhu Y, Feng F, Gong M, Ju X, *et al.*: **Functional and genetic analysis of viral receptor ACE2 orthologs reveals a broad potential host range of SARS-CoV-2**. *PNAS* 2021, **118**:e2025373118.

19. Zhai X, Sun J, Yan Z, Zhang J, Zhao J, Zhao Z, Gao Q, He W-T, Veit M, Su S, *et al.*: **Comparison of severe acute respiratory syndrome coronavirus 2 spike protein binding to ACE2 receptors from human, pets, farm animals, and putative intermediate hosts**. *J Virol* 2020, **94**:e00831-20.

20. D.R. Adney, J. Lovaglio, J.E. Schulz, C.K. Yinda, V.A. Avanzato, E. Haddock, J.R. Port, M. Holbrook, P.W. Hanley, G. Saturday, et al., Severe acute respiratory disease in American mink (Neovison vison) experimentally infected with SARS-CoV-2, JCI Insight. 7(22), 2022, e159573.

21. Fernández-Bastit L: **Susceptibility of domestic goat (Capra aegagrus hircus) to experimental infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.351/ beta variant**. *Viruses* 2022, **14**:2002.

22. Bosco-Lauth AM, Walker A, Guilbert L, Porter S, Hartwig A, Mcvicker E, Bielefeldt-Ohmann H, Bowen RA: **Susceptibility of livestock to SARS-CoV-2 infection**. *Emerg Mcirobes Infect* 2021, **10**:2199-2201.

23. Gaudreault NN, Cool K, Trujillo JD, Morozov I, Meekins DA, McDowell C, Bold D, Carossino M, Balaraman V, Mitzel D, *et al.*: **Susceptibility of sheep to experimental co-infection with the ancestral lineage of SARS-CoV-2 and its alpha variant**. *Emerg Microbes Infect* 2022, **11**:662-675.

24. Ulrich L, Wernike K, Hoffmann D, Mettenleiter TC, Beer M: **Experimental infection of cattle with SARS-CoV-2**. *Emerg Infect Dis* 2020, **26**:2979-2981.

25. Vergara-Alert J, Rodon J, Carrillo J, Te N, Izquierdo-Useros N, Rodríguez de la Concepción ML, Ávila-Nieto C, Guallar V, Valencia A, Cantero G, *et al.*: **Pigs are not susceptible to SARS-CoV-2 infection but are a model for viral immunogenicity studies**. *Transbound Emerg Dis* 2021, **68**:1721-1725.

26. Pickering BS, Smith G, Pinette MM, Embury-Hyatt C, Moffat E, Marszal P, Lewis CE: **Susceptibility of domestic swine to experimental infection with severe acute respiratory syndrome coronavirus 2**. *Emerg Infect Dis* 2021, **27**:104-112.

27. Munster VJ, Feldmann F, Williamson BN, Van Doremalen N, Pérez-Pérez L, Schulz J, Meade-White K, Okumura A, Callison J, Brumbaugh B, *et al.*: **Respiratory disease in rhesus macaques inoculated with SARS-CoV-2**. *Nature* 2020, **585**:268-271.

28. Schlottau K, Rissmann M, Graaf A, Schön J, Sehl J, Wylezich C, Höper D, Mettenleiter TC, Balkema-Buschmann A, Harder T, *et al.*: **SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens: an experimental transmission study**. *Lancet Microbe* 2020, **1**:e218-e225.

29. Freuling CM, Breithaupt A, Müller T, Sehl J, Balkema-Buschmann A, Rissmann M, Klein A, Wylezich C, Höper D, Wernike K, *et al.*: **Susceptibility of raccoon dogs for experimental SARS-CoV-2 infection**. *Emerg Infect Dis* 2020, **26**:2982-2985.

30. Palmer MV, Martins M, Falkenberg S, Buckley A, Caserta LC, Mitchell PK, Cassmann ED, Rollins A, Zylich NC, Renshaw RW, *et al.*: **Susceptibility of white-tailed deer (Odocoileus virginianus) to SARS-CoV-2**. *J Virol* 2021, **95**:1-16.

31. Muñoz-Fontela C, Widerspickid L, Albrechtid RA, Beer M, Carroll MW, De Witid E, Diamondid MS, Dowlingid WE, Funnell SGP, García-Sastre IdA, *et al.*: **Advances and gaps in SARS-CoV-2 infection models**. *PLoS Pathog* 2022, **18**:e1010161.

