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Review Article

Insight into Past, Present, and Future Perspectives on COVID-19 in Animals

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Abstract

Coronavirus disease (COVID-19) is an infectious disease caused by the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus). Potentially favorable conditions for the emergence of SARS-CoV-2 are viral genetic variation and mutation, interactions of viral spike with ACE2 and other possible cell receptors, group living, and habits. SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19), is suspected to have been first contracted via animal-human interactions; it has further spread across the world by efficient human-to-human transmission. Coronaviruses have been identified in numerous mammalian and avian hosts. Domestic animals such as poultry, domestic dogs, cats, cattle, and equine, and also wild animals like pigs, wild primates, bats, rabbits, and bushy-tailed woodrats. Bovine coronavirus (BCoV) is a well-known cause of enteric disease in cattle, notably causing illnesses such as "winter dysentery" while in equids, equine coronavirus has been associated with diarrhea in foals and lethargy, fever, anorexia, and occasional gastrointestinal signs in adult horses. However, Domestic pigs (Sus scrofa) were found by several studies to be resistant or only marginally susceptible to SARS-CoV-2 infection. In contrast, Bats have been identified as the natural reservoir of severe acute respiratory syndrome (SARS)-like SARS coronaviruses (SLCoV and SCoV). The health impacts of SARS-CoV-2 could be more serious in wild gorillas as they are subject to co-infections and physiological stressors that are absent in captive animals under veterinary care. Natural SARS-CoV-2 infection in rabbits with a low as no instance of natural infection of SARS-CoV-2 has been documented in wildwood rats. Using experimental research, field studies, surveillance, genomics, and modeling as tools for predicting outbreaks and epidemics should help provide the knowledge base and resources necessary to prevent future pandemics.

Keywords: COVID-19; Domestic Animal; Future; Past; Present; Wild Animals

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. The COVID-19 epidemic is a global emergency because of its quick spread and high mortality rate [1]. SARS-CoV-2 is the third zoonotic coronavirus (CoV) after SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV) to trigger an epidemic outbreak in the last two decades. Preliminary data suggests that SARS-CoV-2 spread from Wuhan, China, via zoonotic (animal-to-human) transmission. According to genome research, the bat is the most likely reservoir host of SARS-CoV-2 infection [2,3].

SARS-CoV-2 is most likely a bat virus, comparable to the SARS virus that caused the 2003 SARS outbreak [4]. Live animal markets selling a variety of wild and domestic animals near highly populated human communities are likely to be the genesis of both epidemics [5]. The main mode of transmission is by respiratory droplets, and the angiotensin-converting enzyme 2 (ACE2) receptor located in the lower respiratory tract of humans has been identified as the receptor used for SARS and SARS-CoV-2 cell entrance [6,7].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a novel enveloped RNA virus known as Coronavirus (COVID-19), is most common in humans and wild animals. To present, all four species have been recognized as being responsible for human sickness, causing influenza-like illness (ILI). This virus is related to the Middle East Respiratory Syndrome coronavirus (MERS-CoV) and the related Coronavirus (SARS-CoV) [8].

Coronaviruses have been identified in numerous mammalian and avian hosts. The most widely studied and common occurrence are coronaviruses reported in chickens (Infectious bronchitis virus), turkeys (turkey enteric coronaviruses), cats (feline infectious peritonitis virus and feline enteric coronavirus), dogs (canine en-

teric coronaviruses), swine (Porcine hemagglutinating encephalomyelitis virus, porcine transmissible gastroenteritis virus, and porcine respiratory coronavirus), cattle (bovine enteric and respiratory coronaviruses), mice (Murine hepatitis virus), rats (sialodacyradenitis virus), rabbits (rabbit coronavirus), and humans (respiratory and enteric coronaviruses) [9,10].

As a result, methods to control the spread of SARS-CoV-2 should involve preventing spillover into potential reservoirs, especially because infectious agents can spread quickly in livestock due to the high densities at which some animals are housed. Many techniques for managing future outbreaks can be established, including the following: before any outbreak, and surveillance of wildlife for high-risk diseases in high-risk locations. It also includes antimicrobials administered to animals for growth, which is responsible for the rise in antibiotic resistance around the world. It also covers risk reduction in individuals who have a high possibility of coming into touch with wildlife and those who consume unnaturally. Surveillance to improve biosecurity of the wildlife trade and animal markets. Surveillance of labs performing research on these microorganisms must be conducted. After the outbreak, the most important step to be taken is to revive the economy of all the victims. Specific plans to manage post-outbreak economy loss, especially for the daily wagers should be made [8,9].

