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Nig. Vet. J., March 2022 https://dx.doi.org/10.4314/nvj.v43i1.4 Vol 43 (1): 35 -53. ORIGINAL ARTICLE

REVIEW OF MAN TO ANIMAL TRANSMISSION OF CORONAVIRUS DISEASE 2019 (COVID-19) INFECTION CAUSED BY SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2).

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SUMMARY

Coronaviruses infect a wide variety of animals, including birds and mammals, where they cause infection in animals, mutate and cause disease outbreaks in humans. The review focused on the origin and spread of SARS-CoV-2 from humans to animals. A systematic literature search of PubMed, ProMed-mail, and Google Scholar databases, using keywords "animals", "COVID-19", and "SARS-CoV-2", for articles providing information on animal studies and case reports between December 2019 and September 2021. Published articles included in this review are in English and conducted studies on animals and case reports of human-animal transmission. Fifty-seven COVID-19 in animals published articles featured in this review. Humans can spread the disease to pets (dogs and cats) during close contact when they are clinically infected. Although cats are susceptible to subclinical infection, they developed a robust neutralizing antibody response that prevented re-infection to a second viral challenge in a laboratory setting. Clinically positive Farm workers on mink farms tend to spread the disease to SARS-CoV-2. Companion animals living with infected owners are at risk of Man-to-animal spread of SARS-CoV-2 virus. Therefore, applying basic hygiene measures such as handwashing when handling and caring for animals is suggested.

Keywords: COVID-19, Animals, Severe Acute Respiratory Syndrome Coronavirus 2, Zoonoses, Pandemics, Review.

INTRODUCTION

Coronaviruses identified in the mid-1960s (Tyrrell and Bynoe, 1965; Hamre and Procknow, 1966) infect different types of animals, including birds and mammals. They cause infections in animals, mutate, and cause disease outbreaks in humans (Decaro and Lorusso. 2020). Recognized coronavirus diseases in humans include SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus 2), identified in southern China in 2003; MERS-CoV (Middle Eastern respiratory syndrome), from the Middle East in 2012 (Doucleef, 2012); and SARS-CoV-2 that causes COVID-19 reported in China 2019 and currently a pandemic (WHO, 2020a). In humans, the virus causes respiratory infections that range from mild to fatal (CDC, 2020a). Based on chained databases. current all human Coronavirus have animal origins: SARS-CoV, MERS-CoV, human Coronavirus (HCoV)-NL63, and HCoV-229E have originated from bats; HCoV- OC43 and HKU1 originated from rodents (Decaro & Lorusso, 2020; Forni et al., 2017; Su et al., 2016). Although Coronavirus is most contagious during the first three days of infection following the onset of symptoms, the spread may be possible before symptoms appear and in later stages of the disease (WHO, 2020b). The standard method of testing human samples is real-time reverse transcription-polymerase chain reaction (RT-PCR), the CDC Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay since the CDC 2019-Novel Coronavirus (2019nCoV). Real-Time RT-PCR Diagnostic Panel was discontinued (CDC, 2020b) because of the rapid nature and reduced risk of contamination of this method. Epidemiological investigations linked the outbreak to a seafood market in Wuhan. A study by Wu et al. (2020) stated that

the epidemiological investigations by the Wuhan Center for Disease Control and Prevention reported that the patient revealed he was working at a local seafood market. In addition to fish and shellfish, a variety of live wild animals, including hedgehogs, badgers, snakes, and birds (turtledove), were available for sale in the market before the outbreak began, as well as animal carcasses and animal meat; however, there were no bats available on sale. At the end of 2019, Wuhan, an emerging business hub in China, experienced an outbreak of a novel coronavirus that killed more than eight hundred and infected over seventy thousand individuals within the first fifty days of the epidemic (Shereen et al., 2020). The virus was named SARS-CoV-2 and the disease COVID-19 by the International Committee on Taxonomy of Viruses (ICTV) (Lai et al., 2020; WHO, 2020c; Cui et al., 2019). Despite extensive research, how, when, and where new diseases emerge remains a great source of uncertainty (Wu et al., 2020). As of 10th April 2021, more than 134 million (WHO, 2020d) cases had been reported globally, with 163,581 confirmed cases reported in Nigeria (WHO, 2020d). SARS-CoV-2 appears to have a receptor-binding domain (RBD) that is associated with a significant affinity for Angiotensin-converting enzyme 2 (ACE2) in humans, animals, and cats with a high future homogeneity (Lu et al., 2020a). According to irrefutable Genetic data, SARS-CoV-2 did not arise from any previously used virus backbone (Almazan et al., 2014). Andersen et al. (2020) suggested two possible scenarios for SARS-CoV-2: (1) natural selection in an animal host before animal transport; and (2) natural selection in humans after animal

