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CHAPTER THREE

SARS-CoV-2 in animals: From potential hosts to animal models

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Abstract

Within only one year after the first detection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), nearly 100 million infections were reported in the human population globally, with more than two million fatal cases. While SARS-CoV-2 most likely originated from a natural wildlife reservoir, neither the immediate viral precursor nor the reservoir or intermediate hosts have been identified conclusively. Due to its zoonotic origin, SARS-CoV-2 may also be relevant to animals. Thus, to evaluate the host range of the virus and to assess the risk to act as potential animal reservoir, a large number of different animal species were experimentally infected with SARS-CoV-2 or monitored in the field in the last months. In this review, we provide an update on studies describing permissive and resistant animal species. Using a scoring system based on viral genome detection subsequent to SARS-CoV-2 inoculation, seroconversion, the development of clinical signs and transmission to conspecifics or humans, the susceptibility of diverse animal species was classified on a semi-quantitative scale. While major livestock species such as pigs, cattle and poultry are mostly resistant, companion animals appear moderately susceptible, while several model animal species used in

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research, including several *Cricetidae* species and non-human primates, are highly susceptible to SARS-CoV-2 infection. By natural infections, it became obvious that American minks (*Neovison vison*) in fur farms, e.g., in the Netherlands and Denmark are highly susceptible resulting in local epidemics in these animals.

1. Introduction

The World Health Organization (WHO) defines a pandemic as a global spread of a new disease (WHO, 2010) focusing on the human population. However, as it can be seen during the recent pandemic of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), not only humans but also a variety of other animal species can be affected by the spread of this novel pathogen (Abdel-Moneim and Abdelwhab, 2020; Kiros et al., 2020). From the origin of the virus from a yet unknown animal reservoir (Zhou et al., 2020) to the appearance of new viral variants in farmed minks (Elaswad et al., 2020), and the threat of the establishment of separate transmission cycles in nature (Kiros et al., 2020), animals are an epidemiological part of this pandemic. Thus, the susceptibility of different animal species needs to be assed in order to fully understand the epidemiology of the pandemic (Kiros et al., 2020), and to find suitable animal models (Muñoz-Fontela et al., 2020) to support the development and validation of efficient vaccines and therapeutics.

To date, seven human coronaviruses are known and all of them likely originate from an animal source (Cui et al., 2019). HCoV-OC43 and HCoV-HKU1, which induce only mild upper respiratory disease in immunocompetent humans, likely originated in rodents. Progenitor viruses of HCoV-229E and HCoV-NL63, which likewise usually cause only mild human infections, were recently found in African bats (Cui et al., 2019). The remaining three human coronaviruses, namely the Middle East respiratory syndrome coronavirus (MERS-CoV), the first severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 induce severe to fatal diseases in infected humans, and all three are suspected to originate from bats (Cui et al., 2019; WHO, 2003, 2019; Zhou et al., 2020). In addition, a variety of intermediate hosts is discussed. SARS-CoV was found, e.g., in four *Paguma larvata* (Himalayan palm civets) and a *Nyctereutes procyonoides* (raccoon dog) in a live-animal market (Guan et al., 2003) in the province Guangdong, China, which was the center of the SARS-CoV epidemic in 2002/03 (Zhong et al., 2003). This led to a mass killing of these animal species. The analysis of sampled civets

(n = 91) and raccoon dogs (n = 15) showed that all of them were positive for SARS-CoV. However, in civets from 12 other Chinese provinces (n = 1107) no SARS-CoV genomes were detected (Kan et al., 2005).

Further, a serological study found antibodies against SARS-CoV in civets in another market in Guangdong, but not in civets sampled from farms and markets outside of Guangdong (Tu et al., 2004). Both studies support the hypothesis that civets and raccoon dogs are not the original source of the ancestor virus, but rather a recipient in the local market, that acquired the virus from an original source and may have acted as an amplifier for virus spread (Kan et al., 2005; Tu et al., 2004). For MERS-CoV, the human-to-human transmission rate appears to be rather low. Therefore, an animal source for the numerous independent human infections was suspected (Breban et al., 2013). Initial analyses of the exposure history of the first human MERS-CoV cases showed that all patients had contact with livestock animals (WHO, 2013).

Serological studies were conducted in the affected regions of the Arabic peninsula. They found that *Camelus dromedarius* (dromedary camels), but not *Bos taurus* (cattle), *Ovis aries* (sheep) or *Capra aegagrus hircus* (goats) had high antibody prevalence against MERS-CoV (Hemida et al., 2013; Perera et al., 2013; Reusken et al., 2013). Furthermore, MERS-CoV was isolated from a camel farm owned by an infected person (Haagmans et al., 2014). Transmission from dromedary camels to humans also was subsequently demonstrated by RT-PCR-based genome detection and sequence analysis (Azhar et al., 2014). As of now, dromedary camels are seen as the central intermediate host for MERS-CoV (Cui et al., 2019) and are believed to be the source of constant re-introduction of MERS-CoV into the human population (Al-Ahmadi et al., 2020). Nevertheless, the most likely original hosts of a MERS-CoV ancestor virus are bats (Cui et al., 2019).

The most recent human-pathogenic coronavirus, SARS-CoV-2, also is suspected to originate from an animal reservoir, potentially through one or more intermediate hosts. In humans, the clinical presentation of the novel disease, called "Corona Virus Disease 2019 (COVID-19)," ranges from asymptomatic infections or mild respiratory symptoms to pneumonia with acute respiratory distress syndrome, cardiovascular failure, coagulopathy, multiple organ failure and death, with much higher fatality rates in the elderly or when certain underlying health conditions exist (Grasselli et al., 2020; WHO, 2020a; Wu and McGoogan, 2020). Until January 2021, which is only one year after the first cases of SARS-CoV-2 were reported to WHO, about 100 million human infections were reported from 224 countries, with more than 2 million fatal cases (Dong et al., 2020).

Since SARS-CoV-2 very likely has a zoonotic origin, it is important to identify the original animal reservoir to prevent future similar outbreaks. Therefore, during the last months, a significant number of different animal species were either sampled in the field or experimentally infected with SARS-CoV-2, in order to evaluate their susceptibility to infection and to assess their potential as animal reservoirs.

2. Reservoir and intermediate hosts

SARS-CoV-2, SARS-CoV and MERS-CoV very likely originate from an animal reservoir. However, it is not known how, where and when the ancestor virus transferred into the human population. Although highly important to prevent future similar spill-over transmissions of related viruses (Wong et al., 2020), neither SARS-CoV-2 nor an immediate precursor coronavirus in animals has been reported. Nevertheless, given the sequence similarity of about 96% between SARS-CoV-2 and the betacoronaviruses RaTG13 found in *Rinolophus affinus* (intermediate horseshoe bats) in China (Zhou et al., 2020), and the detection of a wide range of further coronaviruses in bats (order *Chiroptera*) (Colunga-Salas and Hernández-Canchola, 2020; Lacroix et al., 2020; Lau et al., 2005; Li et al., 2005; Wacharapluesadee et al., 2021; Yadav et al., 2020), bats are suspected to be the reservoir host for the progenitor virus of SARS-CoV-2 (Latinne et al., 2020; Lu et al., 2020a; Wacharapluesadee et al., 2021; Zhou et al., 2020).