Currently, SARS-CoV-2 is spreading at an alarming rate within the human population. Infected individuals often produce high viral loads that increase the possibility of spill-over to domestic and wild animals. Therefore, the objective of this review is to review past, present, and future perspectives on COVID-19 in domestic and wild animals.

Past perspective of COVID-19 on domestic and wild animals

Coronaviruses (CoVs) are a type of virus that belongs to the Ortho-coronavirinae subfamily of the Coronaviridae family, Order Nidovirales. Coronavirus was isolated for the first time in 1937 from birds infected with the infectious bronchitis virus, which is capable of devastating poultry stock. It all started in 1931, with the first report of a new form of upper respiratory tract disease in chickens in North Dakota, USA. In 1933, the causal agent was discovered as a virus. By 1936, the disease and virus had been identified as distinct from other viral diseases. They were first called infectious bronchitis virus (IBV) but were later renamed Avian coronavirus. In 1961, a novel virus was identified from a youngster in Epsom, England, who had common cold symptoms. In 1966, very identical viruses were identified by medical students at the University of Chicago. Based on a comparison of two viruses, June Almeida and David Tyrrell coined the term coronavirus in 1967, because all of those viruses had solar corona-like projections (called spikes) on their surfaces [11,12].

Over the last two decades, three zoonotic coronaviruses have been discovered as the source of large-scale disease outbreaks: SARS, MERS, and SADS. SARS and MERS developed in 2003 and 2012, respectively, and created global pandemics that claimed thousands of lives, while SADS attacked the swine sector in 2017. They share traits such as being extremely harmful to humans or livestock, having agents derived from bats, and two of them having originated in China [13,14].

SARS-CoV-2 is a virus that belongs to the Coronaviridae family and has one of the biggest single-stranded RNA genomes (29.9 kilobases) for a virus. Spike (S), nucleoprotein, envelope, and membrane proteins are the primary structural proteins encoded by SARSCoV-2. Among these structural proteins, the S protein is required for the virus's receptor-mediated entrance into susceptible cells. The S protein's receptor binding domain (RBD) engages the cellular receptor, angiotensin-converting enzyme-2 (ACE2), allowing the virion particle to enter. Furthermore, transmembrane protease serine 2 (TMPRSS2) aids in the priming of the S protein, which is cleaved to allow the viral envelope to fuse with the cellular membrane [15].

Potentially favourable conditions for the emergence of SARS-CoV-2

Viral genetic variation and mutation

SARS-CoV-2 has split into several clades and lineages. There are now three major nomenclature schemes for the many clades or lineages. The GISAID and Next strain systems have been employed since the beginning of the pandemic, and signature mutations designate clades or lineages. Currently, the GISAID clade is classified into S, L, and V, as well as other clades containing the D614G mutation (G, GH, GR, GV), and O. According to the year and order in which the clade formed, the Nextstrain is separated into 19 (A, B) and 20 (A-J). Although the GISAID and Nextstrain nomenclatures are valuable for studying virus evolution on a macro scale, they are incapable of delineating more precise outbreak cluster information. The Pango lineage, first proposed in July 2020, is a dynamic system, that considers whether the lineage is actively spreading or not [16-18]. The Pango lineage system has a much finer resolution than GISAID or Next strain and is particularly useful for capturing the emergence of novel variants.

Interactions of viral spike with ACE2 and other possible cell receptors

SARS-CoV-2 S protein has a receptor-binding domain (RBD), antigenic epitopes, and a cleavage site (CS) [19]. Host proteases cut the S protein into S1 and S2 subunits, which are responsible for binding to the host cell receptor and fusion of viral and cellular

membranes. The angiotensin-converting enzyme 2 (ACE2) is the eukaryotic cell receptor for SARS-CoV-2. The affinity of the viral S protein (particularly the RBD) to the ACE2 receptor greatly influences the susceptibility of the matching host to infection by this virus. In silico analysis, *in vitro* research utilizing eukaryotic cells, and *in vivo* data in animal models or naturally infected animals can all be used to examine ligand-receptor interactions [20].