transmission. Given SARS-CoV-2's similarity to SARS-CoV bat coronavirus, the bat may act as a reservoir host for its predecessor (Wu et al., 2020). Some pangolin coronaviruses exhibit strong similarities with SARS-CoV-2 in RBD, including all six RBDs (Zhang et al., 2020b). This review provides insight into the structure of the virus and how the virus affects animals and explains the possibility of human-animal transmission. Although the original transmission of SARS-CoV-2 has been through humanhuman and few instances of human-animal, the possibility of animal-human spread, reservoir status of animals, and knowledge in the diagnosis and management of animal infection requires proper investigation and preparation.

MATERIALS AND METHOD

Literature search

A systematic literature search of PubMed, ProMed-mail, and Google Scholar databases was performed between April and September 2021, using the keywords "dogs," "cats," "COVID-19", and "SARS-CoV-2" to obtain articles providing information on animal studies and case report of COVID-19 in animals. The search included additional articles utilizing a snowballing method applied to the references of retrieved papers and from the archives of the reviewers while considering the date of the earliest confirmed reports of COVID-19. One of the authors independently screened the databases and extracted relevant information. Eight hundred and sixty-nine (869) relevant articles were downloaded and analyzed. The result reviewed the origin and how the virus affects animals and explained the possibility of humananimal transmission. It also explains the role of

animals in the spread of the disease.

Eligibility Criteria and Study Selection

Only articles published in English and conducted on animals with the recent coronavirus disease outbreak (COVID-19). and case reports of human-animal transmission, were included in the review, as shown in figure 1. Studies on other coronavirus-related illnesses, such as the Middle East respiratory syndrome (MERS), excluded. Disagreements were were discussed with other reviewers and subsequently resolved via consensus. Full texts were retrieved, analyzed, and developed into an easy-to-understand review.



Figure 1: flow chart of article inclusion

RESULTS

A total of fifty-seven (57) articles were relevant to the study. Twenty-four (42.1%) articles were on susceptibility, infections, and transmission of SARS-CoV-2 in dogs and cats. Ten (17.5%) articles on COVID-19 in mink farms across the Netherlands. Five (8.8%) studies on the possibility of pangolins as reservoir hosts, four (7.0%) of the articles were on susceptibility and possibility of transmission of SARS-CoV-2 from ferrets, and four (7.0%) on various domestic and wild animals. Two articles (3.5%) were case reports of infection in tigers; two (3.5%) studied virus shedding and reinfection in rhesus macaques, and another two (3.5%) on infection rates in non-human primates. One (1.8%) study on pathogenic manifestation in hamsters, one (1.8%) of the studies was on the detection of the virus in Myanmar bats, also one (1.8%) on laboratory infection in rabbits to determine if they show signs of COVID-19 and lastly, one (1.8%) on cattle to determine if they play a role in the human pandemic. The table below shows the main findings from each article on pets and domestic animals included in the review.

Author	Type of animal	Experimental design	Main findings
Temmam <i>et al.</i> , 2020.	Cats and dogs	Domestic cats and dogs living in close contact with some French veterinary students, who were their owners, were investigated for the presence of SARS-CoV-2. Two of these students tested positive for COVID-19 by RT-PCR.	The results reveal evidence for a low or nil COVID-19 rate of infection in companion cats and dogs, even when there are repeated contacts and proximity to infected humans.
Dodds, 2020.	Cats and dogs	OIE statement as of March 14, 2020, reported a dog tested positive for COVID-19 following exposure to its sick owners, though the dog was not showing any clinical signs.	There is no evidence that dogs played a role in the spread of this disease. There is also no evidence to support the movement or trade restrictions on companion animals.
Goumenou <i>et al.,</i> 2020.	Dogs	Italy is the second country in Europe with the highest number of dog owners. After two weeks of movement restrictions, except for mobility for taking out dogs,	Dogs may be an intermediate host, contributing to the high transmission of COVID-19 in Northern Italy.