Interestingly, antisera raised against the bat coronavirus RmYN02 were able to cross-neutralize SARS-CoV-2 (Wacharapluesadee et al., 2021). Whether the pandemic started by a direct spill-over of the SARS-CoV-2 ancestor from bats to humans followed by natural selection in humans, or via another intermediate mammalian host providing further adaptation to the human host, is still under debate (Andersen et al., 2020; Wacharapluesadee et al., 2021).

When assessing the relatedness of coronaviruses to identify potential hosts, the amino acid sequence and structure of the receptor-binding domain (RBD) within the spike (S) protein is relevant, as it mediates binding of the virus to the cellular surface protein angiotensin-converting enzyme 2 (ACE2) (Brooke and Prischi, 2020; Damas et al., 2020). The RBD of the RaTG13 bat coronavirus differs substantially from that of human coronaviruses, suggesting that it may not bind efficiently to the human ACE2 receptor (Andersen et al., 2020; Conceicao et al., 2020). Other bat

coronavirus RBDs are even less similar, making a direct spill-over to humans unlikely. Nevertheless, there could be other more closely related coronaviruses in bats that have not been detected yet, or an intermediate host. To assess whether bats support replication and transmission of SARS-CoV-2, *Rousettus aegyptiacus* (fruit bats) and *Eptesicus fuscus* (North American big brown bats) have been inoculated experimentally (Hall et al., 2020; Schlottau et al., 2020). Big brown bats appear to be resistant, since neither virus excretion, nor virus detection in tissues, signs of disease or transmission were found (Hall et al., 2020). In contrast, SARS-CoV-2 inoculation of fruit bats led to efficient replication in the upper respiratory tract followed by seroconversion in seven out of nine intranasally inoculated animals. Although no clinical signs were observed, immunohistochemical analyses detected the presence of rhinitis. Transmission to in-contact bats of the same species occurred in one out of three animals (Schlottau et al., 2020). Thus, fruit bats show characteristics of a reservoir host and could help to model the physiopathology of SARS-CoV-2 infection in a bat host.

Several candidates for potential intermediate hosts have been proposed. At the beginning of the pandemic, *Pholidota* spp. (pangolins) were implicated because of the identification of several SARS-CoV-2-related coronaviruses in these animals, including viruses with an RBD similar to that of SARS-CoV-2 (Lam et al., 2020b; Xiao et al., 2020; Zhang et al., 2020d). However, the pangolin theory is still up for debate, as it became clear that the pangolin viruses are even less related to SARS-CoV-2 than the currently known bat coronaviruses, meaning that the sequence similarity is not sufficient to either confirm or rule out a role of pangolins in the emergence of SARS-CoV-2 (Liu et al., 2020; Malaiyan et al., 2020; Wacharapluesadee et al., 2021; Wahba et al., 2020). In addition, experimental infection studies are missing.

A wide range of additional wild animals from *Murinae* (e.g., house mouse), *Cricetidae* (e.g., deer-mouse and bank voles) or *Sciuridae* species (e.g., squirrels) to *Serpentes* (snakes), *Feliformia* (cat-like carnivorans), *Caniformia* (dog-like carnivorans), *Viverridae* (e.g., civets), *Cervidae* (deer) and non-human primates including close relatives (e.g., Chinese tree shrew) were analyzed as potential missing links between bats and humans or potential animal reservoirs (Deng et al., 2020b; Zhao et al., 2020b). Some species could be quickly excluded, while others are still up for debate.

Computational analysis may assist in the prediction of a certain species as a potential host for a specific virus. However, this theoretical approach should be viewed with caution and verified by experimental studies.

Snakes, for example, were hypothesized to be a potential host for SARS-CoV-2 by comparison of the relative synonymous codon usage of virus and snake (Ji et al., 2020). However, bioinformatics approaches based on the analysis of their ACE2 receptor (Luan et al., 2020; Zhang et al., 2020b) argued against this assumption. Direct experimental evidence that determines whether snakes can be infected is still missing. By experimental inoculation *Sylvilagus* sp. (cottontail rabbits), *Sciurus niger* (fox squirrels), *Urocitellus elegans* (Wyoming ground squirrels), *Cynomys ludovicianus* (black-tailed prairie dogs), *Mus musculus* (house mice), and *Procyon lotor* (raccoons) were found to be not susceptible to SARS-CoV-2 (Bosco-Lauth et al., 2021).

Carnivora wildlife species that are wide-spread in North America and often live in close proximity to human dwellings are *Mephitis mephitis* (striped skunk) and raccoon. Both species were tested by experimental inoculation with SARS-CoV-2. Virus replication and seroconversion was detected in skunks, but not in raccoons. No clinical or gross pathological signs were observed for either species, but bronchiole associated lymphoid tissue was found in skunks (Bosco-Lauth et al., 2021).

Three species of Cervids show a high similarity in their ACE2 receptor to that of humans: *Odocoileus virginianus* (white-tailed deer), *Rangifer tarandus* (reindeer), and *Elaphurus davidianus* (Père David´s deer) (Damas et al., 2020). In addition, deer lung cells were found to be susceptible to SARS-CoV-2, and the virus replicates to similar titers as in African green monkey (Vero-E6) cells, although markedly delayed (Palmer et al., 2021). Upon intranasal inoculation of white-tailed deer all inoculated fawns shed infectious virus and seroconverted. Noteworthy, also in-contact fawns, separated by plexiglass, became productively infected, most likely by droplets. Virus was isolated from nasal and rectal swabs, and the viral genome was detected mainly in the upper respiratory tract and corresponding lymphatic organs of inoculated animals and deer infected by contact to virus-shedding conspecifics. Body temperature was transiently elevated in some cases, but gross lesions were not obvious. Histologically, acute alveolar damage-related lesions were detected, resembling human infection, but no viral RNA was detected, suggesting that the virus had already been cleared (Damas et al., 2020).

Rodentia (Rodents) is the largest order of mammals encompassing more than 2000 species. Rodents are notorious as hosts for zoonotic viruses. They occur worldwide and some species live in high numbers in close proximity

to humans in urban, suburban and rural setting. Moreover, parental viruses of two human coronaviruses, OC43 and HKU1, have already been found in rodents (Cui et al., 2019).