Group-living and habits

SARS-CoV-2's origin is still unknown. The viral subgenus Sarbecovirus, which includes SARS-CoV, bat SARS-related CoV, and SARS-CoV-2, is prone to recombination [21]. According to several studies, bat SARS-CoV-2-like coronaviruses are recombinants of lineages related to SARS-CoV and SARS-CoV-2, and SARS-CoV-2 may be the result of recombination between these bat SARS-related coronaviruses and the pangolin SARS-related coronavirus [22]. Another study, however, revealed that recombination may not have been involved in the formation of SARS-CoV-2, yet the RBD of SARS-CoV-2 shares the same ancestral feature as bat viruses [23]. SARS-CoV-2 and bat arbovirus diverged in 1948, according to estimates [18].

Current perspective of COVID-19 on domestic and wild animals

The SARS-CoV-2 belongs to the family Coronaviridae and has one of the largest single-stranded RNA genomes (29.9 kilobases) for a virus [15]. At present, the susceptibility of domestic and wild animal species to SARS-CoV-2 has major implications for the development of preventive and control strategies against this pandemic [24]. Although significant pieces of experimental evidence show possible SARS-CoV-2 infection in cats, ferrets, or other domestic/wild animals, none of them conclusively prove infection and transmission among animals or spill-over to humans under natural conditions. To date, there are no reports of SARS-CoV-2 transmission from companion or wild animals to humans. Even if such transmission has occurred, the identification of such a case is very difficult based on the evidence, since it will be masked by the aggressive human-to-human transmission that is characteristic of this disease. The increase in the number of reports of SARSCoV-2 infection in companion and wild animals warrants in silico docking studies as well as sequence-based computational studies to identify host susceptibility to COVID-19. Such a study will not only help evaluate the risk of animal-to-human transmission but also assist in identifying suitable animal models for the evaluation of vaccines and therapeutics against SARS-CoV-2 [3].

Several animals in zoos have contracted COVID-19. They are almost all part of the Felidae family. Overall, seven lions, *Panthera leo*, have been reported to be infected with SARS-CoV-2 (three at the Bronx Zoo in New York and four at the Barcelona Zoo in Spain), as well as seven tigers, including *Panthera tigris jacksoni* and *Panthera tigris altaica* (four at the Bronx Zoo (New York City, NY, USA) and three at the Knoxville zoo (Knoxville, TN, USA), three snow leopards, *Panthera uncia* (Jefferson Zoo in Kentucky, USA), and one cougar, *Puma concolor* (Johannesburg zoo in South Africa). Another Hominidae, the western lowland gorilla, *Gorilla gorilla*, has also been infected with SARS-CoV-2. Indeed, three western lowland gorillas out of eight co-housed together in a troop at the San Diego Zoo in California were confirmed as being positive for SARS-CoV-2. Almost all the animals were symptomatic and presented with mild respiratory signs such as coughing and wheezing. But all are recovered. It was likely that animals were contaminated by a staff member of the zoo infected with SARS-CoV-2. However, it is possible that after contamination of one of the Felidae by a staff member of the zoo, the Felidae contaminated the other animals [20].

Poultry

Birds have long been known as hosts for *Coronaviridae* members and today have been detected in 108 wild bird species [25]. In which there are from the gamma-coronavirus (four species) and delta coronaviruses (seven species) groups dominate. In the 1930s, the first avian coronavirus disease was described by *Schalk and Hawn* (1931) - avian infectious bronchitis (IB) [26]. *Bushnell* L.*D. and Brandly* (1933) concluded that a filterable agent was its cause which was confirmed by electron microscopy in 1964 as coronavirus [27,28]. It was the infectious bronchitis virus (IBV), which remains an economically important respiratory virus for poultry in several countries today [29], high IB-associated losses are recorded despite control attempts using live attenuated vaccines. To date, SARS-CoV-2 has not been established in birds, even in experimental infection of chickens and ducks. Considered is not likely to infect chickens or other poultry. The main reason for non-infection in birds considers that it is that both viruses (SARS-CoV-2 and avian viruses), have different receptors in the hosts and belong to phylogenetically different groups [30].