Table I: Companion and Domestic animal

		there was still an increase in the number of positive covid- 19 cases and death.	
Maïthé, 2020.	Cats	Coronavirus: Belgian cat infected by the owner (A report).	There is a human- animal transmission, but the possibility of animal-human spread is minute.
ProMed-mail, 2020b.	Dog	An eight-nine-year-old dog with a chronic health condition was tested after its owner tested positive for COVID-19.	The dog had to be euthanized because of a preexisting chronic health condition. Pet owners are, therefore, advised to minimize contact with pets to protect them from exposure to infection.
Bosco-Lauth et al., 2020.	Cat, dog	Seven adult cats and three dogs got inoculated with Virus diluted in phosphate-buffered saline (PBS) via pipette into the nares (500ul/nare) for a total volume of 1ml; observed until complete recovery from anesthesia. Virus back- titration was performed on E6 cells immediately following inoculation, confirming that cats received 3.0E5 pfu and dogs received 1.4E5 pfu.	Cats are highly susceptible to subclinical infection, with a prolonged period of oral and nasal viral shedding not accompanied by clinical signs, and are capable of direct contact transmission to other cats.
Halfmann <i>et al.,</i> 2020	Cats	Three domestic cats were inoculated with SARS-CoV-2 on day 0. To assess whether the spread of the virus by direct contact would occur between the cats in each of the three pairs, a cat with no previous SARS-CoV-2	The virus was present in 2 of the inoculated cats on day 1. By day 3, the virus was detectable in all three inoculate cats, with continued detection until day 5 in all cats

		infection was co-housed with the inoculated cats on day one post-inoculation.	and until day 6 in 2 of the three cats. The cats with no previous infection were co- housed with the inoculated cats on day 1. Two days later (day 3), one of the cats with no prior infection had infectious virus detected in a nasal swab specimen. Five days later, the virus was present in all three cats co-housed with the inoculated cats.
Zhang <i>et al.,</i> 2020a	Cats	Cohort of serum samples collected from cats in Wuhan, including 102 samples after and 39 before COVID-19 outbreak.	15 of 102 (14.7%) cat sera collected after the outbreak were positive for the receptor- binding domain (RBD) of SARS-CoV-2 by indirect enzyme-linked immunosorbent assay (ELISA).
Segales <i>et al.</i> , 2020	Cat	A cat suffering from severe respiratory distress and thrombocytopenia living with a family suffering from COVID-19. Euthanasia and a post-mortem was done.	SARS-CoV-2 ribonucleic acid (RNA) was present in nasal swab, turbinates, and lymph nodes of the cat, with no evidence of disease on histopathology.
OIE, 2020	Cat	Three cats near infected persons were tested for SARS-CoV-2.	Viral RNA was detected by RT-PCR in nasal secretions and feces in a cat with a closer link to one of its owners. Viral RNA

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			remaining two cats four to five days later.
OIE; ProMed- mail, 2020	Dog, Cat	Coronavirus Disease 2019 Update: A female domestic cat and a dog without clinical signs living near a household infected with COVID-19 were tested using oral and nasal swabs.	The first sample from the cat was positive, while the specimen collected 11 days after the first came back negative. The dog's came back negative.
Gaudreault <i>et al.</i> , 2020.	Cats	4-5-month-old cats were infected with SARS-CoV-2 via intranasal and oral routes simultaneously. Two sentinel contact cats co-mingled with the principally infected animals one-day post- challenge (DPC). Clinical signs, clinicopathological abnormalities, and viral shedding observed through 21-DPC. Post-mortem was carried out on 4, 7, and 21- DPC to investigate disease progression.	Animals were clinically asymptomatic and were capable of transmitting SARS- CoV-2 to sentinels within 2 days of co- mingling.
ProMed-mail, 2020b	Dog	Coronavirus Disease 2019 Update: Dog tested positive for the virus in Louisiana, USA: A report	It appears that humans can spread the disease to pets during close contact. Though routine testing is not recommended, humans should avoid pet contact when positive
ProMed-mail, 2020a	Cats	Coronavirus Disease 2019 Update: 2 cats tested positive for the virus: A report	Pets are likely to become infected in high-risk households.

