Relevance of animal infections in SARS-Cov-2 spread: an update after 1 year of pandemic.

Running title: SARS-CoV-2 infection in animal species.

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Summary

In December 2019, several cases of pneumonia caused by a novel Coronavirus, later identified as SARS-CoV-2, were detected in the Chinese city of Wuhan. Due to its rapid, worldwide spread, on 11 March 2020 the World Health Organization declared a pandemic state. Since this new virus is genetically similar to the coronaviruses of bats, it was thought to have a zoonotic origin. Within a year of the appearance of SARS-CoV-2, several cases of infection were also reported in animals, suggesting animal-to-human and animal-to-animal transmission within mammals. Natural infection has been found in both companion and captive animals such as lions, tigers and gorillas. Among farm animals, the only ones found to be susceptible to SARS-CoV-2 infection so far are minks. Experimental infections have documented the susceptibility to SARS-CoV-2 of several animal species, such as humanized mice, hamsters, cats, dogs, ferrets, racoon dogs, cattle and non-human primates. Experimental infections are crucial for both elucidation of the role of animals in transmission and development of appropriate animal models for pathogenesis and therapy studies. This review aims to update the knowledge on natural and experimental SARS-CoV-2 infections in animals.

Key words: ACE2, animal infection, Covid-19, , fecal swab, nasal swab, SARS-CoV-2.

Introduction

At the end of December 2019 several cases of atypical pneumonia were reported in China, precisely in the Hubei's capital city, Wuhan. In January 2020, a novel Betacoronavirus (β-CoV) was identified as the causative agent. Based on the availability of genetic analysis, the International Committee for Taxonomy of Viruses named it SARS-CoV-2, while the disease was named COVID-19 by the World Health Organization (WHO) (Ludwig et al. 2020). Despite the Chinese authorities' efforts to curb the circulation of the virus, this spread throughout the world, and on 11 March 2020 the WHO declared a pandemic state. Currently (8th of April, 2021), the SARS-CoV-2 virus has caused the death of 2,875,672 people out of 132,485,386 confirmed cases worldwide since the beginning of the pandemic. The primary source of SARS-CoV-2 was related to the Huanan seafood market, where live wild animals such as birds, snakes, marmots were on sale (Li et al. 2020). Studies have shown that the genome of SARS-CoV-2 is similar to that of SARS-COV (79.6% of sequence homology), the virus that caused the 2002-2003 SARS epidemic. Since SARS-CoV-2 shares 96.2% sequence identity to bat coronavirus RaTG13 (BatCoV RaTG13), it is considered zoonotically derived from it (Zhou et al. 2020). Despite the genomic similarity, the Receptor Binding Domain (RBD) of BatCoV RaTG13 is quite different from the homologous one of SARS-Cov-2, which makes it unlikely that pandemic virus may have jumped directly from bats to humans. Probably, due to selective pressure, SARS-CoV-2 RBD evolved into an intermediate animal species before its passage to humans. In this regard, one of the species suggested as potential intermediary host is the pangolin, because of the high similarity between the human SARS CoV-2 RBD and the Malayan pangolin receptor (Munir et al. 2020). In order to clarify the possible role of animals in the transmission of SARS-CoV-2, we report hereunder the confirmed cases of COVID-19 in companion, livestock, laboratory and wild animals.

Summary of pathogenesis of COVID-19 in humans

SARS-CoV-2, a positive-sense single-stranded RNA virus belonging to the Betacoronavirus genus, is responsible for COVID-19 disease (Domingo et al. 2020). Transmission mainly occurs through exposure of the respiratory tract to the virus, either directly, through contact of contaminated hands with eyes, and the subsequent passage of the virus through the naso-lacrimal duct, or nose, or indirectly through inhalation of contaminated droplets released by an infected person coughing or sneezing (Cao et al 2020).

The virus reaches the lungs through the respiratory tract after passing the mucous membranes of the upper respiratory tract, where the virus begins to replicate (primary amplification); then it often reaches the lungs where it further replicates (secondary amplification) and enters the bloodstream, which enables the virus to reach the target organs. Since the internalization of the virus occurs through the binding to the cellular receptor known as angiotensin-converting enzyme 2 (ACE2), all the target organs express this receptor: lungs, heart, blood vessels, kidney and gastrointestinal tract (Cao et al 2020; Dan et al. 2002). ACE2 is expressed by multiple human cell types, such as type II alveolar cells (AT2), oral, oesophageal, ileal epithelial cells, myocardial cells, proximal tubule cells of the kidneys and urothelial cells of the bladder (Zou et al. 2020). The viral protein involved in cell entry is a glycoprotein spike trimer (S protein, SP), which undergoes a proteolytic cut necessary to extrude the RBD of one of the subunits, which in turn binds the target peptide domain of ACE2 (Kordzadeh-Kermani et al. 2020). In addition to this, Wang et al. have identified an alternative entry route, through the binding of SARS-CoV-2 SP with CD147 (Wang et al. 2020). CD147, also known as basigin or EMMPRIN, is a membrane glycoprotein of the immunoglobulin superfamily, involved in tumor development, Plasmodium invasion, and bacterial and virus infections (Biswas et al. 1995). It is expressed by epithelial cells, endothelial cells and leukocytes (Biswas et al. 1995).

In 80% of the cases the disease is mild and confined to the upper respiratory tract (Wu et al. 2020). The remaining 20% of patients experience virus invasion of lungs, that often gives rise to a severe interstitial inflammation caused by vascular injuries (Xu et al. 2020). The virus infects the alveolar cells compromising the gas exchanges and the renin-angiotensin system. Together with its direct cytopathic activity, the virus induces a strong immune response mediated by both nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and nucleotide-binding oligomerization domain-like receptors (NLRs) activation (Chen et al. 2019). The ensuing high proinflammatory cytokine production underlies the so-called cytokine storm leading to severe symptoms and lesions such as vasculopathy, coagulopathy and multiple organ injuries that represent the major mortality cause (Varga et al. 2020).

Animal reservoirs of SARS-CoV-2

Since bats, and in particular the horseshoe bat (Chakraborty et al. 2020), are the main natural reservoirs of various coronaviruses (CoVs), from the beginning it was thought that they could play the same role also for SARS-CoV-2. Genomic sequencing and evolutionary analyses showed 96.2% identity between SARS-CoV-2 and BatCoV RaTG13 (Zhou et al. 2020). Therefore, this similarity suggested that SARS-CoV-2 may have originated from bats (Zhou et al. 2020; Sharun et al. 2020). In particular, the two bat species *R. affinis* and *R. malaynus* could be the natural hosts of SARS-CoV-2 (Wong et al 2020). However, SARS-CoV-2 presents mutations in both S-glycoprotein and N-protein sequences, which differentiate the virus from BatCoV RaTG13. This suggested that the virus may have infected intermediate hosts, where it presumably mutated and acquired the ability to infect humans (Ji et al. 2020; Benvenuto et al. 2020). This hypothesis is also supported by the fact that bats were not available for sale in the Huanan Seafood Market (Wu et al. 2020). Few animal species are under study to identify the putative intermediate host of the virus. Among them are pangolins, turtles and snakes. Malaysian pangolins are nocturnal mammals found in South-East Asia, but not in China, where they arrive via illegal smuggling as they are highly sought after for traditional Chinese medicine and their meat (Wong et al. 2020; Volpato et al. 2020). Studies have revealed that a group of β-CoVs found in pangolins share only about 85-92% nucleotide sequence homology with SARS-CoV-2 (Ye et al. 2020; Yuen et al. 2020; Zhang et al. 2020). Although the percentage of homology is lower than that found between BatCoV RaTG13 and SARS-CoV-2, the pangolin CoV shares with SARS-CoV-2 four of the five key amino acids of RBD region, while bat RaTG13 CoV shares only one amino acid in RBD region. (Zhao et al. 2020). Furthermore, the receptor binding domain (RBD) of pangolin-CoV is very similar to that of SARS-CoV-2, and shows a strong binding capacity to human ACE2 (Xiao et al. 2020). These data, in addition to the observation that pangolins showed clinical signs, histological changes and circulating antibodies, highlighted the possible role of pangolins for inter-species jumping of SARS-CoV-2. Although pangolins are not indigenous to China, but as previously mentioned enter illegally, they share ecological niches with bats. Therefore, they may have come into contact with bats, from which they possibly contracted SARS CoV 2 infection as possible intermediate hosts (Xiao et al. 2020; Li et al 2020). At the same time, phylogenetic analyses ruled out the hypothesis that pangolins could be the natural host of SARS-CoV-2 (Liu et al. 2020).