According to a study by Swayne., *et al*. [8] Groups of nine 3-week-old domestic geese (*Anser anser domesticus*), 3-week-old domestic Pekin ducks (*Anas platyrhyncos*), 4-week-old chickens (*Gallus gallus domesticus*), 3-week-old turkeys (*Meleagris gallopavo*), and 5-week-old Japanese quail (*Coturnix coturnix japonic*a) were each injected intratracheally with $10^{6.2}$ mean tissue culture infective doses ($TCID_{50}$) of Vero E6 propagated Urbani SARS-CoV per bird in a volume of 0.1 mL. The inoculum was the third passage in Vero E6 cells from the original throat swab specimen of the patient. The chickens were specific pathogens–free from an in-house flock. The other four species were conventional birds obtained at 1 day (geese, turkeys, and ducks) or 5 weeks of age (quail) from com-

mercial hatcheries and raised on-site. Oropharyngeal and cloacal swabs were obtained on days 0, 1, 2, 3, 4, and 10 after injection from five birds per group for virus detection by real-time RT-PCR and virus isolation on Vero E6 cells. RNA for RRT-PCR was extracted with the Trizol LS reagent (Invitrogen, Carlsbad, CA) by the manufacturer's instructions. Two hydrolysis probe type real-time RT-PCR assays, both targeting the ORF 1b gene, were optimized and run on a Smart Cycler (Cepheid, Sunnyvale, CA) with the superscript platinum taq one-step RT-PCR kit (Invitrogen, Carlsbad, CA). Real-time RT-PCR tests included negative (noninfected tissue culture media, infectious bronchitis coronavirus, and turkey enteric coronaviruses) and positive (Vero E6 propagated SARS-CoV) controls. Two injected birds of each species were euthanized. After necropsy, their tissues were collected for histopathologic examination (all tissue types) and virus detection (plasma, trachea, lung, spleen, kidney, and heart) on days 2 and 4 after injection, and at termination on day 10 after injection. For determination of infection, serum was collected on days 0 and 10 after injection from all birds and tested by indirect enzyme-linked immunosorbent assay for anti-SARS-CoV antibodies. The antigen used to coat plates was tissue culture propagated Urbani strain of SARS-CoV inactivated by γ irradiation [31].

Secondary "anti-bird" antibody (Bethyl Laboratories, Montgomery, TX) for testing quail and goose serum or plasma, and secondary anti-duck, anti-chicken, and anti-turkey antibodies (Kirkegaard and Perry Laboratories, Inc., Gaithersburg, MD) for testing duck, chicken, and turkey serum and plasma, respectively, were used. Two birds of each species received uninoculated tissue culture fluid and served as the sham-inoculated groups for real-time RT-PCR, standard RT-PCR, virus isolation, and histopathologic and serologic assays [9].

Domestic dogs

Perhaps the greatest opportunities for close interactions between humans and free-living canids involve feral and community-owned dogs, whereas human contact with wild species is likely to be mostly restricted to hunting or pest management. However, many wild canid species are opportunistic scavengers (e.g. jackals, red foxes) which may bring them into contact with potential sources of infection such as mink farms. In China raccoon dogs are farmed for their fur and hence similar to mink farms in the potential for spillover of SARS-CoV-2 from infected workers to captive animals, followed by onward spread and spillback to humans [24,32].

The first COVID-19 case in companion animals was reported in a Pomeranian dog from Hong Kong, China in February 2020 [32]. Later in March 2020, COVID-19 was reported from a cat in the same country (These two cases were found after their owners were reported positive for COVID-19 [33,34].

Here, using PCR with reverse transcription, serology, sequencing the viral genome, and virus isolation, we show that 2 out of 15 dogs from households with confirmed human cases of COVID-19 in Hong Kong were found to be infected with SARS-CoV-2. SARS-CoV-2 RNA was detected in five nasal swabs collected over 13 days from a 17-year-old neutered male Pomeranian. A 2.5-year-old male German shepherd was positive for SARS-CoV-2 RNA on two occasions and the virus was isolated from nasal and oral swabs [35]. These two cases in Hong Kong demonstrate that dogs can acquire infection in households with SARS-CoV-2-infected humans.