Reeder, 2020	Dogs, cats, and horses	Idexx Laboratories tested 3500 samples from cats, dogs, and horses.	None of the results returned positive, which suggests that COVID-19 spread from person to person and pets are not likely to contract the disease.
Deng et al., 2020	Domestic, companion, and wild animals	One thousand, nine hundred and fourteen (1914) serum samples were obtained from 35 species of animals; domestic livestock (dog, sheep, cow, pig), poultry, experimental animals, companion animals, and wild animals. A commercial double antigen sandwich ELISA was then used for detection of SARS-CoV-2-specific antigens.	This study excludes the possibility of domestic animals as intermediate hosts of SARS-CoV-2 to humans. Companion animals, including pet dogs, and cats, street dogs, and cats, tested serologically negative for SARS-CoV-2, relieving public concerns for them as carriers.
Ruiz-Arrondo <i>et</i> <i>al.</i> , 2021	Mammalian pets	Oropharyngeal and rectal swabs were collected from twenty-three asymptomatic mammalian pets that were under quarantine from seventeen households with confirmed human cases of COVID-19 infection. The samples were preserved at 4°C in 2 mL Dulbecco's Modified Eagle Medium (DMEM) with penicillin (100 units/mL) and streptomycin (100 µg/mL) (Sigma-Aldrich, Manheim, Germany).	Detection of an asymptomatic cat with SARS-CoV-2 in Spain, probably associated with close contact with its owner with active COVID-19 infection.
Shi et al., 2020	Ferrets, cats, dogs, and	The replication and transmission dynamics of	Ferrets and cats are highly susceptible to

SARS-CoV-2 in ferrets, cats, SARS-CoV-2.

Dogs

domestic

	livestock chickens, ducks)	(Pigs, and	dogs, and domestic livestock (pigs, chickens, and ducks) after they were inoculated intranasally. They were euthanized, and their organs collected for viral RNA detection.	have a low susceptibility, while chickens, ducks, and pigs are not prone to the virus.
et al., 2020	Pets domestic animals	and	The risk of SARS-CoV-2 transmission to pets and other wild animals strongly mandates a one-health strategy to control the COVID-19 pandemic: A review.	Epidemiological, and biological, and virological features of coronaviruses suggest that its spread to pets from sick owners is not only likely but expected. Although viral shedding from pets does not appear sufficient to infect family members, usual precautionary measures are followed as part of a global and one-health approach.

DISCUSSION

Leroy

Sources of infection in animals

The Minnesota Board of Animal Health released the findings that confirmed the infection of a cat with SARS-CoV-2 seven days after its owner was confirmed positive for COVID-19. The cat was healthy five days after the initial clinic visit but recommended to remain isolated for 14 days following the positive test result (ProMed-mail, 2020a). Also, the United States Department of Agriculture's (USDA) National Veterinary Services Laboratories (NVSL) on 2nd June 2020

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announced the first confirmed case of SARS-CoV-2 infection in a pet dog (German shepherd) in New York State. The dog's owners tested positive for COVID-19, and the second owner showed symptoms consistent with the virus before the dog showed any signs. A second dog in the household has shown no signs of illness; however, antibodies were also identified in the dog, suggesting exposure. The initial dog tested presumptive positive for SARS-CoV-2 at a private veterinary laboratory, which then reported the result to state and federal officials. The confirmatory testing was