The analysis of structural binding mechanisms of SARS-CoV-2 RBD to ACE2 receptors, together with evolutionary studies, suggested that also turtles (*Chrysemys picta bellii*, *Pelodiscus sinensis* and *Chelonia mydas*) and snakes (*Bungarus multicinctus* and *Naja atra*) could have served as intermediate hosts for SARS-CoV-2 (Ji et al. 2020; Liu et al. 2020; Chen et al. 2020). However, Luan et al. reported that, in both snakes and turtles, ACE2 is unable to bind to the S protein of SARS-

CoV-2; this could lead to the conclusion that these animals were unlikely to serve as intermediate hosts for the virus (Luan et al. 2020). The identification of an intermediate host allowing for interspecies jumping of the virus from bats to humans is still an open issue.

Occurrence of SARS-CoV-2 in animals

SARS-CoV-2 has spread rapidly across all continents, finding a receptive population in the human species and allowing efficient intraspecies transmission. Highly circulating among humans, the virus may occasionally leap from humans to animals that share the environment with them.

Companion animals

Dog

The first dogs testing positive for COVID-19 were identified in Hong Kong between February and March 2020; 27 dogs were tested, whose owners had contracted COVID-19; only two (a 17-year-old Pomeranian and a 2.5-year-old German Shepherd) resulted positive for SARS-CoV-2 RNA in nasal and oral swabs (Abdel-Moneim et al. 2020; Sit et al. 2020; Mallapaty et al. 2020; USDA APHIS 2020). After few days/weeks, neutralizing antibodies were detected in blood samples of the two dogs (Abdel-Moneim et al. 2020). Neutralizing antibodies against SARS-CoV-2 were detected in other dogs belonging to COVID-19-positive owners in the Netherlands and in New York State (USA) (https://www.avma.org/resources-tools/animal-health-and-welfare/covid-19/sars-cov-2-animals-including-pets; https://www.avma.org/resources-tools/animal-health-and-welfare/covid-19/sars-cov-2-animals-including-pets). A study was conducted by Patterson et al. between March and May 2020 on dogs from Italian families; oropharyngeal, nasal, and/or rectal swabs were collected from 314 dogs; none of them tested positive for SARS-CoV-2 RNA. While SARS-CoV-2-neutralizing antibodies were detected in 15 dogs (3.3%, 15/451) with titers ranging from 1:20 to 1:160. None of these animals displayed respiratory signs at the time of sampling (Patterson et al. 2020). Also, in Northern Italy, one of the most affected areas in the world, some dogs were found positive to SARS-CoV-2 (Goumenou et al. 2020). In all cases the animals showed an infection restricted to the upper respiratory tract, with no apparent capability to transmit the infection to humans or other animals (Stout et al. 2020). These observations were confirmed by an experimental infection of dogs. The experimentally infected animals presented seroconversion, but were not able to infect other dogs in proximity (Shi et al. 2020).

Cats

Also pet cats were tested for antibodies against SARS-CoV-2 using ELISA, Virus Neutralization Test (VNT) and Western Blot. In particular, from January to March 2020 in the city of Wuhan 15 cats out of 102 were ELISA positive, and a further 11 were VNT positive (Zhang et al. 2020). In addition to the antibody test, the animals were also swabbed, but none of them resulted positive (Qiang et al. 2020). In mid-March 2020 in Belgium and Hong Kong, SARS-CoV-2 RNA had been detected by RT-qPCR in samples from two cats presenting with diarrhoea, vomit, and labored breathing (https://www.brusselstimes.com/all-news/belgium-allnews/103003/coronavirus-belgian-woman-infected-her-cat; https://www.info.gov.hk/gia/general/202003/31/P2020033100717.htm). Patterson et al. conducted a study in Italy on 180 cats. All of them tested negative for SARS-CoV-2 RNA, while SARS-CoV-2-neutralizing antibodies were detected in 11 cats (5.8%, 11/191), with titers ranging from 1:20 to 1:1280 (Patterson et al. 2020). A very low percentage (around 0.7%) of antibody positive samples was observed in Germany on 920 cats randomly enrolled (Michelitsch et al. 2020). On April 2020, two cats from New York State (USA), both presenting with sneezing and nasal discharge, tested positive for SARS-CoV-2 by RT-qPCR (https://www.cdc.gov/media/releases/2020/s0422-covid-19-cats-NYC.html). In Spain only one female cat already suffering from other diseases (chronic feline gingivostomatitis, feline idiopathic cystitis, chronic kidney disease and feline asthmatic bronchitis), out of 8 belonging to COVID-19 diseased persons, was oropharyngeal swab-positive but faecal swab-negative (Ruiz-Arrondo et al. 2020). In France, a study on a small cohort of veterinary students and their pets reported that 3 cats showed respiratory and gastrointestinal signs, but no one tested positive for viral RNA (Temmam et al. 2020).

Very recently (19 of March 2021), the Istituto Zooprofilattico Sperimentale del Piemonte, Liguria e Valle d'Aosta (Italy) identified the presence of the English variant of SARS-CoV-2 (lineage B.1.1.7) in an 8-year-old male cat living in Novara (Piedmont) in a domestic setting, where the owners were in isolation because they had tested positive for the English variant of SARS-CoV-2 (http://www.izsto.it/index.php/news/2560-covid-19-identificato-dall-istituto-zooprofilattico-di-torino-il-primo-caso-in-italia-di-variante-inglese-su-gatto).

Also, experimental infection has been reported in cats and, similarly to the natural one, generally results in mild respiratory symptoms, young cats being more susceptible to SARS-CoV-2 (Shi et al. 2020). The antibody response observed in cats could be induced by a prior exposure to a Feline Coronavirus (Alphacoronavirus, FCoV), suggesting a careful interpretation of serological testing, where a positive result could be due to cross-reactivity. Moreover, the possible cross-protection of the FCoV antibodies against SARS-Cov-2 infection is still debated. Finally, different studies suggest the possible direct transmission of SARS-Cov-2 between cats (Halfmann et al 2020). Cats could represent an important reservoir given their habit to wander around different houses and in the wild, but different studies suggest that they remain infectious for short time (Bosco-Lauth et al. 2021).