Domestic dogs (*Canis familiaris*) have been shown in several different studies to have a low susceptibility to SARS-CoV-2 via experimental and natural infection. There is evidence of limited viral replication in a proportion of infected dogs, but no evidence of prolonged acute infection necessary for sustained transmission. Interestingly, most experimentally infected dogs develop an antibody response against SARS-CoV-2, and seroconversion has also been documented in natural human-to-dog transmission events [36].

Domestic cats

Domestic cats are the most abundant felids, reaching densities of over 2000 animals km^2 in urban areas, and their proximity to humans, mobility, and social interactions provide ample opportunities for inter-species pathogen transmission. Although 'stray' and truly feral domestic cats typically have less contact with humans, they may nevertheless be exposed to human-derived infection via fomites in residential areas and farm environments for example. Social interactions amongst colony-living feral cats may be conducive to intra-specific transmission, although there is no current evidence for SARS-CoV-2 maintenance within cat populations, nor for transmission from infected cats to humans. Nevertheless, based on available evidence, surveillance for SARS-CoV-2 in felids could target free-living domestic cat populations, particularly where they are abundant in urban environments or the vicinity of other potential sources of infection such as mink farms. In contrast, wild felid species tend to be solitary, are far less abundant, and seldom come into contact with humans and urban environments, so would not be expected to contribute to virus persistence. However, rare and endangered species could be at risk of exposure to infected humans through research and conservation programs. Domestic cats naturally infected with SARS-CoV-2 have often been reported as showing none or only mild clinical signs, although some instances of more serious disease have been reported [24,37-39].

Domestic cats (*Felis catus*) have been shown by multiple inves-

tigators to be highly susceptible to both experimental and natural SARS-CoV-2 infection. Experimentally infected cats often have an asymptomatic and self-limiting illness that is predominantly restricted to the upper respiratory tract. Under experimental conditions, cats easily transfer the virus to naive cats in close contact. Furthermore, cats produce a robust neutralizing immune response that appears to protect them from re-infection in the short term [36].

The first positive case (cat 1) was from a household that had 3 persons with confirmed cases of COVID-19; their symptoms (fever, cough, or shortness of breath) started on March 20, 29, and 30, 2020. Their 7-year-old, female, domestic short-hair cat was examined by a veterinarian at admission on day 1 (March 30) and reported to be clinically healthy. Nasal, oral, and rectal swab specimens collected on day 1 were positive for SARS-CoV-2 RNA; viral nucleoprotein gene copy numbers were $\log_{10}$ 6.3/mL, $\log_{10}$ 5.6/mL, and 3.2 $\log_{10}$/mL, respectively [40].

Thirty-one cats were infected with SARS-CoV-2 in North America, with all of them being in the United States. Thirty cats had clinical data; ten were asymptomatic, and the rest had mild respiratory symptoms. Six cats were identified with COVID-19 in South America, including three in Chile, one in Brazil, and two in Argentina. In Asia, 10 cats (eight in Hong Kong and two in Japan) were found to be SARS-CoV-2 positive; all were asymptomatic [20,35,40].

Cattle

Bovine coronavirus (BCoV) is a well-known cause of enteric disease in cattle, notably causing illnesses such as "winter dysentery". These illnesses can cause weight loss, dehydration, decreased milk production, depression, and potentially death, all of which can lead to significant economic loss [41].