Based on comparative sequence and structural analyses of the SARS-CoV-2-binding receptor ACE2, some rodents were identified as in a high-risk group for susceptibility (Damas et al., 2020). Though house mice could be excluded as an amplifying host by experimental infection (Bosco-Lauth et al., 2021), some species of the family Cricetidae support virus replication. *Neotoma cinerea* (bushy tailed woodrats) shed virus from their oral cavity and developed specific antibodies subsequent to experimental infection, and during necropsy, mild signs indicative for inflammation were found (Bosco-Lauth et al., 2021). Further Cricetidae species that are susceptible to SARS-CoV-2 include *Peromyscus maniculatus* (North American deer mice), *Peromyscus leucopus* (white-footed mice), and *Myodes glareolus* (European bank vole) (Bosco-Lauth et al., 2021; Fagre et al., 2020; Griffin et al., 2020; Ulrich et al., 2020a). After experimental intranasal infection, deer mice carry high amounts of infectious virus in their respiratory organs and also in the intestine, whereas infectious virus is shed at significantly lower levels in a biphasic pattern from the mouth and nose (Bosco-Lauth et al., 2021;Fagre et al., 2020; Griffin et al., 2020). Transmission to contact animals was successful for deer mice (Fagre et al., 2020; Griffin et al., 2020) and antibodies were produced by the animals, in which viral replication took place. Although histopathology revealed signs of inflammation and pneumonia in the lungs as well as inflammatory alterations and presence of viral antigen in head ganglia and cerebral portions of the brain, clinical disease was not obvious (Bosco-Lauth et al., 2021; Fagre et al., 2020; Griffin et al., 2020). Expression of cytokines and inflammatory cells, resembling that of the human COVID-19 disease, have been described (Fagre et al., 2020; Griffin et al., 2020). Intranasal inoculation of bank voles with SARS-CoV-2 likewise led to viral replication in the respiratory tract without inducing any obvious clinical signs, detection of low amounts of viral genome in the central nervous and lymphatic systems, and seroconversion (Ulrich et al., 2020a). Intra-species transmission to direct in-contact animals was not observed (Ulrich et al., 2020a).

When SARS-CoV-2 was detected in a mink farm in the Netherlands (ProMED-mail, 2020b), fur-bearing animals kept for pelt production, particularly the three main species *Neovison vison* (mink), foxes (several genera of the family Canidae), and raccoon dogs, became a focus of interest.

These animals also are held in large numbers in China (ACT Asia, 2019) and raccoon dogs had already been considered as potential intermediate hosts for SARS-CoV. The Netherlands reported its first case of SARS-CoV-2 in a mink farm at the end of April 2020, which was amid the first wave of the pandemic. Shortly afterwards, the virus was detected in a second farm. Both farms reported respiratory symptoms and the latter an increase in mortality (OIE, 2021b). A first epidemiological investigation demonstrated that the virus was most likely introduced by infected farm workers on two separate occasions. In addition, the airborne inhalable dust on the farm was found positive for viral RNA and suspected to be the source of transmission within the farm to both mink and workers. On both farms the outbreak was reported to be self-limiting, as the symptoms disappeared together with the viral RNA in the dust. Seroconversion was found in nearly all sampled animals (Oreshkova et al., 2020) indicating a high infection rate. As of January 6, 2021, the number of infected farms had risen to 69 farms in the Netherlands alone, of which 29 (42%) reported respiratory clinical signs in their mink. An evaluation of these cases focusing on virus introduction and transmission is currently under way (OIE, 2021b). Besides the Netherlands, Denmark, Sweden, the USA, Canada, France, Spain, Greece, Lithuania and Poland (OIE, 2021b; Rabalski et al., 2020) reported SARS-CoV-2 infections in mink farms. SARS-CoV-2 positive workers could be identified in the vast majority of cases as the source of infection (OIE, 2021b). Like in the Netherlands, respiratory symptoms were reported in the animals for a subset of farms by the other countries as well, occasionally accompanied by an increase in mortality (OIE, 2021b). Pathological examination found an interstitial pneumonia in almost all sampled mink that supposedly died because of the SARS-CoV-2 infection (Molenaar et al., 2020; Oreshkova et al., 2020).

In Denmark, an intensive surveillance program was started after the first farms tested positive in June 2020, leading to the detection of 25 infected holdings until the 1st of October 2020 and 67 additional farms until the 16th of October (OIE, 2021b). By the 1st of December, this number had increased to 289 farms, which represents 20% of the Danish mink farms (WHO, 2020b). In about a third of the affected farms, no clinical signs were observed (Boklund et al., 2021). An extensive sampling of the environment and of numerous animals roaming around the farms did not lead to a conclusive explanation of the transmission mode between farms, except for direct transfer by infected humans (Boklund et al., 2021). Particularly worrying, mink to human transmission occurred in the affected farms

and pelting facilities, resulting in at least 982 mink-associated human infections by November 2020 (Oude Munnink et al., 2020; WHO, 2020b). Moreover, a new mutation within the viral genome was found in SARS-CoV-2 of mink-origin, comprising characteristic S-protein changes, subsequently referred to as cluster V mutations (Frutos and Devaux, 2020; Koopmans, 2020; Lassaunière et al., 2020; OIE, 2021b). Preliminary findings suggested decreased sensitivity of this variant toward neutralization by convalescent patient serum that could potentially interfere with vaccine efficiency (Lassaunière et al., 2020). Furthermore, the deletion of amino acids 69 and 70 within the S-coding region is likely to perturb detection by RT-PCR (ECDC, 2020). However, a broadly-based sequencing campaign of positive human patient samples revealed that the proportion of infection with the mink virus variant continuously decreased from June to mid-November (from 60% to 31%), and from the 20th of November onwards no new human cluster V infections were detected (WHO, 2020b). Hence, this mink-associated virus variant is believed to be extinct by now (Mallapaty, 2020; WHO, 2020c). Overall, mink in fur farms appear to be highly susceptible for SARS-CoV-2 outbreaks. A high proportion of mink in the infected premises were infected within a short period of time, with only a subset of animals, if any, developing clinical signs (Boklund et al., 2021; Hamer et al., 2020; OIE, 2021b). Both, the high susceptibility of mink as well as the lack of clinical signs imply a potential hazard for workers on mink farms and continuous re-emergence of SARS-CoV-2 variants (Koopmans, 2020). Furthermore, mink might play a potential role as an animal reservoir or intermediate host, especially since natural infection of wild free-ranging mink also has been reported (ProMED-mail, 2020d).

Another animal species kept for fur production is the raccoon dog (ACT Asia, 2019). In the aftermath of the first SARS outbreak in China, raccoon dogs sampled at a wet market were found to carry SARS-CoV and related viruses (Guan et al., 2003; Kan et al., 2005). Due to this finding and because of the high similarity of SARS-CoV sequences from raccoon dogs and humans (Bolles et al., 2011; Gautam et al., 2020; Graham and Baric, 2010; Lam et al., 2020a), raccoon dogs are considered to be one of the key amplifying hosts for SARS-CoV, with intra-species spread and transmission to humans. To investigate their susceptibility for SARS-CoV-2, raccoon dogs were experimentally infected and co-housed with uninfected controls (Freuling et al., 2020). Viral replication to relatively high titers without obvious clinical signs followed by seroconversion could be observed in six of nine intranasally inoculated animals and two of three

in-contact animals. Virus distribution and pathological changes resembled a transient subclinical infection, with a restriction of virus replication to the nasal cavities (Freuling et al., 2020). Because of the combination of rapid virus replication and shedding without clinical disease, raccoon dogs could represent a putative amplifying host and may have served as an intermediate host in the initial spread of SARS-CoV-2 from a presumed bat reservoir to humans.

To summarize the current knowledge about potential intermediate hosts, members of the Feliformia and Caniformia, the same subfamilies as involved in the SARS-CoV epidemic in 2002–2003, are the mammals that most likely play a role as intermediate hosts of SARS-CoV-2, since they are susceptible, replicate the virus to high titers and transmit to other animals and occasionally to humans. In addition, members of the Cricetidae family are susceptible to SARS-CoV-2 and shed the virus to an appreciable amount.

