

Concerns on the Emerging Research of SARS-CoV-2 on Felines: Could They be Significant Hosts/Reservoirs?

D. Katterine Bonilla-Aldana^{1,2} , Julian Ruiz-Saenz³ , Marlen Martinez-Gutierrez³ , Ruchi Tiwari⁴ , Kuldeep Dhama⁵ , Javier A. Jaimes⁶ , and Alfonso J. Rodriguez-Morales^{2,7*} 

¹Incubator in Zoonosis (SIZOO), Biodiversity and Ecosystem Conservation Research Group (BIOECOS), Fundacion Universitaria Autonoma de las Americas, Sede Pereira, Pereira, Risaralda, Colombia. ²Public Health and Infection Research Group and Incubator, Faculty of Health Sciences, Universidad Tecnologica de Pereira, Pereira, Risaralda, Colombia. ³Grupo de Investigacion en Ciencias Animales, Universidad Cooperativa de Colombia, Bucaramanga, Santander, Colombia. ⁴Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences, Uttar Pradesh Pandit Deen Dayal Upadhyaya Pashu Chikitsa Vigyan Vishwavidyalaya Evam Go Anusandhan Sansthan (DUVASU), Mathura, India –281001, India. ⁵Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly- 243 122, Uttar Pradesh, India. ⁶Department of Microbiology & Immunology, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA. ⁷Grupo de Investigacion Biomedicina, Faculty of Medicine, Fundacion Universitaria Autonoma de las Americas, Pereira, Risaralda, Colombia.

Abstract

With the growing evidence of cases and studies showing natural and experimental infection due to SARS-CoV-2 in felines, including cats, lion, and tigers, there is also an increasing concern about its susceptibility and their role in urban cycles of SARS-CoV-2 transmission, initially from humans-to-animals, but with uncertainty about reverse transmission. In this review, we addressed the evidence around this situation.

Keywords: SARS-CoV-2, COVID-19, Animals, Feline, Anthroozoonotic, Pandemic

*Correspondence: ajrodriguezmm@gmail.com

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INTRODUCTION

Coronaviruses (CoV) are a group of widely known enveloped single-stranded, non-segmented RNA viruses. These belong to the *Orthocoronavirinae* subfamily, *Coronaviridae* family, in the order *Nidovirales*, and they are classified into four genera: Alpha, Beta, Gamma, and Deltacoronavirus¹. CoVs are worldwide distributed pathogens², can infect both animals and humans, and transmission between species is a common feature of these viruses³. Currently, one CoV is causing a pandemic⁴.

CoVs are commonly circulating in animal and human populations around the world, as is the case of the human CoVs NL63, 229E, OC43, and HKU1⁵. These viruses mainly cause minor respiratory problems and are not a matter of concern, as long as they do not infect immunocompromised a patient, where infection may lead to fatal outcomes⁶. However, preoccupation comes from CoVs may spill from natural hosts, infect intermediate hosts, and finally reach human populations⁷, like the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) caused⁸.

Animal origins

The SARS-CoV emerged in 2002⁹. The SARS-CoV transmission was initially linked to the Himalayan palm civet (*Paguma larvata*)¹⁰. However, there are other animal species involved. Animals such as bats but also Chinese ferret-badgers (*Melogale moschata*) and raccoon-dogs (*Nyctereutes procyonoides*)^{11,12} have been involved. A decade later, other CoVs caused preoccupation when the epidemiological links of the Middle East Respiratory Syndrome coronavirus (MERS-CoV) between human and camel cases were also confirmed^{13,14}, indicating animal-human transmission was a recurrent event for CoVs. More recently, during the last month of 2019, a new CoV emerged in Wuhan City in Hubei Province of mainland China, causing a mostly mild respiratory disease, with fatal consequences for elders and people with co-morbidities^{15,16}. The outbreak has been associated to a wet market where more than 120 live animal species were found, which people are in contact with or consume different animals, primarily fish and sea food^{4,17-20}. The virus was initially named 2019-nCoV, but the name was later changed to SARS-CoV-2, and the disease

it caused was named Coronavirus Disease 2019 (COVID-19)²¹. While the origin of the virus has been related to SARS-like CoVs circulating in bat populations, an intermediate host between bats and humans is yet to be determined²². Multiple phylogenetic studies have also served as an approach for hypothesis in the animal origins of SARS-CoV-2^{15,16}. At the moment, multiple animals are a matter of investigation as possible susceptible hosts for SARS-CoV-2²³.

SARS-CoV-2 Infection in Domestic Animals and Felines

Throughout SARS-CoV-2 studies, there have been concerns about infection in animals, mainly domestic, and there have been sporadic reports in dogs²⁴ and, subsequently, feline case in Hong Kong²⁵. That domestic cat was the property of an adult man hospitalized due to SARS-CoV-2 infection and was quarantined on March 30, 2020. After veterinary examination, nasal, oral, and rectal swabs were collected when the cat was admitted to the quarantine center. All samples tested positive for RT-qPCR for SARS-CoV-2²⁵. Another domestic cat in Belgium, living with a human diagnosed with SARS-CoV-2 infection have also been reported to be infected with SARS-CoV-2²⁶. Additionally, recently a tiger tests positive for SARS-CoV-2 at the Bronx Zoo in New York City, while six others are exhibiting signs consistent with the SARS-CoV-2 infection²⁷.