According to a study by Soules., *et al*. [11]. calves challenged with BCoV displayed clinical symptoms of disease, most frequently nasal discharge, mild cough, and diarrhea. The challenged calves (Group 1) started displaying nasal discharge on day 4 Post-challenge, at which time 3 out of 15 (20%) of the calves had moderate discharge. Seven of the 10 (70%) challenge calves that remained in the study until day 6 or 8 Post-challenge had moderate nasal discharge on at least 1-day Post-challenge. Fever (rectal temperatures of 103.0°F or greater) was detected in 5 of 15 animals during the first 4 days of infection. Elevated respiratory rates (>60/min) were observed in 3 of 15 calves over that same period. Only one calf (ID #647) displayed an elevated respiratory rate as well as a fever; however, the elevated respiratory rate preceded the fever by 1 day. Clinical symptoms peaked at day 5 Post-challenge with 9 out of 10 (90%) remaining challenge calves displaying some symptoms of BCoV infection, most commonly nasal discharge. Notably, on day 6 Post-challenge 60% of the remaining challenge calves were observed to have a mild cough, while none of the control calves had coughing symptoms throughout the duration of the study. Diarrhoea was observed in a control calf on day 3 and another on day 6, subsequently leading to the development of minor clinical signs.

Equine

Coronaviruses are a family of RNA viruses that cause disease in mammals and birds. The equine coronavirus has been linked to diarrhea in foals as well as lethargy, fever, anorexia, and sometimes gastrointestinal signs in adult horses. Although horses appear to be sensitive to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) due to strong homology to the ACE-2 receptor, they appear to be incidental hosts due to SARS-CoV-2 spillover from people on occasion. However, it is critical to monitor equids for probable transmission from humans with clinical or asymptomatic COVID-19 until further clinical and seroepidemiological data are available [42].

Equine coronavirus (ECoV) infection was first documented in neonatal foals (less than 2 weeks old) with and without clinical indications of enteritis. ECoV outbreaks have been reported in adult horses at racing venues and boarding stables. There are no reports of ECoV virus epidemics involving breeding farms or young horses (under a year old) [43].

ECoV is spread when an infected horse's feces is ingested by another horse (fecal-oral transmission). The virus can also be spread when horses come into touch with infected feces-contaminated surfaces or objects. Fomites (things or materials that can host ECoV) include stalls, muck forks, manure spreaders, thermometers, and clothing. ECoV is most typically diagnosed during the winter. ECoV appears to be particular for horses, with no evidence of infection or transmission to people or other animals; however, adequate biosecurity precautions should be implemented with all horses experiencing diarrhea or exhibiting clinical indications associated with ECoV [44].

According to a study by Williams., *et al.* [45]. in the United Kingdom, quarantine and social distancing measures were implemented with immediate effect on 17 March 2020, resulting in a rapid change to the way owners managed and interacted with their horses. We surveyed 6259 horse owners to evaluate the impact of COVID-19 on themselves and their horses. The majority of horse owners were visiting and riding their horses less, with increased restrictions experienced by owners who kept their horses at private livery yards. Whilst social distancing and visiting restrictions were in place at livery yards, nearly half were not providing hand

sanitization or disinfection protocols for shared areas/equipment to prevent the spread of the virus between owners. Horse owners expressed concern that equine health and welfare would be negatively affected by the restrictions put in place and of financial consequences as a result of the pandemic. The majority of respondents also felt their mental health and well-being were being adversely affected by not being able to visit/interact as they normally would with their horses. Equestrian influencers and national bodies should engage in increased communication and education to support horse owners through the pandemic in the short, medium, and long term.

Pigs

Several investigations have shown domestic pigs (Sus scrofa) to be resistant or only marginally susceptible to SARS-CoV-2 infection. The discovery of viable SARS-CoV-2 virus or viral RNA in clinical samples from SARS-CoV-2-inoculated pigs was, at best, limited and intermittent. Furthermore, clinical indications were rarely noticed, and no tests revealed any viral transmission to naive contact pigs. Some investigations did discover occasional modest antibody responses; nevertheless, a robust neutralizing antibody response was only detected in pigs who were infected intravenously or intramuscularly [36].

The ability of SARS-CoV-2 was determined as follows (i) replicate in porcine cell lines, (ii) establish infection in domestic pigs via experimental oral/intranasal/intratracheal inoculation, and (iii) transmit to co-housed naïve sentinel pigs [46]. SARS-CoV-2 was able to replicate in two different porcine cell lines with cytopathic effects. Interestingly, none of the SARS-CoV-2-inoculated pigs showed evidence of clinical signs, viral replication, or SARS-CoV-2-specific antibody responses. Moreover, none of the sentinel pigs displayed markers of SARS-CoV-2 infection. These data indicate that although different porcine cell lines are permissive to SARS-CoV-2, five-week-old pigs are not susceptible to infection via oral/intranasal/intratracheal challenge. Pigs are therefore unlikely to be significant carriers of SARS-CoV-2 and are not a suitable preclinical animal model to study SARS-CoV-2 pathogenesis or efficacy of respective vaccines or therapeutics [46].