Ferrets

The results of experimental infections of ferrets were similar to those seen in cats: evidence of upper respiratory airways infection with mild clinical signs, elimination of the virus with faeces and evidence of conspecific transmission of the virus (Kim et al. 2020; Shi et al. 2020). SARS-CoV-2 can replicate in the upper respiratory tract of ferrets, but replication in other organs has never been detected (Kim et al. 2020; Shi et al. 2020). The transmission of the virus in this species can occur both directly and indirectly, but the direct way leads to the development of more symptoms, such as increased temperature and decreased activity, as seen in humans (Kim et al. 2020; Richard et al. 2020).

Livestock animals

Poultry

Schlottau et al. inoculated chickens oculo- and oro-nasally to assess their susceptibility to SARS-CoV-2. Any injected animal showed clinical symptoms, and all swabs and organ samples were negative for viral RNA and none of the animals seroconverted (Schlottau et al 2020). In another experiment, chickens, turkeys, ducks, quails, and geese were inoculated with SARS-CoV-2. Clinical signs were not observed in any of the species tested throughout the trial, viral RNA was not detected in the swabs and antibodies were not present in any of the tested animals (Suarez et al.

2020). Both of these studies suggest that poultry may not allow the virus to replicate properly, or may not be susceptible to infection.

Pigs

Two different experiments were conducted on pigs to test their susceptibility to SARS-CoV-2 infection. The results showed that neither viral RNA nor antibodies were detected in the animals either inoculated or in contact with other infected animals. This demonstrates that the pig is not a susceptible species to SARS-CoV-2 or may be not permissive to virus replication (Schlottau et al 2020; Shi et al. 2020).

Ruminants

Only experimental infections are documented in ruminants. In the first study, calves were intranasally infected with SARS-Cov-2 and did not show any clinical sign of disease (Ulrich et al. 2020). Viral replication was evident in only 2 out of 6 calves, as confirmed by positive results in RT real time PCR in nasal swabs only, whereas seroconversion was evident in a single animal (Ulrich et al. 2020). The authors did not observe intra-species transmission to other cattle reared in contact with the infected ones (Ulrich et al. 2020). The study also demonstrated that pre-existing infections with BoCoV did not protect the animals (Ulrich et al. 2020). The capability of SARS-Cov-2 to infect bovine tissues was also assessed by *ex vivo* organ cultures (EVOCs), demonstrating that respiratory tissues of cattle and sheep allow the replication of the virus, as opposed to pig tissues (Di Teodoro et al. 2021). These data urge a careful investigation into SARS-Cov-2 natural infection in ruminant farms and possible presence of the virus in the slaughterhouses.

Minks

This species is associated with large-scale SARS-Cov-2 animal infection. Indeed, at the end of April 2020, in a Dutch farm with 13,000 minks, two of them tested positive for SARS-CoV-2. The infection rapidly spread through the farm with a high number of animals clinically affected (Oreshkova et al. 2020). The transmission of the virus from an infected worker of the farm to the animals was suspected (Oreshkova et al. 2020). Minks showed clinical signs ranging from nasal exudate to severe respiratory syndrome, together with gastrointestinal disorders (Molenaar et al. 2020). Several animals died and the necropsies revealed severe pneumonia. The viral infection was also found in other mink farms in Italy (https://www.oie.int/fileadmin/Home/MM/Italy_COVID_30.10.2020.pdf), Denmark (https://www.foedevarestyrelsen.dk/Nyheder/Aktuelt/Sider/Pressemeddelelser%202020/Covid-19-i-nordjysk-minkbes%C3%A6tning.aspx), Spain (https://www.elperiodicodearagon.com/noticias/aragon/detectado-brote-coronavirus-granja-visones-teruel_1422007.html), Sweden (https://www.oie.int/fileadmin/Home/MM/Sweden_mink_6Nov2020.pdf), Greece and United States (https://www.oie.int/en/scientific-expertise/specific-information-and-recommendations/questions-and-answers-on-2019novel-coronavirus/events-in-animals/). Genetic and epidemiologic investigations demonstrated animal to human and human to animal transmission of the virus (Oude Munnink et al. 2020). These data stir up concerns about the possible infection of wild mustelids, that could become permanent reservoirs of the virus (Manes et al. 2020). Indeed, in October 2020 a wild mink in Utah (USA) tested positive, resulting in the first case of infection in wild animals (Utah's Department of Agriculture and Food). The possibility that a wild animal turns into a SARS-CoV-2 reservoir raises more concern than the same case in a domesticated animal, which can be easily checked through quarantine, vaccination or culling (Mallapaty 2021).

Captive animals

In early April 2020, at the Bronx Zoo in New York (USA), animals including Malayan tigers, Siberian tigers and African lions showed respiratory symptoms. In the face of this evidence, the United States Department of Agriculture (USDA) notified that the swab sample of a 4-year-old Malaysian tiger tested positive for SARS-CoV-2 by RT-qPCR. (https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=3388589). The positivity of an African lion was also confirmed (https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=34054). After some days, the stool samples of the animals that showed symptoms tested positive for SARS-CoV-2 by RT-qPCR (https://newsroom.wcs.org/News-Releases/articleType/ArticleView/articleId/14084/Update-Bronx-Zoo-Tigers-and-Lions-Recovering-from-COVID-19.aspx). The hypothesis was put forward that an asymptomatic employee of the zoo might have infected the Malayan tiger, that resulted the first case of non-domestic animal infected by humans (WCS 2020).

Experimentally infected racoon dogs presented viral genome in nasal and oral swabs and transmitted the virus to contact animals suggesting their role as potential reservoirs (Freuling et al. 2020).

Very recently (12 of January 2021), some captive gorillas at the San Diego zoo (USA) showed respiratory symptoms. The RNA of SARS-Cov-2 was found in their faeces. Also in this case, an asymptomatic member of the wild-life team was suspected to be responsible for the infection of the apes (https://www.sciencemag.org/news/2021/01/captive-gorillas-test-positive-coronavirus). All the animals showed mild signs of disease, but this event may cause concerns for the wild endangered great apes, that cannot be assisted as in captivity.

A recent study demonstrated the susceptibility of white-tailed deer (*Odocoileus virginianus*) to Sars-Cov-2 infections. The animals experimentally infected resulted in subclinical infection and eliminated viral particles in nasal secretions, transmitting the virus to contact animals; viral genome was detected in different organs and neutralizing antibodies were present in all experimentally infected and contact deer (Palmer et al. 2021).

Laboratory animals

The spread of the COVID-19 pandemic necessitated the search for a model that could faithfully reproduce the biological cycle of the virus and the pathogenesis of the disease. Cell lines and organoids have been used for this purpose, but because of the complex pathophysiology of SARS-CoV-2, animal models also had to be used (Takayama 2020). To this end, several animal species were analysed.

Mouse

Wild-type laboratory mice did not show susceptibility to SARS-Cov-2 infection presumably due to significant differences between murine and human ACE2 receptors (Zou et al 2020). To overcome this problem, humanized mice expressing hACE2 were generated (McCray et al., 2007; Tseng et al., 2007). Experiments in humanised mice expressing hACE2 showed that, following infection with SARS-CoV2, high levels of viral replication were detected in the lungs, with spread to other organs (Sun et al. 2020; Winkler et al. 2020). Different humanized mice expressing hACE2 were generated (transgenic, adenovirus, K18) and in the last 15 months more than 45 references in the literature used them to investigate pathogenesis, infection, immune response, therapies and vaccines against SARS-CoV-2.