32. Zhang W, Shi K, Geng Q, Ye G, Aihara H, Li F: **Structural basis for mouse receptor recognition by SARS-CoV-2 omicron variant**. *PNAS* 2022, **119**:e2206509119.

33. •• Wei C, Shan K, Wang W, Zhang S: **Evidence for a mouse origin of the SARS-CoV-2 Omicron variant**. *J Genet Genom* 2021, **48**:1111-1121.

The study found that RBD of the Omicron variant is adapted to the murine ACE2 (mACE2) significantly better than for the human ACE2 receptor. Three specific mutations in the Omicron RBD are uniquely adapted to the mACE2, supporting a murine origin of the Omicron variant and subsequently transmission to humans.

34. World Organization for Animal Health: **SARS-COV-2 in Animals – Situation Report 22**. 2023. https://www.woah.org/app/uploads/2023/07/sars-cov-2-situation-report-22.pdf.

35. Sit THC, Brackman CJ, Ip SM, Tam KWS, Law PYT, To EMW, Yu VYT, Sims LD, Tsang DNC, Chu DKW, *et al.*: **Infection of dogs with SARS-CoV-2**. *Nature* 2020, **586**:776-778.

36. Garigliany M, Laere A-SVan, Clercx C, Giet D, Escriou N, Huon C, Van Der Werf S, Eloit M, Desmecht D: **SARS-CoV-2 natural transmission from human to cat, Belgium, March 2020**. *Emerg Infect Dis* 2020, **26**:3069-3071.

37. Račnik J, Kočevar A, Slavec B, Korva M, Rus KR, Zakotnik S, Zorec TM, Poljak M, Matko M, Rojs OZ, *et al.*: **Transmission of SARS-CoV-2 from human to domestic ferret**. *Emerg Infect Dis* 2021, **27**:2450-2453.

38. Sailleau C, Dumarest M, Vanhomwegen J, Delaplace M, Caro V, Kwasiborski A, Hourdel V, Chevaillier P, Barbarino A, Comtet L, *et al.*: **First detection and genome sequencing of SARS-CoV-2 in an infected cat in France**. *Transbound Emerg Dis* 2020, **67**:2324-2328.

39. Segalés J, Puig M, Rodon J, Avila-Nieto C, Carrillo J, Cantero G, Terrón MT, Cruz S, Parera M, Noguera-Julián M, *et al.*: **Detection of SARS-CoV-2 in a cat owned by a COVID-19-affected patient in Spain**. *PNAS* 2020, **117**:24790-24793.

40. Fernández-Bastit L, Rodon J, Pradenas E, Marfil S, Trinité B, Parera M, Roca N, Pou A, Cantero G, Lorca-Oró C, *et al.*: **First detection of SARS-CoV-2 delta (B.1.617.2) variant of concern in a dog with clinical signs in Spain**. *Viruses* 2021, **13**:2526.

41. Hosie MJ, Epifano I, Herder V, Orton RJ, Stevenson A, Johnson N, MacDonald E, Dunbar D, McDonald M, Howie F, *et al.*: **Detection of SARS-CoV-2 in respiratory samples from cats in the UK associated with human-to-cat transmission**. *Vet Rec* 2021, **188**:e247.

42. Hosie MJ, Hofmann-Lehmann R, Hartmann K, Egberink H, Truyen U, Addie DD, Belák S, Boucraut-Baralon C, Frymus T, Lloret A, *et al.*: **Anthropogenic infection of cats during the 2020 COVID-19 pandemic**. *Viruses* 2021, **13**:185.

43. Gortázar C, Barroso-Arévalo S, Ferreras-Colino E, Isla J, de la Fuente G, Rivera B, Domínguez L, de la Fuente J, Sánchez-Vizcaíno JM, Gortázar C, *et al.*: **Natural SARS-CoV-2 infection in kept ferrets, Spain**. *Emerg Infect Dis* 2021, **27**:1994-1996.

44. Giner J, Villanueva-Saz S, Tobajas AP, Dolores Pérez M, González A, Verde M, Yzuel A, García-García A, Taleb V, Lira-Navarrete E, *et al.*: **SARS-CoV-2 seroprevalence in household domestic ferrets (Mustela putorius furo)**. *Animals* 2021, **11**:667.