3. Pet animals and their non-domesticated counterparts

Pet animals live in close contact with humans and in most cases share a common living space. The close interaction between humans and pets poses a potential risk for the transmission of zoonotic pathogens (Chomel, 2014). Among companion animals, *Felis catus* (cats) and *Canis familiaris* (dogs) are at the center of attention, since they are the most common pet species and tend to have contact to humans outside of their own household (Overgaauw et al., 2020).

Both dogs and cats were shown to be susceptible to an experimental infection with SARS-CoV-2. In an initial animal trial, subadult dogs (3 months) showed a low susceptibility to infection, as only two of five animals seroconverted, and no transmission to uninoculated co-housed dogs was observed (Shi et al., 2020). Juvenile (<100 days old) and subadult (6–9 months old) cats, on the other hand, proved to be highly susceptible to a SARS-CoV-2 infection, since all inoculated animals became positive by RT-PCR in various organs, and developed antibodies. In addition, two of six in-contact cats became infected through intra-species transmission. They seroconverted and were positive by RT-PCR in organs of the upper respiratory tract and nasal washing (Shi et al., 2020). A subsequent experimental study confirmed these results for adult animals. Additionally, several of the infected cats were challenged with an additional inoculation of SARS-CoV-2 after 28 days. No shedding of virus was detected after the second

inoculation, indicating an effective protection against a secondary virus infection (Bosco-Lauth et al., 2020). None of the experimental studies to this date described clinical signs in any of the infected animals (Bosco-Lauth et al., 2020; Gaudreault et al., 2020; Halfmann et al., 2020; Shi et al., 2020). However, histopathological analyses revealed lesions in the nasal and tracheal mucosa epitheliums and lungs (Bosco-Lauth et al., 2020; Gaudreault et al., 2020; Shi et al., 2020).

The susceptibility of cats and dogs was further confirmed by serosurveillance studies. The first surveillance study was conducted in Wuhan during the initial outbreak. Out of 102 randomly sampled cat sera, antibodies against SARS-CoV-2 were found by ELISA in 15 sera (14.7%). In addition, 11 of the ELISA-positive sera tested positive in serum neutralization assays (Zhang et al., 2020a). In Italy, a similar survey was conducted during a time of frequent human infections. In that study, 11 out of 191 cats (5.8%) and 15 out of 451 (3.3%) dogs tested positive for neutralizing antibodies (Patterson et al., 2020). Another surveillance study performed in Germany during the first wave of the pandemic found 6 out of 920 randomly sampled cat sera positive for SARS-CoV-2 antibodies by ELISA. The prevalence of 0.7% in the sampled cat sera corresponded with the estimated prevalence of human infection of 0.85% during the sampling period. In two of the six positive sera, neutralizing antibodies could be detected (Michelitsch et al., 2020). In a study performed in France, two out of 13 dogs (15.4%) and eight out of 34 cats (23.5%) from households that were known to be infected with SARS-CoV-2 were found positive for SARS-CoV-2-specific antibodies. Another positive sample was found among 16 cats from households with an unknown infection status (Fritz et al., 2021). For details about seroprevalence studies performed in cats and dogs see Table 1. Overall, these initial surveillance studies show that infections of cats and dogs with SARS-CoV-2 occur frequently.

To assess the impact of inter-species transmission on the course of the pandemic, single case reports need to be investigated, in which transmission to co-housed pets and re-infection of humans might be observed. In six case studies, the course of infection was described for two dogs and a total of 14 cats (Barrs et al., 2020; Garigliany et al., 2020; Neira et al., 2020; Newman et al., 2020; Sailleau et al., 2020; Segalés et al., 2020; Sit et al., 2020). While the dogs remained free of clinical signs, six of the cats were described to have clinical signs similar to COVID-19 disease in humans. The cats were reported to show mild respiratory signs, sneezing and ocular discharge. In none of the studies was transmission from an infected pet to a

Table 1 Overview of the surveillance studies of SARS-CoV-2 in pets.

Sampling period	Species	Prevalence	Household	Neutral. AB	Country	References
January–March 2020	Cat	15/120 (14.7%)	Unknown	11/15	China	Zhang et al. (2020a)
March–May 2020	Cat	11/191 (5.8%)	Unknown	11/11	Italy	Patterson et al. (2020)
March–May 2020	Dog	15/451 (3.3%)	Unknown	15/15	Italy	Patterson et al. (2020)
April–September 2020	Cat	6/920 (0.7%)	Unknown	2/6	Germany	Michelitsch et al. (2020)
May–June 2020	Cat	8/34 (23.5%)	Infected	n.a.	France	Fritz et al. (2021)
May–June 2020	Dog	2/13 (15.4%)	Infected	n.a.	France	Fritz et al. (2021)

Testing was performed on serum samples. Prevalence gives the rate of positive samples in relation to all tested samples. Neutral. AB: number of positive samples that tested positive for neutralizing antibodies. n.a.: data is not available

human or a co-housed pet described (Barrs et al., 2020; Garigliany et al., 2020; Neira et al., 2020; Newman et al., 2020; Sailleau et al., 2020; Segalés et al., 2020). Further, additional cases are constantly reported to the world organization for animal health (OIE) and displayed on their official website (OIE, 2021b). The following analysis is based on the reports that were submitted until January 15, 2021. Seventeen countries had reported SARS-CoV-2 infection in a pet animal.

Altogether 103 SARS-CoV-2 infected animals, 57 cats and 46 dogs were reported to the OIE. The reports mentioned symptoms that could be linked to a SARS-CoV-2 infection in 26 cats (45.6%) and 21 dogs (45.7%), of which 7 cats (26.9%) and 2 dogs (9.5%) were reported to have preexisting comorbidities. Clinical signs in cats were mostly described as respiratory (13/26; 50.0%), of which 38.5% (5/13) were defined as very mild or mild, or as nasal (7/26, 26.9%) or ocular discharge (2/26, 7.7%). Dogs were also reported to show respiratory signs (9/21; 42.9%), of which 44.4% (4/9) were classified as mild, sneezing (8/21; 38.1%) and nasal discharge (5/21; 23.8%). The majority of cases were found through screening pet animals from households that were confirmed to be SARS-CoV-2 positive. In addition, the USA reported 53 pet animals that were found to be positive for antibodies against SARS-CoV-2 (OIE, 2021b). Although the reported cases hint at frequent inter-species transmission events, a study performed on SARS-CoV-2-infected veterinary students, that tracked their pet animals closely during the course of infection found no signs of infection in the studied nine cats and 12 dogs (Temmam et al., 2020).

In summary, the transmission of SARS-CoV-2 to animals from infected humans happens on a regular basis. Since clinical signs are mostly described as mild or in the context of severe comorbidities, and considering the experimental infection studies, the course of infections in cats and dogs seems to be mild. To date, no transmission of SARS-CoV-2 from an infected pet to its owner, to another house pet or a human was described (Barrs et al., 2020; Garigliany et al., 2020; Neira et al., 2020; Newman et al., 2020; Sailleau et al., 2020; Segalés et al., 2020). However, hygienic standards should be applied when interacting with a potentially infected animal and quarantine requirements should be extended to animals that had extensive contact with an infected human. Recommendations can be found from the various official institutions (ABCD (Advisory Board on Cat Diseases), 2021; CDC (Centers for Disease Control and Prevention), 2021; WSAVA (World Small Animal Veterinary Association), 2020).