Hamster

Hamsters had already been successfully used to assess SARS-CoV replication (Roberts et al. 2008; Roberts et al. 2005), so they were deemed to be a good model for SARS-CoV-2 as well. The experiments conducted so far showed that following virus inoculation, clinical signs such as lethargy, shaggy fur and weight loss occurred in Syrian Golden hamsters with subsequent development of the disease and detection of viral RNA (Chan et al. 2020; Sia et al. 2020). Furthermore, clinical features, virus replication kinetics, histopathological changes, and immune responses in SARS-CoV-2-infected Syrian hamsters were similar to those described in human patients affected by COVID-19 (Chan et al. 2020). Additionally, also intraspecific transmission has been demonstrated (Chan et al. 2020; et al. 2020). As hamsters proved to be a good small animal model for studying the virus, the roles of Types I and III IFNs in the pathogenesis of SARS-CoV-2 infection were investigated. Experiments performed on wild type, STAT2-/- (lacking type I and III IFN signalling) and IL28R-α -/- (lacking IFN type III signalling) hamsters showed that STAT2 signalling is a double-edged sword: on the one hand it restricted viral dissemination but, on the other hand, it caused severe pneumonia in SARS-CoV-2 infected hamsters (Boudewijns et al. 2020).

Non-human primates

Several non-human primates were experimentally infected in order to define a suitable non-human primate (NHP) model of COVID-19. In particular Old World monkeys (*Macaca mulatta* and *Macaca fascicularis*) and New World monkey (*Callithrix jacchus*) were tested. All the species developed symptoms and the viral RNA was detected in swab and blood samples from all animals. *M. mulatta* was the most susceptible one to SARS-Cov-2 infection in terms of inflammatory cytokine expression and lung pathological lesions, representing the most suitable model of COVID-19 (Lu et al. 2020).

Figure 1 summarizes the possible circulation of SARS-CoV-2 among different animal species based on available data on natural and experimental infections.

Conclusions

Given the high transmissibility and zoonotic origin of COVID-19, it is necessary to investigate the role animals might play in SARS-CoV-2 epidemiology. Different studies investigated the potential susceptibility to the infection based on the similarity/homology of ACE2 homologue protein to that of humans (Xiao et al. 2020; Ji et al. 2020; Liu et al. 2020; Chen et al. 2020; Luan et al. 2020; Zou et al 2020; Alexander et al. 2020). Indeed, the species (apes, felines, cattle, hamster, ferrets) showing a higher homology of their ACE2 to the human one, proved more susceptible *in vivo* to both natural and experimental infections (Xiao et al. 2020; Ji et al. 2020; Liu et al. 2020; Chen et al. 2020; Luan et al. 2020; Zou et al 2020; Alexander et al. 2020).

Studies have shown that among companion animals, cats are more susceptible than dogs to viral infection. They are mostly asymptomatic or paucisymptomatic and can transmit the virus to their conspecifics, but so far there is no evidence of direct animal-to-human transmissibility.

All the natural infections of animals reported so far (cats, dogs, tigers, gorillas, mink) occurred probably following a contact with an asymptomatic person or with the virus-positive owner. Therefore, it is important to protect the pets of patients with COVID-19 by limiting the exposure to their owners.

The demonstration of the susceptibility of animals living in close contact with humans imposes a One-Health approach to the study and the management of the pandemic. This means that more investigation is needed to elucidate the role of domestic and wild animals in the circulation of SARS-Cov-2. In particular, it is critical to understand the susceptibility of animals to SARS-CoV-2 in order to check the spread of the virus. Although no study conclusively demonstrated that animals can transmit the virus to humans, there is a raising fear that animals, once infected, could represent a possible threat to man. The experience in mink farms is a clear example of this risk. Moreover, a new variant of the virus could find a wild animal species as a permanent reservoir, keeping the virus circulation in the world or recombining with species-specific coronaviruses. Moreover, in the One Health approach, the long experiences of veterinarians on animal coronavirus infections could really support the investigations on the origin and spread of Sars-CoV-

2, but also guide future studies for the definition of effective therapeutic protocols and the discover of new efficacious vaccines for humans (Decaro et al. 2020).

Different animal models that mime the development of the disease in humans has been used so far in order to develop and evaluate vaccines, immunotherapy and other therapies to fight SARS-CoV-2. If the vaccines have been developed so fast, we need to thank also valid laboratory animal models.

Sars-CoV-2 pandemic taught us that the virus spilled over from animals to humans and, following the global movement of people and their contact with domestic and peri-domestic animals, it spread all over the word spilling back into a wide range of animal species. The interspecies transmission of the virus promotes its evolution and the appearance of new variants, as attested by the mink infection. In this scenario, the possible role of animals in the emergence of new variants needs to be carefully monitored (Bashor et al. 2021). For example, Gu and colleagues demonstrated the adaptation of a variant of SARS-CoV-2 in BALB/c mice (Gu et al. 2020).

Interestingly, a careful monitoring of the spread of SARS-CoV-2 among animals, domestic, captive and wild, has been activated all over the word and a surveillance program has been unified among the OIE, the WHO and the US Centers for Disease Control and Prevention with the publication of a guidance on surveying animals, and monthly meetings with researchers in the field (Mallapaty 2021).

Conflict of interest: all the authors declare no conflict of interest.

References:

1. A Tiger at Bronx Zoo Tests Positive for COVID-19; The Tiger and the Zoo’s Other Cats Are Doing Well at This Time. (2020). WCS. https://newsroom.wcs.org/
2. Abdel-Moneim, A. S., & Abdelwhab, E. M. (2020). Evidence for SARS-CoV-2 Infection of Animal Hosts. Pathogens (Basel, Switzerland), 9(7), 529. doi:10.3390/pathogens9070529
3. Alexander, M. R., Schoeder, C. T., Brown, J. A., Smart, C. D., Moth, C., Wikswo, J. P., Capra, J. A., Meiler, J., Chen, W., & Madhur, M. S. (2020). Predicting susceptibility to SARS-CoV-2 infection based on structural differences in ACE2 across species. FASEB journal: official publication of the Federation of American Societies for Experimental Biology, 34(12), 15946–15960. doi:10.1096/fj.202001808R