In addition to the reports mentioned above, major international concern has been reached over new data generated in two studies about SARS-CoV-2 in cats²⁸. First, it was a study conducted at five cats to investigate the susceptibility of them and other animals in close contact with humans with SARS-CoV-2 infection. They found canines, pigs, chickens, and ducks were not susceptible to the virus, while ferrets and cats were. Interestingly, the study also suggested that transmission between infected and non-infected cats as possible, as one naïve cat became positive after having close contact with a previously infected cat. In the study, cats were intranasally inoculated with 10⁵ PFU of CTan-H, an isolated virus from a human (SARS-CoV-2/CTan/human/2020/Wuhan)²³. After six days, two cats were euthanized, and the viral RNA was detected in the nasal turbinates, soft palates, and tonsils of both animals, in the trachea of one animal, and

the small intestine of the other. However, viral RNA was not detected in the lungs. A similar result was obtained in the cats that were euthanized after 12 days. Antibodies against SARS-CoV-2 were detected in all three virus-inoculated subadult cats and one exposed cat by use of an ELISA and neutralization assay, although without relevant clinical findings²³. According to the authors, the cats used in the study were outbred and were also highly susceptible to SARS-CoV-2, which replicated and transmitted efficiently to naïve cats²³.

The other study focused mainly on detecting specific serum antibodies in cats infected with SARS-CoV-2²⁹. The authors assessed a cohort of serum samples collected from cats in Wuhan, 102 of them obtained after the beginning of the COVID-19 emergency, and 39 before the start of this outbreak. 15 out of 102 (14.7%) serum samples collected after the beginning of the outbreak were positive for antibodies against the receptor-binding domain (RBD) of SARS-CoV-2 by indirect enzyme-linked immunosorbent assay (ELISA). Among the positive samples, 11 had SARS-CoV-2 neutralizing antibodies with a titer ranging from 1/20 to 1/1080. The 39 serum samples collected before the outbreak's onset were negative²⁹. Additionally, no serological cross-reactivity was detected between the SARS-CoV-2 and type I or II of feline infectious peritonitis virus (FIPV). According to their results, the authors suggested that the studied cat population in Wuhan was infected with SARS-CoV-2 after the start of the outbreak²⁹.

The U. S. Department of Agriculture (USDA), U.S. Centers for Disease Control and Prevention (CDC), National Veterinary Services Laboratories and Wildlife Conservation Society (WCS) have confirmed that big cat Nadia, as a four-year-old Malayan tiger was found positive for SARS-CoV-2 and thereby is the first animal acquiring the SARS-CoV-2 infection through human workers at the Bronx Zoo, New York, United States³⁰. Several other lions and tigers inside the Bronx Zoo also presented clinical signs of respiratory distress as claimed by USDA but have not been tested to date by laboratory investigations³¹. The World Organization for Animal Health (OIE) has advised as SARS-CoV-2 is widely prevalent in the human population, hence the risk of its transmission to jointly residing pets, domestic animals, and

zoo animals cannot be ignored. This probability was confirmed after getting positive reports of SARS-CoV-2 from dogs, cats and tigers, recently from different countries³². The U.S. CDC has recommended persons who are asymptomatic but suspected for SARS-CoV-2 or those who are infected should avoid proximity to susceptible animals³³. More recently in New York also, two cats reportedly tested positive for SARS-CoV-2 in New York. Both had owners who were COVID-19 positive, and both animals were reportedly exhibiting respiratory signs. Additional samples are reportedly being sent to the National Veterinary Services Laboratories for confirmation³⁴.

The present results cannot be separated from the results previously obtained during the beginning of the century during the first SARS-CoV outbreak. As is well known, SARS-CoV-2 is a virus highly related to SARS-CoV, causing the pandemic in late 2002 and that by mid-2003 was distributed to 29 countries, leaving an estimated number of 8,098 people 2002⁹. During this pandemic event, the presence of SARS-CoV was also reported in cats in places where positive symptomatic humans lived, some of these animals with signs of disease³⁵. As in the present outbreak, studies of experimental infection in cats and ferrets demonstrated the high infectious capacity of SARS-CoV in these species, evidencing the spread of infection to multiple organs and viral excretion with the ability to infect susceptible animals in close contact³⁶. From a pathological point of view, it was shown that cats could carry the disease subclinically and present lesions similar to those found in humans infected with this virus, characterized by the presence of diffuse alveolar damage associated with the presence of SARS-CoV and, especially in cats, the presence of tracheobronchadenitis³⁷.