Given the regular transmission of SARS-CoV-2 from infected owners to their pet cats and dogs, it was to be expected that the virus might also be spread to non-domesticated felines or canines. Infections of felines in zoos were indeed reported to the OIE (OIE, 2021b). Early in the pandemic, the Bronx Zoo in New York reported the infection of four *Panthera tigris* (tigers), and three *Panthera leo* (lions), which exhibited mild respiratory clinical signs for up to 2 weeks. A fifth tiger remained asymptomatic (Bartlett et al., 2020). Sequence analysis from samples of the affected animals showed that the tiger SARS-CoV-2 belonged to a different genotype than the lion viruses. Both genotypes were also found in the corresponding animal caretakers. Therefore, a transmission from the attending humans to the cared-for animals seems to have happened on two different occasions (McAloose et al., 2020). Three other zoos in the United States reported SARS-CoV-2 infections in large felids, three additional tigers and a *Panthera uncia* (snow leopard) with mild respiratory symptoms (OIE, 2021b). In South Africa, a *Puma concolor* (puma) acquired a SARS-CoV-2 infection from a zookeeper. No symptoms were reported, and the contact animals were negative by RT-PCR (OIE, 2021b). In addition, news outlets reported the infection of four additional lions in a zoo in Barcelona, Spain, and a tiger and four lions in a zoo in Sweden. They showed mild respiratory symptoms and were most likely infected by an asymptomatic zookeeper in whom an infection with SARS-CoV-2 was subsequently diagnosed (ProMED-mail, 2020a,c).

Tigers, snow leopards and lions are members of the genus *Panthera*, and pumas belong to the genus *Puma*. Both genera are part of the phylogenetic family Felidae, the same family to which the genus (*Felis*) of the domestic cat belongs. Keeping in mind the several reports of SARS-CoV-2 infections in cats (Barrs et al., 2020; Garigliany et al., 2020; Neira et al., 2020; Newman et al., 2020; Sailleau et al., 2020; Segalés et al., 2020), it is no surprise that large cats were also found to be infected in zoos. Although, reverse transmission from zoo animal to human has not been observed until know, strict hygiene rules should be implemented in the management of zoo animals.

4. Livestock animals

As the SARS-CoV-2 outbreak evolved rapidly into a global pandemic and the zoonotic origin of the pathogen became obvious, there were apprehensions that farmed livestock species could be involved in virus

transmission. The world livestock population is by far larger than the human population (Tomley and Shirley, 2009) and livestock demand will continue to increase with human population growth and socio-economic trends (Alexandratos and Bruinsma, 2012; Herrero and Thornton, 2013). Furthermore, close connection between humans and farmed animals exists in small-scale agriculture as well as in intensified livestock-producing-systems. This close contact is considered to be a fundamental driver of emerging zoonotic diseases, of which viral diseases have become increasingly important (Gilbert et al., 2020; Klous et al., 2016; Wiethoelter et al., 2015). Although the origin of the SARS-CoV-2 pandemic was suspected to be traced to the Huanan Seafood Market (Huang et al., 2020), concerns were raised about the susceptibility of major mammalian livestock and poultry species, particularly as the first ever described coronavirus was infectious bronchitis virus (IBV) of chickens in 1931 (Schalk and Hawn, 1931). Besides IBV, many other livestock-affecting coronaviruses of different genera have been found (e.g., additional bird, bovine, and porcine coronaviruses) (Clark, 1993; Wang et al., 2019; Wille and Holmes, 2020). Of these livestock species, cattle with an estimated global population of 1.5 billion (FAO, 2020) were discovered to be the potential intermediate host for HCoV-OC43, one of the only two human coronaviruses that were known until SARS-CoV emerged in 2002/03 (Cui et al., 2019; Drexler et al., 2014; Forni et al., 2017). Because of the close relatedness of bovine coronaviruses and human HCoV-OC43 (Bidokhti et al., 2013; Vijgen et al., 2005; Vijgen et al., 2006), and also due to the similarity of the cattle ACE2 receptor to that of humans (Damas et al., 2020; Luan et al., 2020), concerns about the potential role of cattle in the SARS-CoV-2 pandemic were raised. Susceptibility of bovine tracheal and lung *ex vivo* organ cultures (EVOCs) toward SARS-CoV-2 was tested in an air–liquid interface system using two different SARS-CoV-2 isolates and viral titers were found to be higher in bovine lung EVOCs than tracheal EVOCs (Di Teodoro et al., 2020). In an *in vivo* study, experimental SARS-CoV-2 infection of 6-month-old Holstein-Friesian dairy calves resulted in a short virus replication in the upper respiratory tract in two out of six animals that subsequently seroconverted. One calf was found positive in a nasal swab on days two and three after infection, another one on day three only. Transmission to commingled cattle did not occur. Despite viral replication and seroconversion, clinical disease was not observed (Ulrich et al., 2020b). Furthermore, no serological cross-reactivity of antibodies against bovine coronavirus and SARS-CoV-2 was recorded (Ulrich et al., 2020b).

For *Sus scrofa* (pigs), another major livestock species (Gilbert et al., 2018), the susceptibility for SARS-CoV-2 was suspected, as they can be infected with MERS-CoV and were found to host several other coronaviruses (de Wit et al., 2017; Gong et al., 2017; Opriessnig and Huang, 2020; Pan et al., 2017; Vergara-Alert et al., 2017a,b; Wang et al., 2019; Widagdo et al., 2019a). In addition, computational analyses of the porcine ACE2 protein revealed that it shares significant identity with human ACE2 in residues contacting the viral spike protein (Wan et al., 2020). *In vitro*, SARS-CoV-2 bound to HeLa cells expressing the porcine ACE2 instead of the human orthologue (Zhou et al., 2020). Furthermore, SARS-CoV-2 replicated in porcine SK-6 and ST cell lines (Meekins et al., 2020; Schlottau et al., 2020), but not in swine tracheal and lung EVOCs (Di Teodoro et al., 2020). In experimental infections, the outcome seems to be dependent on the inoculation route and virus titer. Nevertheless, in general the susceptibility of pigs for SARS-CoV-2 appears very low. Intranasal application of 10^5 plaque forming units (PFU) or 10^5 tissue culture infectious dose 50% ($TCID_{50}$) of SARS-CoV-2 did not lead to virus replication or seroconversion in 40-day old Landrace × Large White pigs of both sexes or 9-week old German Landrace pigs, respectively (Schlottau et al., 2020; Shi et al., 2020). Clinical signs as well as pathological lesions were also absent and transmission to contact animals did not occur (Schlottau et al., 2020; Shi et al., 2020). Meekins et al. (2020) used younger piglets and simultaneously infected them intranasally, orally, and intratracheally with a higher $TCID_{50}$ of 10^6, while Vergara-Alert et al. (2020) investigated among other infection routes intramuscular and intravenous application using $10^{5.8}$ $TCID_{50}$ of culture-grown SARS-CoV-2. Seroconversion was reported for parenterally infected animals (Meekins et al., 2020; Vergara-Alert et al., 2020). Remarkably, one intranasally inoculated piglet was found positive for viral RNA in the proximal trachea on the day after inoculation (Vergara-Alert et al., 2020). In another *in vivo* study, inoculation of 10^6 PFU of SARS-CoV-2 simultaneously into the nostrils and the pharynx of 8-week-old American Yorkshire crossbred piglets resulted in mild clinical signs in at least 5 out of 19 animals (Pickering et al., 2021). Ocular discharge, nasal secretion and cough were observed within the first days after infection, but body temperature remained normal. Nasal, oral, and rectal swab samples tested negative for SARS-CoV-2 genome. Two pigs, however, tested weakly positive in a nasal wash sample collected 3 days after infection. In addition, infectious virus was isolated 13 days after infection from the submandibular lymph

node of a sacrificed pig. Two other pigs tested positive for serum antibodies and anti-SARS-CoV-2 antibodies were also detected in saliva recovered from chewing-ropes (Pickering et al., 2021).