conducted at NVSL and included a collection of additional samples (ProMed-mail, 2020b). In addition, rabbit farms also were screened for SARS-CoV-2. None of the rabbit farms had any positive cases of COVID-19 at the time of the report. The risk of spreading through rats and mice is small; these species have very different receptors than the receptors to which coronaviruses attach (ProMed-mail, 2020c). In a study by Ruiz-Arrondo et al. (2021), an oropharyngeal swab sample from a female cat tested positive for SARS-CoV-2 by the three RT-qPCR assays performed. The female domestic European cat did not show any coronavirus-related clinical signs, revealing the first-ever asymptomatic case of a cat in close contact with a COVID-positive owner (Ruiz-Arrondo et al., 2021). In Germany, SARS-CoV-2 infection confirmed by SARS-CoV-2-specific RT-PCR diagnostics by the Bavarian Office for Health and Food Safety, Erlangen, Bavaria, in a 6-year-old female cat living with its owner in a retirement home. The owner died due to COVID-19 on 12 Apr 2020. There were also two other cats (female 15-year-old, male 10-yearold) living in the same retirement home, with an ongoing COVID-19 outbreak scenario. All three cats had contact with the residents, but none of the cats had any signs of respiratory disease (ProMed-mail, 2020d). A second cat tested positive for coronavirus in France after having probably, been infected by its owners, announced the National Veterinary School of Toulouse (ENVT) in a press release. The cat suffered from respiratory disorders and was examined several times by a veterinarian, who reported persistent cough despite anti-infective and anti-inflammatory treatment (Promed-mail, 2020e). A cat was placed under quarantine on 30th March 2020 after its owner became hospitalized due to a COVID-19 infection.

Following veterinary examination, samples collected included nasal, oral, and rectal swab samples, and all the samples tested positive for SARS-CoV-2. A virus-neutralizing antibody was, however, detected in a follow-up blood sample (ProMed-mail, 2020f).

COVID-19 in animals

Animals can become infected through direct contact with infected humans and exposure to other infected animals. The infected animal may show clinical signs such as diarrhea, vomiting, shortness of breath, dry cough, and loss of appetite. Cats and ferrets are more susceptible to the disease, and transmission between cats through respiratory droplets is possible. Syrian hamsters and monkeys are equally prone to SARS-CoV-2 infection and may be promising as potential animal models for COVID-19. Since the outbreak of COVID-19 in mink farms in the Netherlands, precautions adopted include; the the mandatory notification of disease suspicion by keepers, veterinarians, and laboratories; the compulsory early warning (EW) survey (weekly submission of deceased animals); and the mandatory serological screening test on the farms (research on antibodies). Findings have shown predominant route of transmission of SARS-CoV-2 was from human to human. However, reports have documented that humans seem to remain the significant source of infection in animals, domestic cat tested positive after developing symptoms (diarrhea, vomiting, and shortness of breath) a week after its owner tested positive (Maithe, 2020). Tigers at the Bronx Zoo also tested positive for the virus and showed symptoms of COVID-19, including dry cough and loss of appetite. Public health

officials believed the large cats caught COVID-19 from a zoo employee (Goldstein, 2020). The spread of infection from sick owners to their pets is not only likely but expected (Leroy et al., 2020). However, Temmam et al. (2020) reported a low evidence or nil COVID-19 infection rate in companion cats and dogs, even when there is repeated contact and proximity to infected humans. Furthermore, viral shedding from pets does not appear to be sufficient to infect family members. Standard precautionary measures should be a part of a global and one-health approach (Leroy et al., 2020). Findings from experimental animal studies by Shi et al. (2020) on the susceptibility of experimentally inoculated animals with SARS-CoV-2 revealed that cats and ferrets are susceptible, dogs are less susceptible, with low levels of viral replication. Livestock: pigs, chickens, and ducks were not susceptible to the virus. The study concluded that the virus is transmissible between cats through respiratory droplets, and it can reproduce in the upper respiratory tract of the ferret for up to eight days without causing severe illness or death (Shi et al., 2020). Young-Il et al. (2020) conducted a study using 105.5 TCID50 of NMC-nCoV02, a strain isolated from a patient confirmed with COVID-19 in South Korea. Six direct contacts and six indirect contact ferrets exposed to ferrets inoculated intranasally. The six direct contact ferrets were positive on PCR and virus and antibody isolation. Two indirect contact ferrets were positive on PCR and one on the antibody. Wan et al. (2020) reported that pigs, cats, ferrets, and non-human primates have similar or identical SARS cellular receptors to those found in humans. A virus-host prediction (VHP) method proposed by Guo et al. (2020) based on a learning algorithm found that bat and mink viruses resembled infectious patterns of SARS-

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CoV-2. Mink outbreaks experienced in the Netherlands, Denmark, Italy, and the USA are zoonosis in reverse; the most likely explanation for the extensive infection on the mink farms might be the result of human-mink transmission (Singla *et al.*, 2020).