Supporting the *in vivo* experimental studies, recent *in silico* analysis of the interaction between the SARS-CoV-2 spike protein and the cellular receptor ADE2 in various animal species, suggests that the majority of wild and domestic cats are susceptible to SARS-CoV-2. However, the domestic cat would be more likely to act as a reservoir or intermediary animal, considering the interaction between these cellular and viral proteins is very similar to observed in humans³⁸.

Feline coronaviruses

Cats can naturally become infected with

other Coronaviruses, such as feline coronavirus (FCoV)³⁹, which belongs to the Alphacoronavirus genus, along with canine coronavirus (CCoV) and transmissible gastroenteritis virus (TEGV) of pigs. Alphacoronavirus species⁴⁰. The FCoV is known to occur in two pathotypes: the enteric coronavirus that invades the digestive tract – FECV (Feline Enteric Coronavirus Virus), and the virus responsible for feline infectious peritonitis (FIP) is known as FIPV (Feline Infectious Peritonitis Virus)⁴¹. Feline and canine coronaviruses usually do not infect human beings and mostly affect dogs and cats. However, the most recent report of one big cat at the zoo found positive for SARS-CoV-2, the emerging novel coronavirus that was initially claimed to affect man only but not the animals³³.

The FECV virus is responsible for the infection of cats' digestive epithelial cells. This infection is mainly asymptomatic and remains undetected or causes mild and transient diarrhea⁴². The virus is highly contagious and is believed to transmit horizontally through the fecal-oral route. Kittens are usually infected with FECV at an early age in the litter, most likely through viruses in the mother's feces. Since persistently infected cats shed the virus in their feces for prolonged periods, they play a central role in the spread and maintenance of FECV in populations. This infection can be diagnosed by smearing cells from the anal swabs and by detecting the virus's RNA using the Polymerase Chain Reaction⁴³. FIP is a fatal disease, being common in young cats (under three years old and especially two years old). The virus is not infectious, but it has been suggested to arise from the FECV mutation in a small percentage of infected cats and then causes FIPV disease^{44,45}. Mutations in the accessory genes and the FCoV S gene have been associated with the development of FIP. FIPV replicates efficiently in monocytes and macrophages and induces systemic diseases. The disease is characterized by fibrinous and granulomatous serositis, serous effusion rich in proteins in body cavities, and granulomatous lesions (pyogranulomas)⁴⁶. Clinical signs of infected cats include lethargy, anorexia, weight loss, or inability to gain weight, stunted growth in younger cats⁴⁴.

The definitive diagnosis of FIPV is based on the histopathological examination of the tissues, generally with the detection of the virus

within the lesions by immunohistochemistry (IHC) for the FCoV antigen. Immunostaining of the FCoV antigen in secretion samples is also an option in cases with a secretion biochemical and cytological characteristics compatible with FIP. There are currently no treatments available for FIPV, although some novel treatments, including protease inhibitors, are promising⁴⁷.

For many years, the origin of FIPV was unclear and was discussed in quite a controversial way. In the first investigations, FECV and FIPV were considered different virus species. In subsequent studies, FECV and FIPV were proposed to be closely related to viruses with distinct virulence properties. In recent years, many aspects of FCoV biology have been studied, providing an attractive new look at the pathogenesis of FIP; however, several important questions remain to be answered⁴⁸.

Here, we have discussed the principal characteristics of two different infectious agents: SARS-CoV-2 and FCoV. While the latter is a well-known infectious agent of felids, the former appears to arise as a new threat to these animals. The reasons behind this phenomenon could be related to the relative similarity between the human and the angiotensin-converting enzyme 2 (ACE2), which is used by the SARS-CoV-2 to colonize the cells⁴⁹. However, how the SARS-CoV-2 could infect cats, is a concerning aspect yet of being elucidated. Indeed, the worrisome findings of recent case reports and studies, move toward more research and careful management of the interaction between humans and cats in the context of COVID-19.

CONCLUSIONS

Definitive conclusions in this matter cannot be generated until further investigations are performed. Surveillance for SARS-CoV-2 in cats should be considered as an adjunct to a better understanding of COVID-19's epidemiology and dynamic in humans and animals. As the current reports have shown that cats can be infected as a consequence of close contact with SARS-CoV-2 infected people, further considerations must be taken to reduce the risk of infection to cats. The available studies have not addressed the study of the human-cat transmission of SARS-CoV-2. Therefore, the question about the role of cats

in the transmission of SARS-CoV-2 to humans is still unanswered. While this topic may become a matter of concern and debate until more research data is available, cats must not be considered part of the transmission cycle of SARS-CoV-2.

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CONFLICT OF INTEREST

The listed author(s) declare no conflict of interest in any capacity, including competing or financial.

AUTHORS' CONTRIBUTION

AJRM conceived the idea of the Mini-Review. DKBA perform a review of the literature on the topic related; all authors read the cited literature; AJRM developed the first draft of the manuscript; all authors contributed consequently with newer versions; all authors approved the final submitted version.

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ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

AVAILABILITY OF DATA

Not applicable.

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