In conclusion, available studies indicate that pigs are poorly susceptible to SARS-CoV-2 infection. They are unlikely to be significant carriers of SARS-CoV-2 nor a significant source of transmission of this coronavirus to humans [20].

Bats

Bats have been identified as the natural reservoir of SARS coronaviruses (SLCoV and SCoV) that are similar to SARS [21]. Bats are suitable reservoir hosts for CoVs because the viruses are persistent and asymptomatic in bats. They move around the forests in quest of food, spreading the virus to a variety of individuals with whom they come into touch [13,14].

Studies in which bats and select small mammals were experimentally exposed to SARS-CoV-2 showed that some species (i.e., fruit bats [*Rousettus aegyptiacus*] and tree shrews [*Tupaia belangeri*]) are capable of minimal viral replication, but others (big brown bats [*Eptesicus fuscus*]) do not become infected, which suggests that although the virus might have originated in bats, they are unlikely to serve as reservoir hosts [47,48]. Because clinical responses to infection differ between closely related species, predicting repercussions on animals and their potential for reservoir maintenance is difficult. Despite the best efforts to anticipate host susceptibility based on receptor similarities or other modeling approaches, experimental infections continue to be the gold standard for assessing an animal's susceptibility to infection and tracking the disease's progression [36].

Wild primates

The health impacts of SARS-CoV-2 may be more severe in wild gorillas due to co-infections and physiological stressors that do not exist in confined animals under veterinary care. It is also difficult to predict the potential effects of SARS-CoV-2 infection in other wild primates; therefore, given the history of human-derived respiratory infections and the precarious conservation status of wild great ape populations, the risk of adverse health and population impacts should be regarded as high and managed accordingly. This could include strict health surveillance and vaccination of tourists, researchers, and conservation workers who come into contact with primates, improved hygiene and sanitation, the use of protective equipment, and safe distancing, as well as quarantine measures where management interventions necessitate moving animals [24,47]. A vaccine developed for use in great apes has been administered to captive bonobos (*Pan paniscus*) and orangutans (*Pongo* sp.) and this approach could also be applied during rehabilitation and in habituated free-living primates [24].

Rabbits

Rabbits have made significant contributions to biomedical research. While mice remain the most commonly utilized study animal due to cost and availability, laboratory rabbits have numerous

advantages as a model for human disease [48]. Mykytyn., *et al.* [51] intranasally infected three-month-old female New Zealand White Rabbits (Oryctolagus cuniculus) with 106 TCID50 SARS-CoV-2. These animals were observed for 21 days after infection. There were no clinical symptoms of infection in any of the three inoculated animals. Although there was high variability between animals, viral RNA was detected in nasal swabs up to 21 dpi, in throat swabs up to 14 dpi, and in rectal swabs up to 9 dpi. Infectious virus was detected in the nose up to 7 dpi, but not in the throat (except in one animal at 1 dpi) and in rectal swabs. All animals were monitored for three weeks seroconverted, with serum-neutralizing antibodies ranging from 1:40 to 1:640 [20].

Another study by Fritz., *et al*. [52] found that between November 2020 and June 2021, 2022 pet rabbits were tested in France for antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using a microsphere immunoassay. We discovered the first natural SARS-CoV-2 infection in rabbits, with a low observed seroprevalence of 0.7% to 1.4%.

Bushy-tailed woodrats

A single study revealed that bushy-tailed woodrats (also known as packrats, Neotoma cinerea) are vulnerable to SARS-CoV-2. They are also members of the Cricetidae family and are found in a variety of environments in the western United States and Canada. A SARS-CoV-2 dose of 3 104 to 8 104 pfu per animal was delivered nasally to wild, captured wood rats. Inoculation caused a prolific infection, with infectious virus secreted orally from 1 to 5 DPC. Throughout the length of the infection, none of the animals demonstrated any clinical symptoms, such as changed temperature, weight loss, or behavioral changes. However, mild histopathological lesions were observed in the lungs of some of the wood rats during the period of acute infection (3 DPC). Infectious virus was detected in a proportion of nasal turbinate, trachea, and lung samples on 3 DPC. Neutralizing antibodies were detected in the wood rats at 28 DPC. The ability of wood rats to transmit the virus to naïve animals was not tested [36,53,54].