Several studies have shown that Malayan pangolin (Manisjavanica) is a potential natural reservoir or an intermediate host of HCoV-19 (Zhang et al., 2020b; Lam et al., 2020; Xiao et al., 2020). Other studies showed that Syrian hamsters (Chan et al., 2020) and monkeys (Bao et al., 2020; Lu et al., 2020b; Munster et al., 2020; Rockx et al., 2020) were also susceptible to SARS-CoV-2 infection and may be promising as potential animal models for COVID-19, this further suggests a possibility of interspecies spread of SARS-CoV-2 in animals. Also, pangolins acting as an intermediate host of SARS-CoV-2 in animals is possible (Lam et al., 2020). However, there is currently no evidence in support of a direct pangolin origin of SARS-CoV-2 due to the sequence divergence between SARS-CoV-2 and pangolin SARS-CoV-2-related beta-CoVs (Ye et al., 2020). Most positive samples in the Guano specimen suggest a significant route for CoV shedding from bats (Valitutto et al., 2020). Companion animals, including pet dogs and cats, street dogs and cats, tested serologically negative for SARS-CoV- 2, relieving public concerns for them as carriers (Deng et al., 2020). Idexx Laboratories, an American multinational corporation, and a global leader in veterinary diagnostics, started testing samples from dogs, cats, and horses for the coronavirus strain responsible for COVID-19. More than 3,500 specimens from dogs, cats, and horses in South Korea and all 50 U.S. states were

submitted, including areas experiencing human COVID-19 cases like Seattle; they were 55% dogs, 41% cats, and 4% horses; none of the results came back positive (Reeder, 2020).

From this review, there has been, so far, not enough evidence to conclude that pets are responsible for spreading SARS-CoV-2 to humans. There was no evidence to suggest that pets infected by humans played a role in the transmission of COVID-19 and that the current wave of COVID-19 resulted from the humanhuman spread.

CONCLUSIONS

Man-to-animal spread of the SARS-CoV-2 virus is possible, especially to companion pets living near infected owners. Basic hygiene measures such as handwashing before and after should be implemented by handlers/pet owners when handling and caring for all animals. Also, avoid kissing, being gently licked, or sharing food with the animals. People suspected or confirmed positive for SARS-CoV-2 should also minimize constant physical contact with animals. including livestock, zoo, other captive animals, and wildlife, particularly species that have sufficiently demonstrated to be susceptible to infection with SARS-CoV-2. They should not only distance themselves from other people but also their pets by isolating them far from them. As the best practice, when humans are in contact with a group of animals, appropriate and effective biosecurity measures should be implemented on farms, at zoos, and in animal shelters. OIE recommended RT-PCR for testing oral, nasal, and fecal/rectal samples if a decision for risk assessment in a companion animal that maintained close contact with has а person/owner infected with SARS-CoV-2 is needed (OIE, 2020). Based on the available

information, the risk of companion animals spreading the virus to people is low, and, as such, there is no justification for taking measures against pets that may threaten their welfare (ProMed-mail, 2020b).

Examining the potential effects of zoonotic diseases reduces the possibilities for adverse effects on each animal population while attempting to adequately control the reintroduction of the adapted animal virus into humans. Development of Harmonized guidelines for surveillance and intervention in wild, captive, and companion animals to facilitate a more thorough understanding of viral spread in novel host populations is necessary. The SARS-CoV-2 pandemic and its resulting pandemic underscore the necessity for a one-health approach, and such proposed interventions should include quarantine and care packages for infected animals (Gollakner and Capua, 2020). In addition, tracing the susceptible animals and effective surveillance of SARS-CoV-2related viruses would be significant for preventing similar emerging viruses in the future (Wong et al., 2020). It is crucially important to clarify the potential sources of SARS-CoV-2 in untamed animals and prevent a viral resurgence in countries with excellent management of the pandemic. In summary, based on the available data, we

recommend that in this period, all COVID-19 protocols, including physical distancing and screening of the pets, must be observed between infected owners and their pets.

Conflict of interest

The authors declare that they have no conflict of interest.

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