Although mammals were identified as key players in SARS-CoV and MERS-CoV emergence and distribution (de Wit et al., 2016), SARS-CoV-2 susceptibility of different bird species was elucidated by several groups. Following oculo-oronasal inoculation of *Gallus gallus domesticus* (chickens) with high-titer virus preparations, neither virus replication nor seroconversion or transmission to in-contact chickens could be observed (Schlottau et al., 2020; Shi et al., 2020). *In vivo* experimental infection studies using *Anas platyrhynchos domesticus* (ducks) led to identical results, i.e., neither virus replication nor seroconversion occurred (Shi et al., 2020). Besides chicken and ducks, *Meleagris galloparvo* (turkey), *Coturnix japonica* (Japanese quail) and *Anser cygnoides* (Chinese goose) were experimentally infected. None of the tested poultry species showed any susceptibility toward SARS-CoV-2 infection (Berhane et al., 2020; Suarez et al., 2020). Further, the ability of SARS-CoV-2 to replicate in embryonated chicken eggs was evaluated. Inoculation into the yolk sac, the chorio-allantoic membrane or the chorio-allantoic sac did not lead to virus replication and embryogenesis was not impaired (Barr et al., 2020; Berhane et al., 2020; Schlottau et al., 2020; Suarez et al., 2020).

5. Animal models in SARS-CoV-2 research

Suitable animal models reflecting different aspects of SARS-CoV-2 pathogenesis are required to assist in development of antiviral vaccines and treatment options, and also to study the mechanistic basics of SARS-CoV-2 infections.

One of the most widely used laboratory animal in biomedical research is the mouse. For SARS-CoV-2, however, infection studies in wild-type mice are hampered by the lack of appropriate receptors to initiate viral infection, as murine ACE2 does not bind the viral spike protein effectively (Wan et al., 2020). This obstacle might be overcome by either virus adaptation to mice or by expression of human ACE2 in genetically modified mice. Both approaches were successful for the closely related MERS-CoV (Kim et al., 2020a; Li and McCray, 2020), in which the murine dipeptidyl peptidase 4 receptor failed to support MERS-CoV infection. For SARS-CoV-2, genetically modified mice were generated that express human ACE2, e.g., driven

by the mouse ACE2 promotor (ACE2-hACE2 mice), by the human keratin 18 promoter (K18-hACE2 mice), by the human lung ciliated epithelial cell-specific HFH4/FOXJ1 promoter (HFH4-hACE2 mice) or by the cytomegalovirus enhancer followed by the chicken β-actin promoter (Bao et al., 2020a,b; Jiang et al., 2020; Oladunni et al., 2020; Tseng et al., 2007; Winkler et al., 2020). Human ACE2 was also expressed by insertion into the endogenous mouse ACE2 gene locus via CRISPR/Cas9 technology (Sun et al., 2020b). Another approach to rapidly produce susceptible mice without additional breeding utilized the transduction of human ACE2 into cells of the respiratory tract through intranasal, intratracheal or oropharyngeal instillations of adenoviral vectors expressing human ACE2 (Han et al., 2020; Hassan et al., 2020; Israelow et al., 2020; Sun et al., 2020a). Independent of the protein expression approach, mouse breed and experimental design, all mice expressing the human ACE2 receptor instead of the mouse orthologue are susceptible to SARS-CoV-2 as demonstrated by a robust virus replication in the respiratory tract. However, varying degrees of disease were observed. Clinical signs ranged from weight loss and pneumonia to pathological alterations also found in human COVID-19 patients and, in some studies, brain infestation and differing numbers of fatalities (Golden et al., 2020; Han et al., 2020; Hassan et al., 2020; Israelow et al., 2020; Jiang et al., 2020; Rathnasinghe et al., 2020; Sun et al., 2020a,b; Yinda et al., 2021). Hence, human ACE2 expressing mice facilitate investigations of the pathogenesis of severe COVID-19 by, e.g., histopathological analyses at varying time points after infection, measuring the cytokine responses (Israelow et al., 2020; Oladunni et al., 2020) or analyzing the transcriptome of lungs of diseased mice (Han et al., 2020). However, this mouse model currently does not reflect all aspects of COVID-19, since unusual features such as the hyperinflammatory syndromes that are sometimes seen in children (Yasuhara et al., 2021) have not been observed in human ACE2 mice. Nevertheless, as human ACE2 expressing mice shed high viral titers and efficiently transmit SARS-CoV-2 to naïve in-contact animals (Bao et al., 2020b), they represent a useful model for transmission studies. In addition, human ACE2 expressing mice provide a suitable tool to evaluate vaccines and therapeutics, as has been demonstrated by research groups worldwide (e.g., Hassan et al., 2020; Ku et al., 2020; Li et al., 2020a,b; Seo and Jang, 2020; Sun et al., 2020a; Zheng et al., 2020a). A further approach to circumvent the lack of susceptibility of wild-type mice to SARS-CoV-2 is the use of mice displaying a humanized immune system induced by infusion of human hematopoietic stem cells, which leads to

severe COVID-19-like symptoms in the respective mouse line (Brumeanu et al., 2020). Besides the adaptations of mice to SARS-CoV-2, one could use a reverse approach and adapt the virus to mice (Dinnon et al., 2020; Gu et al., 2020; Wang et al., 2020). Mouse-adapted SARS-CoV-2 would allow the use of more readily available mouse strains. However, a major disadvantage is the limited suitability for pathogenesis studies, when new virus mutants that emerge in the field have to be rapidly tested for altered *in vivo* behavior. Nevertheless, this animal model of wild-type mouse/adapted virus is still applicable to test therapeutics and preventive measures (Dinnon et al., 2020; Wang et al., 2020).