45. Molini U, Coetzee LM, Engelbrecht T, de Villiers L, de Villiers M, Mangone I, Curini V, Khaiseb S, Ancora M, Cammà C, *et al.*: **SARS-CoV-2 in Namibian dogs**. *Vaccines* 2022, **10**:3-7.

46. Sirakov I, Rusenova N, Rusenov A, Gergova R: **Human ELISA detects anti-SARS-CoV-2 antibodies in cats: seroprevalence and risk factors for virus spread in domestic and stray cats in Bulgaria**. *Vet Sci* 2023, **10**:1-10.

47. Barroso-Arévalo S, Barneto A, Ramos ÁM, Rivera B, Sánchez R, Sánchez-Morales L, Pérez-Sancho M, Buendía A, Ferreras E, Carlos Ortiz-Menéndez J, *et al.*: **Large-scale study on virological and serological prevalence of SARS-CoV-2 in cats and dogs in Spain**. *Transbound Emerg Dis* 2022, **69**:e759-e774.

48. Patterson EI, Elia G, Grassi A, Giordano A, Desario C, Medardo M, Smith SL, Anderson ER, Prince T, Patterson GT, *et al.*: **Evidence of exposure to SARS-CoV-2 in cats and dogs from households in Italy**. *Nat Commun* 2020, **11**:6231.

49. Barrs VR, Peiris M, Tam KWS, Law PYT, Brackman CJ, To EMW, Yu VYT, Chu DKW, Perera RAPM, Sit THC: **SARS-CoV-2 in quarantined domestic cats from COVID-19 households or close contacts, Hong Kong, China**. *Emerg Infect Dis* 2020, **26**:3071-3074.

50. Fritz M, Rosolen B, Krafft E, Becquart P, Elguero E, Vratskikh O, Denolly S, Boson B, Vanhomwegen J, Gouilh MA, *et al.*: **High prevalence of SARS-CoV-2 antibodies in pets from COVID-19+ households**. *One Health* 2021, **11**:100192.

51. Zhao Y, Yang Y, Gao J, Huang K, Hu C, Hui X, He X, Li C, Gong W, Lv C, *et al.*: **A serological survey of severe acute respiratory syndrome coronavirus 2 in dogs in Wuhan**. *Transbound Emerg Dis* 2022, **69**:591-597.

52. • Fernández-Bastit L, Marfil S, Pradenas E, Valle R, Roca N, Rodon J, Pailler-García L, Trinité B, Parera M, Noguera-Julian M: **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and humoral responses against different variants of concern in domestic pet animals and stray cats from North-Eastern Spain**. *Transbound Emerg Dis* 2022, **69**:3518-3529.

Domestic pet animals (cats, dogs and ferrets) are able to neutralize different VOCs of SARS-CoV-2 after natural infection or viral exposure. Similar prevalence of virus and antibodies occurred in cats and dogs.

53. Hamer SA, Pauvolid-Corrêa A, Zecca IB, Davila E, Auckland LD, Roundy CM, Tang W, Torchetti MK, Killian ML, Jenkins-Moore M, *et al.*: **SARS-CoV-2 infections and viral isolations among serially tested cats and dogs in households with infected owners in Texas, USA**. *Viruses* 2021, **13**:938.

54. Kuhlmeier E, Chan T, Agüí CV, Willi B, Wolfensberger A, Beisel C, Topolsky I, Beerenwinkel N, Stadler T, Jones S, *et al.*: **Detection and molecular characterization of the SARS-CoV-2 delta variant and the specific immune response in companion animals in Switzerland**. *Viruses* 2023, **15**:245.

55. • de Souza Barbosa AB, Barbosa DS, Bach L, Doline FR, Rejane S, Silveira R, Ana P: **Infection of SARS-CoV-2 in domestic dogs associated with owner viral load**. *Res Vet Sci* 2022, **153**:61-65.
Molecular detection of SARS-CoV-2 in household dogs was associated with presence of clinical signs in owners, number of positive person in the household and higher viral loads. Owners with COVID-19 should take preventive measures when interacting with their pets to prevent cross-species transmission.

56. Piewbang C, Poonsin P, Lohavicharn P, Wardhani SW, Dankaona W, Puenpa J, Poovorawan Y, Techangamsuwan S: **SARS-CoV-2 transmission from human to pet and suspected transmission from pet to human, Thailand**. *J Clin Microbiol* 2022, **60**:1-14.