4. Aragòn, E. P. (2020, May 21). Detectado un brote de coronavirus en una granja de visones en Teruel. El Periodico de Aragòn. https://www.elperiodicodearagon.com/noticias/aragon/detectado-brote-coronavirus-granja-visones-teruel_1422007.html
5. Bashor, L., Gagne, R. B., Bosco-Lauth, A., Bowen, R., Stenglein, M., & VandeWoude, S. (2021). SARS-CoV-2 evolution in animals suggests mechanisms for rapid variant selection. bioRxiv : the preprint server for biology, 2021.03.05.434135. doi:10.1101/2021.03.05.434135
6. Benvenuto, D., Giovanetti, M., Ciccozzi, A., Spoto, S., Angeletti, S., & Ciccozzi, M. (2020). The 2019-new coronavirus epidemic: Evidence for virus evolution. Journal of medical virology, 92(4), 455–459. doi:10.1002/jmv.25688
7. Biswas, C., Zhang, Y., DeCastro, R., Guo, H., Nakamura, T., Kataoka, H., & Nabeshima, K. (1995). The human tumor cell-derived collagenase stimulatory factor (renamed EMMPRIN) is a member of the immunoglobulin superfamily. Cancer research, 55(2), 434–439.
8. Bosco-Lauth, A. M., Root J.J., Porter, S. M., Walker, A. E., Guilbert, L., Hawvermale, D., Pepper, A., Maison, R. M., Hartwig, A. E., Gordy, P., Bielefeldt-Ohmann, H. & Bowen, R. A. (2021) Survey of peridomestic mammal susceptibility to SARS-CoV-2 infection Preprint at bioRxiv. doi:10.1101/2021.01.21.427629.
9. Boudewijns, R., Thibaut, H. J., Kaptein, S., Li, R., Vergote, V., Seldeslachts, L., Van Weyenbergh, J., De Keyzer, C., Bervoets, L., Sharma, S., Liesenborghs, L., Ma, J., Jansen, S., Van Looveren, D., Vercruysse, T., Wang, X., Jochmans, D., Martens, E., Roose, K., De Vlieger, D., … Dallmeier, K. (2020). STAT2 signaling restricts viral dissemination but drives severe pneumonia in SARS-CoV-2 infected hamsters. Nature communications, 11(1), 5838. doi:10.1038/s41467-020-19684-y
10. Cao, W., & Li, T. (2020). COVID-19: towards understanding of pathogenesis. Cell research, 30(5), 367–369. https://doi.org/10.1038/s41422-020-0327-4
11. Chakraborty, C., Sharma, A.R., Bhattacharya, M., Sharma, G., Lee, S.S. (2020) The 2019 novel coronavirus disease (COVID-19) pandemic: A zoonotic prospective. Asian Pac J Trop Med. 13:242-6. doi: 10.4103/1995-7645.281613
12. Chan, J. F., Zhang, A. J., Yuan, S., Poon, V. K., Chan, C. C., Lee, A. C., Chan, W. M., Fan, Z., Tsoi, H. W., Wen, L., Liang, R., Cao, J., Chen, Y., Tang, K., Luo, C., Cai, J. P., Kok, K. H., Chu, H., Chan, K. H., Sridhar, S., … Yuen, K. Y. (2020). 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. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, 71(9), 2428–2446. doi:10.1093/cid/ciaa325

13. Chen, I. Y., Moriyama, M., Chang, M. F., & Ichinohe, T. (2019). Severe Acute Respiratory Syndrome Coronavirus Viroporin 3a Activates the NLRP3 Inflammasome. Frontiers in microbiology, 10, 50. doi:10.3389/fmicb.2019.00050.
14. Chen, Y., Guo, Y., Pan, Y., & Zhao, Z. J. (2020). Structure analysis of the receptor binding of 2019-nCoV. Biochemical and biophysical research communications, 525(1), 135–140. Advance online publication. doi:10.1016/j.bbrc.2020.02.071
15. Chini, M. (2020, March 30). Coronavirus: Belgian cat infected by owner. The Brussels Times. https://www.brusselstimes.com/news/belgium-all-news/103003/coronavirus-belgian-woman-infected-her-cat/
16. Confirmation of COVID-19 in Two Pet Cats in New York | CDC Online Newsroom | CDC. (2020). Centers for Disease Control and Prevention. https://www.cdc.gov/media/releases/2020/s0422-covid-19-cats-NYC.html
17. Corona fundet i nordjyske mink. (2020). Ministry of Environment and Food of Denmark. https://www.foedevarestyrelsen.dk/Nyheder/Aktuelt/Sider/Pressemeddelelser%202020/Covid-19-i-nordjysk-minkbes%C3%A6tning.aspx
18. COVID-19 Portal. Events in animals. (2020). World Organisation for Animal Health. https://www.oie.int/en/scientific-expertise/specific-information-and-recommendations/questions-and-answers-on-2019novel-coronavirus/events-in-animals Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., Hu, Y., Tao, Z. W., Tian, J. H., Pei, Y. Y., Yuan, M. L., Zhang, Y. L., Dai, F. H., Liu, Y., Wang, Q. M., Zheng, J. J., Xu, L., Holmes, E. C., & Zhang, Y. Z. (2020). Author Correction: A new coronavirus associated with human respiratory disease in China. Nature, 580(7803), E7. doi:10.1038/s41586-020-2202-3
19. Decaro, N., Martella, V., Saif, L. J., & Buonavoglia, C. (2020). COVID-19 from veterinary medicine and one health perspectives: What animal coronaviruses have taught us. Research in veterinary science, 131, 21–23. doi:10.1016/j.rvsc.2020.04.009
20. Di Teodoro, G., Valleriani, F., Puglia, I., Monaco, F., Di Pancrazio, C., Luciani, M., Krasteva, I., Petrini, A., Marcacci, M., D'Alterio, N., Curini, V., Iorio, M., Migliorati, G., Di Domenico, M., Morelli, D., Calistri, P., Savini, G., Decaro, N., Holmes, E. C., & Lorusso, A. (2021). SARS-CoV-

2 replicates in respiratory ex vivo organ cultures of domestic ruminant species. Veterinary microbiology, 252, 108933. doi:10.1016/j.vetmic.2020.108933

21. Domingo P, Mur I, Pomar V, Corominas H, Casademont J, de Benito N. (2020) The four horsemen of a viral Apocalypse: The pathogenesis of SARS-CoV-2 infection (COVID-19). EBioMedicine. 58:102887. doi:10.1016/j.ebiom.2020.102887.
22. Freuling, C. M., Breithaupt, A., Müller, T., Sehl, J., Balkema-Buschmann, A., Rissmann, M., Klein, A., Wylezich, C., Höper, D., Wernike, K., Aebischer, A., Hoffmann, D., Friedrichs, V., Dorhoi, A., Groschup, M. H., Beer, M., & Mettenleiter, T. C. (2020). Susceptibility of Raccoon Dogs for Experimental SARS-CoV-2 Infection. Emerging infectious diseases, 26(12), 2982–2985. doi:10.3201/eid2612.203733
23. G. (2020). Covid-19, identificato dall'istituto zooprofilattico di torino il primo caso in italia di variante inglese su gatto. Istituto Zooprofilattico Sperimentale del Piemonte, Liguria e Valle d'Aosta. http://www.izsto.it/index.php/news/2560-covid-19-identificato-dall-istituto-zooprofilattico-di-torino-il-primo-caso-in-italia-di-variante-inglese-su-gatto
24. Goumenou, M., Spandidos, D. A., & Tsatsakis, A. (2020). [Editorial] Possibility of transmission through dogs being a contributing factor to the extreme Covid-19 outbreak in North Italy. Molecular medicine reports, 21(6), 2293–2295. doi:10.3892/mmr.2020.11037
25. Halfmann, P. J., Hatta, M., Chiba, S., Maemura, T., Fan, S., Takeda, M., Kinoshita, N., Hattori, S. I., Sakai-Tagawa, Y., Iwatsuki-Horimoto, K., Imai, M., & Kawaoka, Y. (2020). Transmission of SARS-CoV-2 in Domestic Cats. The New England journal of medicine, 383(6), 592–594. doi:10.1056/NEJMc2013400
26. Harmer, D., Gilbert, M., Borman, R., & Clark, K. L. (2002). Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS letters, 532(1-2), 107–110. https://doi.org/10.1016/s0014-5793(02)03640-2
27. Ji, W., Wang, W., Zhao, X., Zai, J., & Li, X. (2020). Cross-species transmission of the newly identified coronavirus 2019-nCoV. Journal of medical virology, 92(4), 433–440. doi:10.1002/jmv.25682
28. Kim YI, Kim SG, Kim SM, Kim EH, Park SJ, Yu KM, Chang JH, Kim EJ, Lee S, Casel MAB, Um J, Song MS, Jeong HW, Lai VD, Kim Y, Chin BS, Park JS, Chung KH, Foo SS, Poo H, Mo IP, Lee OJ, Webby RJ, Jung JU, Choi YK. Infection and Rapid Transmission of SARS-CoV-2 in Ferrets. Cell Host Microbe; 27(5):704-709.e2 (2020). 10.1016/j.chom.2020.03.023.