Another widely used small animal model in research of human diseases is the hamster. *In silico* comparisons of the ACE2 receptor suggested that hamsters, in contrast to mice, might be susceptible to SARS-CoV-2 infection without any further adaptation (Damas et al., 2020). Consequently, *Mesocricetus auratus* (golden Syrian hamster), *Cricetulus griseus* (Chinese hamster), *Phodopus roborovskii* (Roborovski dwarf hamster), *Phodopus campbelli* (Campbell's dwarf hamster) and *Phodopus sungorus* (Djungarian hamster) have been explored regarding their suitability to support SARS-CoV-2 replication and to develop disease similar to human COVID-19 (Bertzbach et al., 2020; Imai et al., 2020; Osterrieder et al., 2020; Rosenke et al., 2020; Trimpert et al., 2020). All investigated hamster species are susceptible. However, the course of disease and the outcome of infection vary dramatically. While Campbell's or Djungarian dwarf hamsters show either no or only mild clinical signs, Roborovski dwarf hamsters develop a fulminant disease characterized by decrease of body temperature, weight loss, snuffling, dyspnea, ruffled hair and strongly reduced activity within the first three days following infection. By day four or five after infection, most individuals reached a pre-defined humane endpoint (Trimpert et al., 2020). In golden Syrian hamsters, experimental SARS-CoV-2 infection induced weight loss, ruffled fur, postural changes, labored breathing, damage of the olfactory epithelium and severe lung pathology mimicking that of COVID-19 in humans, associated with virus replication to high titers in the upper and lower respiratory and gastrointestinal tracts followed by a profound immune response (Bertzbach et al., 2020; Boudewijns et al., 2020; Bryche et al., 2020; Imai et al., 2020; Osterrieder et al., 2020; Rosenke et al., 2020; Sia et al., 2020; Tostanoski et al., 2020). Furthermore, microcomputed tomographic imaging of hamster lung samples revealed severe injury, with characteristics shared with COVID-19-diseased humans (Imai et al., 2020). Co-infection with influenza A virus led to a more severe course of disease

(Zhang et al., 2020c). Moreover, older hamsters exhibited more pronounced and consistent weight loss, while young animals launched an earlier and stronger immune cell influx into the lungs resulting in a faster recovery from the disease compared with aged hamster (Osterrieder et al., 2020). Hence, golden Syrian hamsters reflect the age-dependent disease progression seen in human patients, with the limitation that they do not develop the fatal course of disease that often occurs in elderly humans. This obstacle could be overcome by chemically induced immunosuppression or by using genetically modified animals, e.g., recombination activating gene 2-knockout hamster, which develop more pronounced clinical signs and fatalities (Brocato et al., 2020). Nevertheless, even wild-type golden Syrian hamsters might be used for comparative preclinical assessments of treatment options in young versus elderly individuals. As golden Syrian hamsters shed the virus to high titers and efficiently transmit SARS-CoV-2 by direct contact and via aerosols (Chan et al., 2020; Sia et al., 2020), they are also used as a model to study the mechanisms of intra-species transmission.

The third frequently used small model animal is rabbit. This species is used mainly for immunization, but also for implant research (Mapara et al., 2012) as well as a model for various human infectious diseases, among them norovirus infections, syphilis, tuberculosis, or human papillomavirus infections (Esteves et al., 2018). Important for SARS-CoV-2 research, rabbits were already proven to be susceptible for MERS-CoV (Haagmans et al., 2015; Houser et al., 2017; Widagdo et al., 2019b) and *in silico* analyses using different animal ACE2 receptors predicted rabbits to be also susceptible for SARS-CoV-2 (Damas et al., 2020). Further, it was shown that SARS-CoV-2 replicated in the rabbit derived cell-line RK-13 (Chu et al., 2020). Hence, experimental SARS-CoV-2 infection studies in rabbits seemed obvious. Surprisingly, to date only one study is published (Mykytyn et al., 2021). Three-month-old New Zealand white rabbits were intranasally inoculated, which resulted in virus replication and shedding from the nose and throat followed by seroconversion. Four days after infection, the olfactory epithelium showed hyperplasia and hypertrophy, along with multifocal eosinophilic and lymphoplasmacytic infiltration. Antigen was not detected in immunohistochemical stainings of the lungs. Alveolar macrophages and neutrophils, however, were increased. In the terminal region of the bronchioles, mildly thickened septa and inflammatory cells could be detected. Alveolar epithelium cells showed mild necrosis and peribronchiolar and peribronchial lymphoid tissue proliferation, and tracheo-bronchial lymph nodes were enlarged. Despite the histopathologic abnormalities, clinical disease was not present in rabbits.

An animal model used especially in studies that investigate the pathogenesis and transmission of human respiratory viruses such as influenza virus is ferrets (*Mustela putorius*), since their lungs share many similarities with that of humans. As previous studies have shown that ferrets are susceptible to SARS-CoV infection and readily transmit the virus to in-contact animals (Martina et al., 2003), this animal model was tested very early during the pandemic for susceptibility to SARS-CoV-2. After experimental infection with SARS-CoV-2, high level virus replication was observed in the upper respiratory tract associated with either no or only mild clinical signs such as transient loss of appetite or elevated body temperature (Kim et al., 2020b; Marsh et al., 2021; Ryan et al., 2021; Schlottau et al., 2020; Shi et al., 2020). Importantly, air-borne transmission via respiratory droplets and/or aerosols to in-contact animals could be demonstrated (Richard et al., 2020), making the ferret a highly suitable model for transmission studies and for testing (mucosal) vaccines and therapeutics for their effect on virus shedding (Cox et al., 2020; Proud et al., 2020). Moreover, a first natural infection of a ferret that was kept as a pet in a SARS-CoV-2 positive household was reported to the OIE at the end of November, further proving the high susceptibility of ferrets to SARS-CoV-2 infection (OIE, 2021b).

When a severe acute respiratory syndrome emerged as a novel human infectious disease in 2002 non-human primate models were used to demonstrate that SARS-CoV was the etiological agent (Fouchier et al., 2003). Based on these studies, non-human primates also were investigated regarding their suitability as animal models to study the pathogenesis of MERS-CoV-2 (de Wit et al., 2013; Falzarano et al., 2014) and recently also for SARS-CoV-2. So far *Macaca fascicularis* (Cynomolgus macaque), *Macaca mulatta* (rhesus macaque), *Chlorocebus aethiops* (African green monkey), *Callithrix jacchus* (common marmoset) and *Papio hamadryas* (baboon) have been experimentally infected with SARS-CoV-2 (Lu et al., 2020b; Rockx et al., 2020; Shan et al., 2020; Singh et al., 2021; Woolsey et al., 2020).

Although a certain variability in clinical manifestations was seen between "Old World" and "New World" monkeys with Old World monkeys developing a more severe disease, the virus replicated efficiently in the upper and lower respiratory tract of all investigated primate species, leading to pathological features of a viral pneumonia. The clinical course is either inapparent or mild to moderate, where the symptoms include rise in body temperature, weight loss, reduced appetite, hunched posture, dyspnea or increased respiration rate (Blair et al., 2020; Deng et al., 2020a; Ishigaki et al., 2020; Koo et al., 2020; Lu et al., 2020b; Munster et al., 2020;