57. Jairak W, Chamsai E, Udom K, Charoenkul K, Chaiyawong S, Techakriengkrai N, Tangwangvivat R, Suwannakarn K, Amonsin A: **SARS-CoV-2 delta variant infection in domestic dogs and cats, Thailand**. *Sci Rep* 2022, **12**:1-12.

58. •• Sila T, Sunghan J, Laochareonsuk W, Surasombatpattana S, Kongkamol C, Ingviya T, Siripaitoon P, Kositpantawong N, Kanchanasuwan S, Hortiwakul T, *et al*.: **Suspected cat-to-human transmission of SARS-CoV-2, Thailand, July-September 2021**. *Emerg Infect Dis* 2022, **28**:1485-1488.
First time evidence of a cat-to human transmission of SARS-CoV-2 by genomic sequencing analysis. The cat transmitted the virus to a veterinarian clinician after sneezing; their genomic sequences were identical to those from the cat owner's.

59. •• Yen H, Sit THC, Brackman CJ, Chuk SSY, Gu H, Tam KWS, Law PYT, Leung GM: **Transmission of SARS-CoV-2 delta variant (AY.127) from pet hamsters to humans, leading to onward human-to-human transmission: a case study**. *Lancet* 2022, **399**:1070-1078.
Pet hamsters can be naturally infected by SARS-CoV-2 and can transmit the virus back to humans. An outbreak of SARS-CoV-2 delta variant (AY.127) was first detected in a pet shop worker leading to subsequent multiple cases of hamster-to-human and subsequent human-to-human transmission.

60. Trinité B, Tarrés-Freixas F, Rodon J, Pradenas E, Urrea V, Marfil S, Luisa M, De La Concepción R, Ávila-Nieto C, Aguilar-Gurrieri C, *et al*.: **SARS-CoV-2 infection elicits a rapid neutralizing antibody response that correlates with disease severity**. *Sci Rep* 2021, **11**:2608.

61. Bae D, Tark D, Moon S, Oem J, Kim W, Park C, Na K, Park C, Oh Y, Cho H: **Evidence of exposure to SARS-CoV-2 in dogs and cats from households and animal shelters in Korea**. *Animals* 2022, **12**:2786.

62. Villanueva-Saz S, Giner J, Tobajas AP, María, Pérez D, Andrés, González-Ramírez M, Macías-León J, González A, Verde M, *et al*.: **Serological evidence of SARS-CoV-2 and co-infections in stray cats in Spain**. *Transbound Emerg Dis* 2022, **69**:1056-1064.

63. Spada E, Vitale F, Bruno F, Castelli G, Reale S, Perego R, Baggiani L, Proverbio D: **A pre-and during pandemic survey of Sars-Cov-2 infection in stray colony and shelter cats from a high endemic area of Northern Italy**. *Viruses* 2021, **13**:618.

64. • Doliff R, Martens P: **Cats and SARS-CoV-2: a scoping review**. *Animals* 2022, **12**:1-25.
This review suggests a very limited role of cats in the spread of SARS-CoV-2 considering experimental studies, natural infections, large-scale studies in prevalence and seroprevalence of cats worldwide and reverse zoonotic transmission cases described until March 2022.

65. • Van Aart AE, Velkers FC, Fischer EAJ, Broens EM, Egberink H, Zhao S, Engelsma, M, Hakze-Van Der Honing RW, Harders F, De Rooij MMT, *et al*.: **SARS-CoV-2 infection in cats and dogs in infected mink farms**. *Transbound Emerg Dis* 2022, **69**:3001-3007.
One of the first reports of interspecies transmission of SARS-CoV-2 in which viral transmission from farm minks to feral cats was supported by sequencing analysis, leading to consider it as a potential risk for viral spread.

66. Bao L, Song Z, Xue J, Gao H, Liu J, Wang J, Guo Q, Zhao B, Qu Y, Qi F, *et al*.: **Susceptibility and attenuated transmissibility of SARS-CoV-2 in domestic cats**. *J Infect Dis* 2021, **223**:1313-1321.

67. Cerino P, Buonerba C, Brambilla G, Atripaldi L, Tafuro M, Concilio DDi, Vassallo L, Conte GLo, Cuomo MC, Maiello I, *et al*.: **No detection of SARS-CoV-2 in animals exposed to infected keepers: results of a COVID-19 surveillance program**. *Futur Sci OA* 2021, **7**:FSO711.