29. Kordzadeh-Kermani, E., Khalili, H., & Karimzadeh, I. (2020). Pathogenesis, clinical manifestations and complications of coronavirus disease 2019 (COVID-19). Future microbiology, 15, 1287–1305. doi:10.2217/fmb-2020-0110

30. Li, H., Liu, S. M., Yu, X. H., Tang, S. L., & Tang, C. K. (2020). Coronavirus disease 2019 (COVID-19): current status and future perspectives. International journal of antimicrobial agents, 55(5), 105951. doi:10.1016/j.ijantimicag.2020.105951

31. Li, X., Zai, J., Zhao, Q., Nie, Q., Li, Y., Foley, B. T., & Chaillon, A. (2020). Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2. Journal of medical virology, 92(6), 602–611. doi:10.1002/jmv.25731

32. Liu, P., Jiang, J. Z., Wan, X. F., Hua, Y., Li, L., Zhou, J., Wang, X., Hou, F., Chen, J., Zou, J., & Chen, J. (2020). Are pangolins the intermediate host of the 2019 novel coronavirus (SARS-CoV-2)?. PLoS pathogens, 16(5), e1008421. doi:10.1371/journal.ppat.1008421

33. Liu, Z., Xiao, X., Wei, X., Li, J., Yang, J., Tan, H., Zhu, J., Zhang, Q., Wu, J., & Liu, L. (2020). Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. Journal of medical virology, 92(6), 595–601. doi:10.1002/jmv.25726

34. Lu, S., Zhao, Y., Yu, W., Yang, Y., Gao, J., Wang, J., Kuang, D., Yang, M., Yang, J., Ma, C., Xu, J., Qian, X., Li, H., Zhao, S., Li, J., Wang, H., Long, H., Zhou, J., Luo, F., Ding, K., … Peng, X. (2020). Comparison of nonhuman primates identified the suitable model for COVID-19. Signal transduction and targeted therapy, 5(1), 157. doi:10.1038/s41392-020-00269-6

35. Luan, J., Jin, X., Lu, Y., & Zhang, L. (2020). SARS-CoV-2 spike protein favors ACE2 from Bovidae and Cricetidae. Journal of medical virology, 92(9), 1649–1656. doi:10.1002/jmv.25817

36. Ludwig, S., & Zarbock, A. (2020). Coronaviruses and SARS-CoV-2: A Brief Overview. Anesthesia and analgesia, 131(1), 93–96. doi:10.1213/ANE.0000000000004845.

37. Mallapaty, S. (2021) The hunt for coronavirus carriers. Nature, 591: 26-28. doi:10.1038/d41586-021-00531-z

38. Manes, C., Gollakner, R., & Capua, I. (2020). Could Mustelids spur COVID-19 into a panzootic. Veterinaria italiana, 56(2), 65–66. doi:10.12834/VetIt.2375.13627.1

39. McCray, P. B., Jr, Pewe, L., Wohlford-Lenane, C., Hickey, M., Manzel, L., Shi, L., Netland, J., Jia, H. P., Halabi, C., Sigmund, C. D., Meyerholz, D. K., Kirby, P., Look, D. C., & Perlman, S.

(2007). Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. Journal of virology, 81(2), 813–821. doi:10.1128/JVI.02012-06

40. Michelitsch, A., Hoffmann, D., Wernike, K., & Beer, M. (2020). Occurrence of Antibodies against SARS-CoV-2 in the Domestic Cat Population of Germany. Vaccines, 8(4), 772. doi:10.3390/vaccines8040772
41. Molenaar, R. J., Vreman, S., Hakze-van der Honing, R. W., Zwart, R., de Rond, J., Weesendorp, E., Smit, L., Koopmans, M., Bouwstra, R., Stegeman, A., & van der Poel, W. (2020). Clinical and Pathological Findings in SARS-CoV-2 Disease Outbreaks in Farmed Mink (Neovison vison). Veterinary pathology, 57(5), 653–657. doi:10.1177/0300985820943535
42. Munir, K., Ashraf, S., Munir, I., Khalid, H., Muneer, M. A., Mukhtar, N., Amin, S., Ashraf, S., Imran, M. A., Chaudhry, U., Zaheer, M. U., Arshad, M., Munir, R., Ahmad, A., & Zhao, X. (2020). Zoonotic and reverse zoonotic events of SARS-CoV-2 and their impact on global health. Emerging microbes & infections, 9(1), 2222–2235. doi:10.1080/22221751.2020.1827984
43. Oreshkova, N., Molenaar, R. J., Vreman, S., Harders, F., Oude Munnink, B. B., Hakze-van der Honing, R. W., Gerhards, N., Tolsma, P., Bouwstra, R., Sikkema, R. S., Tacken, M. G., de Rooij, M. M., Weesendorp, E., Engelsma, M. Y., Bruschke, C. J., Smit, L. A., Koopmans, M., van der Poel, W. H., & Stegeman, A. (2020). SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. Euro surveillance: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin, 25(23), 2001005. doi:10.2807/1560-7917.ES.2020.25.23.2001005
44. Oude Munnink, B. B., Sikkema, R. S., Nieuwenhuijse, D. F., Molenaar, R. J., Munger, E., Molenkamp, R., van der Spek, A., Tolsma, P., Rietveld, A., Brouwer, M., Bouwmeester-Vincken, N., Harders, F., Hakze-van der Honing, R., Wegdam-Blans, M., Bouwstra, R. J., GeurtsvanKessel, C., van der Eijk, A. A., Velkers, F. C., Smit, L., Stegeman, A., ... Koopmans, M. (2021). Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. Science (New York, N.Y.), 371(6525), 172–177. doi:10.1126/science.abe5901
45. Palmer, M. V., Martins, M., Falkenberg, S., Buckley, A., Caserta, L. C., Mitchell, P. K., Cassmann, E. D., Rollins, A., Zylich, N. C., Renshaw, R. W., Guarino, C., Wagner, B., Lager, K., & Diel, D. G. (2021). Susceptibility of white-tailed deer (Odocoileus virginianus) to SARS-CoV-2. Journal of virology, JVI.00083-21. Advance online publication. doi:10.1128/JVI.00083-21