Williamson et al., 2020). The high susceptibility of monkeys followed by the development of mild clinical signs is further supported by natural infections of *Gorilla gorilla* (gorillas) that are kept in human care in zoos and that had contact to infected animal keepers (OIE, 2021b). In some experimentally infected animals, besides direct clinical symptoms, increased inflammatory cytokine and chemokine expression, reduced pulse oxygen levels or alterations of the level of selected plasma proteins, e.g., the release of acute-phase-proteins like CRP, decreased serum albumin or hemoglobin and reduced white blood cell and lymphocyte counts could be observed (Chandrashekar et al., 2020; Deng et al., 2020a; Fahlberg et al., 2020; Lu et al., 2020b; Singh et al., 2021; Zheng et al., 2020b). Importantly, older animals were more likely to develop radiological and histopathological changes than young primates, recapitulating the clinical outcome seen in the human population. In addition, aged animals shed virus for longer periods of time, had higher viral loads in lung tissue and showed a delay in the immune response compared to young animals (Rockx et al., 2020; Song et al., 2020; Yu et al., 2020b). Notwithstanding, a profound humoral and cellular immune response that protects from re-infection is induced in the vast majority of infected non-human primates, independent of species and age (Chandrashekar et al., 2020; Deng et al., 2020a; Elizaldi et al., 2020; Ishigaki et al., 2020; McMahan et al., 2020). Therefore and because monkeys reflect the clinical picture seen in humans, non-human primates are used by numerous research groups and pharmaceutical companies to test candidate vaccines and therapeutics against COVID-19 (e.g., Baum et al., 2020; Corbett et al., 2020; Feng et al., 2020; Guebre-Xabier et al., 2020; Hoang et al., 2020; Kim et al., 2021; Maisonnasse et al., 2020; van Doremalen et al., 2020; Williamson et al., 2020; Yu et al., 2020a). However, the resources for those complex trials and the available animals are limited. Therefore, research and testing of therapeutics and vaccines with SARS-CoV-2 and non-human primates need to be well focused.

A species genetically closely related to non-human primates and recently increasingly used in pathogenesis studies for many human pathogens is *Tupaia belangeri chinensis* (Chinese tree shrew) (Li et al., 2018). Experimental SARS-CoV-2 infection of different age groups resulted in viral shedding from various sites (nose, oral cavity, rectum), with higher titers in the early phase after infection in young tree shrews, but longer-lasting in aged individuals (Zhao et al., 2020a). The highest viral loads were detectable in the lungs, again in younger animals in the early phase and in older animals at a later stage after infection, hinting at age-related effects. Clinical signs could

not be observed, except from an increase in body temperature in some animals (Zhao et al., 2020a). Evidence for inflammatory processes in the lungs were found in all age groups, and infiltrates resembled those observed in humans and monkeys (Xu et al., 2020).

6. Concluding remarks

Within only a few months, the novel coronavirus SARS-CoV-2 spread around the globe, resulting in tens of millions of infections in the human population and about two million deaths. The pandemic has affected public and personal life in manifold spheres with an inconceivable impact. Unprecedented research efforts have been implemented to keep up with an exceedingly dynamic virus. To control the pandemic, but also to prevent future outbreaks that might be caused by similar pathogens, main objectives are the discovery of the SARS-CoV-2 ancestor virus, its animal host, as well as potential animal hosts and reservoirs. Moreover, adequate animal models are needed to understand the dynamics of virus infection and the human disease "COVID-19," as well as to test preventive measures and therapy options. In a global effort, an enormous number of research groups tested a plethora of animal species regarding their susceptibility to SARS-CoV-2 and suitability as a COVID-19 animal model resembling the human disease.

Here, we collected evidence from the literature to establish a scoring system considering the proportion of animals in which the viral genome was detectable subsequent to inoculation reflecting virus multiplication, the seroconversion rate, clinical signs and the ability to transmit the virus to conspecifics or humans. For each category zero to three points were awarded. In the category "genome detection" three points were given for the detection of viral RNA in all inoculated or tested animals of a certain species. Two points indicated a frequent detection and one point a sporadic event. The same gradation was applied in the category "seroconversion," but for the detection of antibodies instead of viral RNA. For the "transmission" category three points were awarded for an efficient transmission rate to conspecifics that indicates the potential to develop an independent transmission cycle. Two points were given for a regularly observed intraspecies transmission and one point for an occasional event. The category "clinical signs" was scored as follows: Three points stand for severe pan-respiratory or systemic symptoms that might end in death, two points for moderate respiratory or vascular symptoms and one point for mild,

nonspecific symptoms. The sum of all points was taken as a parameter for the overall susceptibility of each species for SARS-CoV-2. To provide an overview about the susceptibility of diverse animal species and their ability to transmit the virus, we implemented this scoring system whose results are shown in Table 2 and visually summarized in Fig. 1. Fortunately, livestock animals that are kept in very high numbers worldwide appear not to play a

Table 2 Susceptibility of different animal species to SARS-CoV-2.

Animal	Genome detection	Seroconversion	Transmission to conspecifics	Clinics	$\sum$ Awarded points
Chicken	0	0	0	0	0
Duck	0	0	0	0	0
Pig	0	1	0	0	1
Cattle	1	1	0	0	2
Dog	2	1	0	0	3
Rabbit	2	2	0	0	4
Fruit bat	2	1	2	0	5
Bank vole	3	3	0	0	6
Raccoon dog	2	2	2	0	6
Cat	2	2	1	1	6
Deer mouse	3	2	2	1	8
Ferret	3	3	2	0	8
White-tailed deer	3	3	3	0	9
Mink	2	3	3	1	9
Non-human primate	3	3	2	2	10
Hamster	3	3	3	3	12
hACE2 transgenic mouse	3	3	3	3	12

By a semi-quantitative scoring system zero to three points were awarded for each of the categories viral genome detection following SARS-CoV-2 inoculation, seroconversion, transmission to conspecifics and the development of clinical signs.

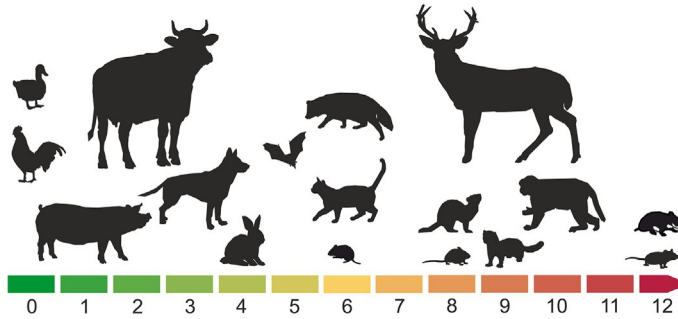

Fig. 1 Visual depiction of the scoring system for the susceptibility of different animal species for SARS-CoV-2. Three points each were awarded for the categories genome detection, seroconversion, transmission to conspecifics and clinical signs. Animal species were placed according to the sum of the awarded points. Zero points stand for no susceptibility and twelve points for a maximal susceptibility to SARS-CoV-2.

noteworthy role in the SARS-CoV-2 pandemics. Although viral replication was detectable in some of the investigated farm animal species (Table 2, Fig. 1), long-term virus shedding at relevant levels was not found, nor did transmission to contact-animals occur in any of these species, which would also make animal-to-human transmission unlikely. Besides some rodents, cervids, primates and related species, numerous Carnivora species have been found to be susceptible not only for experimental, but also for natural SARS-CoV-2 infection and intra-species transmission. In particular minks which are farmed in large numbers for fur production are at risk and mass outbreaks with subsequent culling measures have been seen, e.g., in the Netherlands and Denmark.

Finally, SARS-CoV-2 transmission from an animal reservoir, potentially via intermediate animals hosts, resulting in a global pandemic in the human population highlights the requirement of more holistic approaches in global health, considering the dependence and interaction between human health, animal health and environmental health as incorporated in the "One Health approach" (FAO, 2021; OIE, 2021a; WHO, 2021).

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