68. Wernike K, Böttcher J, Amelung S, Albrecht K, Gärtner T, Donat K, Beer M: **Antibodies against SARS-CoV-2 suggestive of single events of spillover to cattle, Germany**. *Emerg Infect Dis* 2022, **28**:1916-1918.

69. Fiorito F, Iovane V, Pagnini U, Cerracchio C, Brandi S, Levante M, Marati L, Ferrara G, Tammaro V, De Carlo E, *et al*.: **First description of serological evidence for SARS-CoV-2 in lactating cows**. *Animals* 2022, **12**:1459.

70. Lawton K, Keller SM, Barnum S, Arredondo-lopez C, Spann K, Pusterla N: **Seroprevalence of SARS-CoV-2 in 1186 equids presented to a 2020 to 2022**. *Viruses* 2022, **14**:2497.

71. Fusco G, Cardillo L, Levante M, Brandi S, Picazio G, Napoletano M, Martucciello A, Fiorito F, De Carlo E, de Martinis C: **First serological evidence of SARS-CoV-2 natural infection in small ruminants: Brief report**. *Vet Res Commun* (3) 2023, **47**:1741-1748.

72. Pusterla N, Chaillon A, Ignacio C, Smith DM, Barnum S, Lawton KOY, Smith G, Pickering B: **SARS-CoV-2 seroconversion in an adult horse with direct contact to a COVID-19 individual**. *Viruses* 2022, **14**:1047.

73. Oreshkova N, Molenaar RJ, Vreman S, Harders F, Oude Munnink BB, Van Der Honing RWH, Gerhards N, Tolsma P, Bouwstra R, Sikkema RS, *et al*.: **SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020**. *Eurosurveillance* 2020, **25**:2001005.

74. Lu L, Sikkema RS, Velkers FC, Nieuwenhuijse DF, Fischer EAJ, Meijer PA, Bouwmeester-Vincken N, Rietveld A, Wegdam-Blans MCA, Tolsma P, *et al*.: **Adaptation, spread and transmission of SARS-CoV-2 in farmed minks and associated humans in the Netherlands**. *Nat Commun* 2021, **12**:1-12.

75. Dall Schmidt T, Mitze T: **SARS-CoV-2 outbreaks on Danish mink farms and mitigating public health interventions**. *Eur J Public Health* 2022, **32**:151-157.

76. Hammer AS, Quaade ML, Rasmussen TB, Fonager J, Rasmussen M, Mundbjerg K, Lohse L, Strandbygaard B, Jørgensen CS, Alfaro-Núñez A, *et al*.: **SARS-CoV-2 transmission between mink (Neovison vison) and humans, Denmark**. *Emerg Infect Dis* 2021, **27**:547-551.

77. •• Oude Munnink BB, Sikkema RS, Nieuwenhuijse DF, Molenaar RJ, Munger E, Molenkamp R, Van Der Spek A, Tolsma P, Rietveld A, Brouwer M, *et al*.: **Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans**. *Science* 2021, **371**:172-177.
This study provides evidences of multiple cases of SARS-CoV-2 introduction from humans to farm minks and spillback to humans after intra-species transmission.

78. •• Hoffmann M, Zhang L, Krüger N, Graichen L, Kleine-Weber H, Hofmann-Winkler H, Kempf A, Nessler S, Riggert J, Winkler MS, *et al*.: **SARS-CoV-2 mutations acquired in mink reduce antibody-mediated neutralization**. *Cell Rep* 2021, **35**:109017.
The Y453F mutation found in mink-derived sequences of SARS-CoV-2 confers partial escape from therapeutic antibody and allows evasion of antibodies induced by SARS-CoV-2 infection of humans.

79. Fenollar F, Mediannikov O, Maurin M, Devaux C, Colson P, Levasseur A, Fournier PE, Raoult D: **Mink, SARS-CoV-2, and the human-animal interface**. *Front Microbiol* 2021, **12**:663815.

80. Eckstrand CD, Baldwin TJ, Rood KA, Clayton MJ, Lott JK, Wolking RM, Bradway DS, Baszler T: **An outbreak of SARS-CoV-2 with high mortality in mink (Neovison vison) on multiple Utah farms**. *PLoS Pathog* 2021, **17**:e1009952.