46. Patterson, E. I., Elia, G., Grassi, A., Giordano, A., Desario, C., Medardo, M., Smith, S. L., Anderson, E. R., Prince, T., Patterson, G. T., Lorusso, E., Lucente, M. S., Lanave, G., Lauzi, S., Bonfanti, U., Stranieri, A., Martella, V., Basano, F. S., Barrs, V. R., Radford, A. D., … Decaro, N. (2020). Evidence of exposure to SARS-CoV-2 in cats and dogs from households in Italy. bioRxiv: the preprint server for biology, 2020.07.21.214346. doi:10.1101/2020.07.21.214346
47. Pet cat tests positive for COVID-19 virus. (2020). The Government of the Honk Kong Special Administrative Region. https://www.info.gov.hk/gia/general/202003/31/P2020033100717.htm
48. Positive result for SARS-CoV2 in a mink herd located in Cremona Province, Lombardia Region Paris. (2020). Italian Chief Veterinary Officer. https://www.oie.int/fileadmin/Home/MM/Italy_COVID_30.10.2020.pdf
49. Richard, M., Kok, A., de Meulder, D., Bestebroer, T. M., Lamers, M. M., Okba, N., Fentener van Vlissingen, M., Rockx, B., Haagmans, B. L., Koopmans, M., Fouchier, R., & Herfst, S. (2020). SARS-CoV-2 is transmitted via contact and via the air between ferrets. Nature communications, 11(1), 3496. doi:10.1038/s41467-020-17367-2
50. Roberts, A., Lamirande, E. W., Vogel, L., Jackson, J. P., Paddock, C. D., Guarner, J., Zaki, S. R., Sheahan, T., Baric, R., & Subbarao, K. (2008). Animal models and vaccines for SARS-CoV infection. Virus research, 133(1), 20–32. doi:10.1016/j.virusres.2007.03.025
51. Roberts, A., Vogel, L., Guarner, J., Hayes, N., Murphy, B., Zaki, S., & Subbarao, K. (2005). Severe acute respiratory syndrome coronavirus infection of golden Syrian hamsters. Journal of virology, 79(1), 503–511. https://doi.org/10.1128/JVI.79.1.503-511.2005
52. Ruiz-Arrondo, I., Portillo, A., Palomar, A. M., Santibáñez, S., Santibáñez, P., Cervera, C., & Oteo, J. A. (2020). Detection of SARS-CoV-2 in pets living with COVID-19 owners diagnosed during the COVID-19 lockdown in Spain: A case of an asymptomatic cat with SARS-CoV-2 in Europe. Transboundary and emerging diseases, 10.1111/tbed.13803. Advance online publication. doi:10.1111/tbed.13803
53. SARS-CoV-2 in animals. (2020). American Veterinary Medical Association. https://www.avma.org/resources-tools/animal-health-and-welfare/covid-19/sars-cov-2-animals-including-pets

54. SARS-CoV-2 Positive Test Result in a in Tiger in the USA. (2020). World Organization for Animal Health. https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=33885
55. SARS-CoV-2 Positive Test Result in a Lion in the USA. Follow-Up Report No. 2. (2020). World Organization for Animal Health. https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=34054
56. Schlottau, K., Rissmann, M., Graaf, A., Schön, J., Sehl, J., Wylezich, C., Höper, D., Mettenleiter, T. C., Balkema-Buschmann, A., Harder, T., Grund, C., Hoffmann, D., Breithaupt, A., & Beer, M. (2020). SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens: an experimental transmission study. The Lancet. Microbe, 1(5), e218–e225. doi:10.1016/S2666-5247(20)30089-6
57. Sharun, K., Sircar, S., Malik, Y. S., Singh, R. K., & Dhama, K. (2020). How close is SARS-CoV-2 to canine and feline coronaviruses? The Journal of small animal practice, 61(8), 523–526. doi:10.1111/jsap.13207
58. Shi, J., Wen, Z., Zhong, G., Yang, H., Wang, C., Huang, B., Liu, R., He, X., Shuai, L., Sun, Z., Zhao, Y., Liu, P., Liang, L., Cui, P., Wang, J., Zhang, X., Guan, Y., Tan, W., Wu, G., Chen, H., … Bu, Z. (2020). Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. Science (New York, N.Y.), 368(6494), 1016–1020. doi:10.1126/science.abb7015.
59. Sia, S. F., Yan, L. M., Chin, A., Fung, K., Choy, K. T., Wong, A., Kaewpreedee, P., Perera, R., Poon, L., Nicholls, J. M., Peiris, M., & Yen, H. L. (2020). Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. Nature, 583(7818), 834–838. doi:10.1038/s41586-020-2342-5
60. Sit, T., Brackman, C. J., Ip, S. M., Tam, K., Law, P., To, E., Yu, V., Sims, L. D., Tsang, D., Chu, D., Perera, R., Poon, L., & Peiris, M. (2020). Infection of dogs with SARS-CoV-2. Nature, 586(7831), 776–778. doi:10.1038/s41586-020-2334-5.
61. Smith, W., Andrewes, C.H., & Laidlaw P.P. (1933) A Virus Obtained from Influenza Patients. The Lancet; 222(5732):66-68. doi:10.1016/S0140-6736(00)78541-2.
62. Stout, A. E., André, N. M., Jaimes, J. A., Millet, J. K., & Whittaker, G. R. (2020). Coronaviruses in cats and other companion animals: Where does SARS-CoV-2/COVID-19 fit? Veterinary microbiology, 247, 108777. doi:10.1016/j.vetmic.2020.108777

63. Suarez, D. L., Pantin-Jackwood, M. J., Swayne, D. E., Lee, S. A., DeBlois, S. M., & Spackman, E. (2020). Lack of Susceptibility to SARS-CoV-2 and MERS-CoV in Poultry. Emerging infectious diseases, 26(12), 3074–3076. doi:10.3201/eid2612.202989
64. Sun, S. H., Chen, Q., Gu, H. J., Yang, G., Wang, Y. X., Huang, X. Y., Liu, S. S., Zhang, N. N., Li, X. F., Xiong, R., Guo, Y., Deng, Y. Q., Huang, W. J., Liu, Q., Liu, Q. M., Shen, Y. L., Zhou, Y., Yang, X., Zhao, T. Y., Fan, C. F., … Wang, Y. C. (2020). A Mouse Model of SARS-CoV-2 Infection and Pathogenesis. Cell host & microbe, 28(1), 124–133.e4. doi:10.1016/j.chom.2020.05.020
65. Sun, S. H., Chen, Q., Gu, H. J., Yang, G., Wang, Y. X., Huang, X. Y., Liu, S. S., Zhang, N. N., Li, X. F., Xiong, R., Guo, Y., Deng, Y. Q., Huang, W. J., Liu, Q., Liu, Q. M., Shen, Y. L., Zhou, Y., Yang, X., Zhao, T. Y., Fan, C. F., … Wang, Y. C. (2020). A Mouse Model of SARS-CoV-2 Infection and Pathogenesis. Cell host & microbe, 28(1), 124–133.e4. doi:10.1016/j.chom.2020.05.020
66. Swedish Chief Veterinary Officer (CVO) and OIE Delegate (2020, November 6). Information received from the Veterinary Services of Sweden on 6 November 2020 Paris: OIE. Retrieved from: https://www.oie.int/fileadmin/Home/MM/Sweden_mink_6Nov2020.pdf
67. Takayama K. (2020). In Vitro and Animal Models for SARS-CoV-2 research. Trends in pharmacological sciences, 41(8), 513–517. doi:10.1016/j.tips.2020.05.005
68. Temmam, S., Barbarino, A., Maso, D., Behillil, S., Enouf, V., Huon, C., Jaraud, A., Chevallier, L., Backovic, M., Pérot, P., Verwaerde, P., Tiret, L., van der Werf, S., & Eloit, M. (2020). Absence of SARS-CoV-2 infection in cats and dogs in close contact with a cluster of COVID-19 patients in a veterinary campus. One health (Amsterdam, Netherlands), 10, 100164. doi:10.1016/j.onehlt.2020.100164
69. Tseng, C. T., Huang, C., Newman, P., Wang, N., Narayanan, K., Watts, D. M., Makino, S., Packard, M. M., Zaki, S. R., Chan, T. S., & Peters, C. J. (2007). Severe acute respiratory syndrome coronavirus infection of mice transgenic for the human Angiotensin-converting enzyme 2 virus receptor. Journal of virology, 81(3), 1162–1173. doi:10.1128/JVI.01702-06
70. Ulrich, L., Wernike, K., Hoffmann, D., Mettenleiter, T. C., & Beer, M. (2020). Experimental Infection of Cattle with SARS-CoV-2. Emerging infectious diseases, 26(12), 2979–2981. doi:10.3201/eid2612.203799