Woodrats, like other members of the Cricetidae family, are vulnerable to SARS-CoV-2 and acquire a comparable disease course, albeit clinical indicators such as weight loss have not been recorded. There has been no report of SARS-CoV-2 infection in wildwood rats. Active surveillance should be done similarly for this species as for deer mice because of their peri-domestic interaction with human dwellings and potential susceptibility to sensitive farmed (mink, deer) or predatory (cats) species. Their potential usage as a research model is limited as compared to hamsters or deer mice due to a lack of active research colonies and clinical indications [36].

Future perspective of covid-19 in domestic and wild animals

It is interesting to note the uncanny similarity that exists between SARS-CoV-2 and SARS-CoV, such as the susceptibility of cats and ferrets, transmission of infection to cage mates, and resistance of chickens and pigs to infection. The animal models that are currently being used for SARS-CoV-2 are those that were established for SARS-CoV. The production of hACE2 transgenic mice, which was stopped after the SARS outbreak ended, has been resumed to facilitate and promote research on SARS-CoV-2. Significant advances have already been made in the development of several animal models for SARS-CoV and SARS-CoV-2 infection. However, their practical utility has been severely limited due to a lack of clinical resemblance with the human diseases caused by these viruses. Although non-human primate models resemble clinical symptoms of the disease seen in people, they have significant drawbacks that limit their widespread use in testing vaccines and treatments for SARSCoV-2 infection. To establish an agreement on the involvement of animals in the emergence and maintenance of SARS-CoV-2 in the ecosystem, extended COVID-19 surveillance in animal species is required [3,52].

The live-animal markets, like the Huanan South China Seafood Market, will continue to serve as an excellent meeting ground for wild and domestic animal species. As a result of the adaptive genetic recombination that happens in these viruses, the prospect of inter-species transmission of CoV infections in such hot areas is a source of concern for humans. The SARS-CoV-2 outbreak is yet another key example demonstrating the existence of a tight yet simple connection between humans, animals, and environmental health that has the potential to culminate in the establishment of a lethal pandemic [4].

Conclusion

SARS-CoV-2 is the third zoonotic coronavirus (CoV) after SARS-CoV and MERS-CoV that has caused an epidemic outbreak in the past two decades. Preliminary evidence suggests that SARS-CoV-2 emerged from Wuhan, China, via zoonotic (animal-to-human) transmission. Genome analysis has identified the bat as the most probable reservoir host of SARS-CoV-2 infection. All three zoonotic CoVs, i.e., SARS-CoV, MERS-CoV, and SARS-CoV-2, are reported to originate from bats and were transmitted to humans through an intermediate animal host. At present, the susceptibility of domestic and wild animal species to SARS-CoV-2 has major implications for the development of preventive and control strategies against this pandemic. Domestic animal and Wildlife SARS-CoV-2 are intricately involved, from the initial spillover event to potential reverse zoonotic transmission, and we will undoubtedly continue to discover more susceptible species as the search for zoonotic reser-

voirs continues. COVID-19 is just the latest in a series of examples of how the human–wildlife interface continues to drive the emergence of infectious diseases. Using experimental research, field studies, surveillance, genomics, and modeling as tools for predicting outbreaks and epidemics should help provide the knowledge base and resources necessary to prevent future pandemics. Thus, local and international regulatory authorities should develop and implement robust disease control mechanisms that effectively decrease the possibility of human exposure to domestic and wild animals; Experimental research and epidemics should help provide the knowledge base and resources necessary to prevent future pandemics; Large-scale screening of animals on the role of pet animals in the maintenance and transmission of the disease should be studied further; Furthermore, some experiments and studies and serosurveillance studies in different animal species should be continued to reach an effective conclusion and prevention.

Declaration

- **Ethics approval and Consent to participate:** Not applicable.
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