81. Badiola JJ, Otero A, Sevilla E, Marín B, Martínez MG, Betancor M, Sola D, Lázaro SP, Lozada J, Velez C, *et al*.: **SARS-CoV-2 outbreak on a Spanish mink farm: epidemiological, molecular, and pathological studies**. *Front Vet Sci* 2021, **8**:805004.

82. Rabalski L, Kosinski M, Smura T, Aaltonen K, Kant R, Sironen T, Szewczyk B, Grzybek M: **Severe acute respiratory syndrome coronavirus 2 in farmed mink (Neovison vison), Poland**. *Emerg Infect Dis* 2021, **27**:2333-2339.

83. Cai HY, Cai A: **SARS-CoV2 spike protein gene variants with N501T and G142D mutation–dominated infections in mink in the United States**. *J Vet Diagn Invest* 2021, **33**:939-942.

84. Su C, He J, Han P, Bai B, Li D, Cao J, Tian M, Hu Y, Zheng A, Niu S, *et al*.: **Molecular basis of mink ACE2 binding to SARS-CoV-2 and its mink-derived variants**. *J Virol* 2022, **96**:e0081422.

85. Bartlett SL, Wang DG, Laverack M: **SARS-CoV-2 infection and longitudinal fecal screening in Malayan tigers (Panthera tigris Jacksoni), Amur tigers (Panthera tigris Altaica), and African lions (Panthera leo Krugeri) at the Bronx zoo, New York, USA**. *Source J Zoo Wildl Med* 2020, **51**:733-744.

86. McAloose D, Laverack M, Wang L, Killian ML, Caserta LC, Yuan F, Mitchell PK, Queen K, Mauldin MR, Cronk BD, *et al*.: **From people to panthera: natural sars-cov-2 infection in tigers and lions at the bronx zoo**. *MBio* 2020, **11**:1-13.

87. Mishra A, Kumar N, Bhatia S, Aasdev A, Kanniappan S, Sekhar AT, Gopinadhan A, Silambarasan R, Sreekumar C, Dubey CK, *et al*.: **Sars-cov-2 delta variant among asiatic lions, india**. *Emerg Infect Dis* 2021, **27**:2723-2725.

88. Fernández-Bellon H, Rodon J, Fernández-Bastit L, Almagro V, Padilla-Solé P, Lorca-Oró C, Valle R, Roca N, Grazioli S, Trogu T, *et al*.: **Monitoring natural SARS-CoV-2 infection in lions (Panthera leo) at the Barcelona zoo: Viral dynamics and host responses**. *Viruses* 2021, **13**:1683.

89. Wang L, Gyimesi ZS, Killian ML, Torchetti M, Olmstead C, Fredrickson R, Terio KA: **Detection of SARS-CoV-2 clade B.1.2 in three snow leopards**. *Transbound Emerg Dis* 2022, **69**:e3346-e3351.

90. Cushing AC, Sawatzki K, Grome HN, Puryear WB, Kelly N, Runstadler J: **Duration of antigen shedding and development of antibody titers in malayan tigers (Panthera tigris jacksoni) naturally infected with sars-CoV-2**. *J Zoo Wildl Med* 2021, **52**:1224-1228.

91. Mitchell PK, Martins M, Reilly T, Caserta LC, Anderson RR, Cronk BD, Murphy J, Goodrich EL, Diel DG: **SARS-CoV-2 B.1.1.7 variant infection in Malayan tigers, Virginia, USA**. *Emerg Infect Dis* 2021, **27**:3171-3173.

92. Koeppel KN, Mendes A, Strydom A, Rotherham L, Mulumba M, Venter M: **SARS-CoV-2 reverse zoonoses to pumas and lions, South Africa**. *Viruses* 2022, **14**:120.

93. Nagy A, Stará M, Vodička R, Černíková L, Jiřincová H, Křivda V, Sedlák K: **Reverse-zoonotic transmission of SARS-CoV-2 lineage alpha (B.1.1.7) to great apes and exotic felids in a zoo in the Czech Republic**. *Arch Virol* 2022, **167**:1681-1685.

94. Sangkachai N, Chaiwattanarungruengpaisan S, Thongdee M, Suksai P, Tangsudjai S, Wongluechai P, Suwanpakdee S, Wiriyarat W, Buddhirongawatr R: **Serological and molecular surveillance for SARS-CoV-2 infection in captive tigers (Panthera tigris), Thailand**. *Animals* 2022, **12**:3350.