71. Update: Bronx Zoo Tigers and Lions Recovering from COVID-19. (2020). RoomWN. https://newsroom.wcs.org/News-Releases/articleType/ArticleView/articleId/14084/Update-Bronx-Zoo-Tigers-and-Lions-Recovering-from-COVID-19.aspx
72. Varga, Z., Flammer, A. J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A. S., Mehra, M. R., Schuepbach, R. A., Ruschitzka, F., & Moch, H. (2020). Endothelial cell infection and endotheliitis in COVID-19. Lancet (London, England), 395(10234), 1417–1418. doi:10.1016/S0140-6736(20)30937-5
73. Volpato, G., Fontefrancesco, M. F., Gruppuso, P., Zocchi, D. M., & Pieroni, A. (2020). Baby pangolins on my plate: possible lessons to learn from the COVID-19 pandemic. Journal of ethnobiology and ethnomedicine, 16(1), 19. doi:10.1186/s13002-020-00366-4
74. Wang, K., Chen, W., Zhang, Z., Deng, Y., Lian, J. Q., Du, P., Wei, D., Zhang, Y., Sun, X. X., Gong, L., Yang, X., He, L., Zhang, L., Yang, Z., Geng, J. J., Chen, R., Zhang, H., Wang, B., Zhu, Y. M., Nan, G., … Chen, Z. N. (2020). CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. Signal transduction and targeted therapy, 5(1), 283. doi:10.1038/s41392-020-00426-x
75. Winkler, E. S., Bailey, A. L., Kafai, N. M., Nair, S., McCune, B. T., Yu, J., Fox, J. M., Chen, R. E., Earnest, J. T., Keeler, S. P., Ritter, J. H., Kang, L. I., Dort, S., Robichaud, A., Head, R., Holtzman, M. J., & Diamond, M. S. (2020). SARS-CoV-2 infection of human ACE2-transgenic mice causes severe lung inflammation and impaired function. Nature immunology, 21(11), 1327–1335. doi:10.1038/s41590-020-0778-2
76. Wong, G., Bi, Y. H., Wang, Q. H., Chen, X. W., Zhang, Z. G., & Yao, Y. G. (2020). Zoonotic origins of human coronavirus 2019 (HCoV-19 / SARS-CoV-2): why is this work important? Zoological research, 41(3), 213–219. doi:10.24272/j.issn.2095-8137.2020.031
77. Wu, Z., & McGoogan, J. M. (2020). Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA, 323(13), 1239–1242. doi:10.1001/jama.2020.2648
78. Xiao, K., Zhai, J., Feng, Y., Zhou, N., Zhang, X., Zou, J. J., Li, N., Guo, Y., Li, X., Shen, X., Zhang, Z., Shu, F., Huang, W., Li, Y., Zhang, Z., Chen, R. A., Wu, Y. J., Peng, S. M., Huang, M., Xie, W. J., … Shen, Y. (2020). Isolation of SARS-CoV-2-related coronavirus from Malayan pangolins. Nature, 583(7815), 286–289. doi:10.1038/s41586-020-2313-x

79. Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., & Wang, F. S. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet. Respiratory medicine, 8(4), 420–422. doi:10.1016/S2213-2600(20)30076-X
80. Ye, Z. W., Yuan, S., Yuen, K. S., Fung, S. Y., Chan, C. P., & Jin, D. Y. (2020). Zoonotic origins of human coronaviruses. International journal of biological sciences, 16(10), 1686–1697. doi:10.7150/ijbs.45472
81. Yuen, K. S., Ye, Z. W., Fung, S. Y., Chan, C. P., & Jin, D. Y. (2020). SARS-CoV-2 and COVID-19: The most important research questions. Cell & bioscience, 10, 40. doi:10.1186/s13578-020-00404-4
82. Zhang, Q., Zhang, H., Gao, J., Huang, K., Yang, Y., Hui, X., He, X., Li, C., Gong, W., Zhang, Y., Zhao, Y., Peng, C., Gao, X., Chen, H., Zou, Z., Shi, Z. L., & Jin, M. (2020). A serological survey of SARS-CoV-2 in cat in Wuhan. Emerging microbes & infections, 9(1), 2013–2019. doi:10.1080/22221751.2020.1817796
83. Zhang, Q., Zhang, H., Gao, J., Huang, K., Yang, Y., Hui, X., He, X., Li, C., Gong, W., Zhang, Y., Zhao, Y., Peng, C., Gao, X., Chen, H., Zou, Z., Shi, Z. L., & Jin, M. (2020). A serological survey of SARS-CoV-2 in cat in Wuhan. Emerging microbes & infections, 9(1), 2013–2019. doi:10.1080/22221751.2020.1817796.
84. Zhang, T., Wu, Q., & Zhang, Z. (2020). Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak. Current biology: CB, 30(8), 1578. doi:10.1016/j.cub.2020.03.063
85. Zhao, J., Cui, W., & Tian, B. P. (2020). The Potential Intermediate Hosts for SARS-CoV-2. Frontiers in microbiology, 11, 580137. doi:10.3389/fmicb.2020.580137
86. Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H. D., Chen, J., Luo, Y., Guo, H., Jiang, R. D., Liu, M. Q., Chen, Y., Shen, X. R., Wang, X., Zheng, X. S., … Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 579(7798), 270–273. doi:10.1038/s41586-020-2012-7

Figure legend

Figure 1. Scheme of SARS-CoV-2 transmission among different animal species.

The most accredited theory suggests that SARS-CoV-2 derived from a bat coronavirus; after a modification in a putative intermediate host, it acquired the capability to infect humans. The wide spread of the virus among humans determined the pandemic event and it is plausible that infected humans may transmit the virus to different animal species. In order to better understand the role of animals in the epidemiology of SARS-CoV-2 and to define adequate animal models, several species were experimentally infected, but not all of them resulted permissive to the infection. To date, only minks seem to be able to transmit SARS COV-2 infection to humans. Great attention is needed on the monitoring of the new variants of SARS-CoV-2, that could acquire the capability to infect domestic or wild animal reservoirs.