95. Allender MC, Adkesson MJ, Langan JN, Delk KW, Meehan T, Aitken-Palmer C, McEntire MM, Killian ML, Torchetti M, Morales SA, *et al*.: **Multi-species outbreak of SARS-CoV-2 Delta variant in a zoological institution, with the detection in two new families of carnivores**. *Transbound Emerg Dis* 2022, **69**:e3060-e3075.

96. Vercammen F, Cay B, Gryseels S, Balmelle N, Joffrin L, Hoorde KVan: **SARS-CoV-2 infection in captive hippos (Hippopotamus amphibius), Belgium**. *Animals* 2023, **13**:316.

97. Italiya J, Vacek V, Matějů P, Dering C, Celina SS, Ndiaye A, Černý J: **First detection of SARS-CoV-2 in white rhinoceros during a small-scale coronavirus surveillance in the Bandia Reserve, Senegal**. *Animals* 2023, **13**:1-8.

98. Pappas G, Vokou D, Sainis I, Halley JM: **SARS-CoV-2 as a zooanthroponotic infection: spillbacks, secondary spillovers, and their importance**. *Microorganisms* 2022, **10**:2166.

99. Chandler JC, Bevins SN, Ellis JW, Linder TJ, Tell RM, Jenkins-Moore M, Root JJ, Lenoch JB, Robbe-Austerman S, Deliberto TJ, *et al*.: **SARS-CoV-2 exposure in wild white-tailed deer (Odocoileus virginianus)**. *PNAS* 2021, **118**:e2114828118.

100. Palermo PM, Orbegozo J, Watts DM, Morrill JC: **SARS-CoV-2 neutralizing antibodies in white-tailed deer from Texas**. *Vector-borne Zoonotic Dis* 2022, **22**:62-64.

101. •• Hale VL, Dennis PM, Mcbride DS, Nolting JM, Madden C, Huey D, Ehrlich M, Grieser J, Winston J, Lombardi D, *et al*.: **SARS-CoV-2 infection in free-ranging white-tailed deer**. *Nature* 2022, **602**:481-486.
The study demonstrated extensive infection of free-ranging wild white-tailed deer resulting from multiple spillovers from humans followed by efficient transmission between deers. White-tailed deer is considered as a potential reservoir host for SARS-CoV-2.

102. Kuchipudi SV, Surendran-Nair M, Ruden RM, Yon M, Nissly RH, Vandegrift KJ, Nelli RK, Li L, Jayarao BM, Maranas CD, *et al*.: **Multiple spillovers from humans and onward transmission of SARS-CoV-2 in white-tailed deer**. *PNAS* 2022, **119**:E2121644119.

103. •• Marques AD, Sherrill-Mix S, Everett JK, Adhikari H, Reddy S, Ellis JC, Zeliff H, Greening SS, Cannuscio CC, Strelau KM, *et al*.: **Multiple introductions of SARS-CoV-2 alpha and delta variants into white-tailed deer in Pennsylvania**. *Am Soc Microbiol* 2022, **13**:e0210122.
The study aimed to provide new insights on the infection and transmission dynamics of SARS-CoV-2 in white-tailed deer by an experimental infection as a potential animal reservoir of the virus in the wild environment.

104. •• Martins M, Boggiatto PM, Buckley A, Cassmann ED, Falkenberg S, Caserta LC, Fernandes MHV, Kanipe C, Lager K, Palmer MV, *et al*.: **From Deer-To-Deer: SARS-CoV-2 is efficiently transmitted and presents broad tissue tropism and replication sites in white-tailed deer**. *PLoS Pathog* 2022, **18**:e1010197.
The authors identified a new viral lineage (B.1.641) in white tailed deer (WTD), being one of the most divergent SARS-CoV-2 lineages identified so far. This provided evidence of sustained evolution of SARS-CoV-2 in WTD and a potential deer-to human transmission of this viral strain.

105. Pickering B, Lung O, Maguire F, Kruczkiewicz P, Kotwa JD, Buchanan T, Gagnier M, Guthrie JL, Jardine CM, Marchand-Austin A, *et al*.: **Divergent SARS-CoV-2 variant emerges in white-tailed deer with deer-to-human transmission**. *Nat Microbiol* 2022, **7**:2011-2024.

106. Encinas P, Escalera A, Aydillo T, Iglesias I, Nelson MI, Garc A, Real G: **SARS-CoV-2 neutralizing antibodies in free-ranging fallow deer (Dama dama) and red deer (Cervus elaphus) in suburban and rural areas in Spain**. *Transbound Emerg Dis* 2023, **2023**:3324790.

107. Aguiló-Gisbert J, Padilla-Blanco M, Lizana V, Maiques E, Muñoz-Baquero M, Chillida-Martínez E, Cardells J, Rubio-Guerri C: **First description of sars-cov-2 infection in two feral American mink (Neovison vison) caught in the wild**. *Animals* 2021, **11**:1-13.

108. Padilla-Blanco M, Aguiló-Gisbert J, Rubio V, Lizana V, Chillida-Martínez E, Cardells J, Maiques E, Rubio-Guerri C: **The finding of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) in a wild Eurasian river otter (Lutra lutra) highlights the need for viral surveillance in wild mustelids**. *Front Vet Sci* 2022, **31**:826991.

109. Davoust B, Guérin P, Orain N, Fligny C, Flirden F, Fenollar F, Mediannikov O, Edouard S: **Evidence of antibodies against SARS-CoV-2 in wild mustelids from Brittany (France)**. *Transbound Emerg Dis* 2022, **69**:e3400-e3407.

110. Giacobbo A, Rodrigues MAS, Zoppas Ferreira J, Bernardes AM, de Pinho MN: **A critical review on SARS-CoV-2 infectivity in water and wastewater. What do we know?** *Sci Total Environ* 2021, **774**:145721.

111. Sikkema RS, Begeman L, Janssen R, Wolters WJ, Geurtsvankessel C, de Bruin E, Hakze-van der Honing RW, Eblé P, van der Poel WHM, van den Brand JMA, *et al*.: **Risks of SARS-CoV-2 transmission between free-ranging animals and captive mink in the Netherlands**. *Transbound Emerg Dis* 2022, **69**:3339-3349.

112. Shriner SA, Ellis JW, Root JJ, Roug A, Stopak SR, Wiscomb GW, Zierenberg JR, Ip HS, Torchetti MK, DeLiberto TJ: **SARS-CoV-2 exposure in escaped mink, Utah, USA**. *Emerg Infect Dis* 2021, **27**:988-990.

113. Mahajan S, Karikalan M, Chander V, Pawde AM, Saikumar G, Semmaran M, Lakshmi PS, Sharma M, Nandi S, Singh KP, *et al*.: **Detection of SARS-CoV-2 in a free ranging leopard (Panthera pardus fusca) in India**. *Eur J Wildl Res* 2022, **68**:1-5.

114. Pereira AH, Vasconcelos AL, Silva VL, Nogueira BS, Silva AC, Pacheco RC, Souza MA, Colodel EM, Ubiali DG, Biondo AW, *et al*.: **Natural SARS-CoV-2 infection in a free-ranging black-tailed marmoset (Mico melanurus) from an urban area in mid-west Brazil**. *J Comp Pathol* 2022, **194**:22-27.

115. Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, Luo SW, Li PH, Zhang LJ, Guan YJ, *et al*.: **Isolation and characterization of viruses related to the SARS coronavirus from animals in Southern China**. *Science (80-)* 2003, **302**:276-278.

116. Lytras S, Hughes J, Martin D, Swanepoel P, de Klerk A, Lourens R, Kosakovsky Pond SL, Xia W, Jiang X, Robertson DL: **Exploring the natural origins of SARS-CoV-2 in the light of recombination**. *Genome Biol Evol* 2022, **14**:evac018.

117. Mostaghimi D, Valdez CN, Larson HT, Kalinich CC, Iwasaki A: **Prevention of host-to-host transmission by SARS-CoV-2 vaccines**. *Lancet Infect Dis* 2022, **22**:e52-e58.

118. Tabynov K, Orynbassar M, Yelchibayeva L, Turebekov N, Yerubayev T, Matikhan N, Yespolov T, Petrovsky N, Tabynov K: **A spike protein-based subunit SARS-CoV-2 vaccine for pets: safety, immunogenicity, and protective efficacy in juvenile cats**. *Front Vet Sci* 2022, **9**:815978.