CHAPTER

6

Zoonosis and reverse zoonosis of SARS-CoV-2 from the perspective of the One Health

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ABSTRACT

According to the WHO, as of July 26, 2022, there were 568,773,510 confirmed cases of COVID-19 and 6,381,643 deaths recorded because of this disease worldwide (WHO, 2022). The etiologic agent of COVID-19 is the SARS-CoV-2 coronavirus, an RNA virus of the family Coronaviridae and subfamily Orthocoronavirinae (XAVIER et al., 2020). Humans infected with SARS-CoV-2 have clinical signs such as fever, non-productive cough, shortness of breath, and may progress to pneumonia, acute respiratory syndrome, and kidney failure, although a few other signs, symptoms, and clinical forms may be observed less frequently (SAXENA et al., 2020). The evolution of the infection to severe acute respiratory syndrome can lead to death from COVID-19. These patients have a strong inflammatory response, like that of cytokine release syndrome, and increased migration of neutrophils to lung tissue triggered by inflammatory mediators released by epithelial, endothelial cells of infected tissue and by immune system cells attracted to the site of infection (MANGIAVACCHI et al., 2020; MERAD et al. 2022; BHARDWAJ et al., 2022; LI & LI, 2022).

Keywords: COVID-19, Zoonosis.

1 INTRODUCTION

According to the WHO, as of July 26, 2022, there were 568,773,510 confirmed cases of COVID-19 and 6,381,643 deaths recorded because of this disease worldwide (WHO, 2022). The etiologic agent of COVID-19 is the SARS-CoV-2 coronavirus, an RNA virus of the family Coronaviridae and subfamily Orthocoronavirinae (XAVIER et al., 2020). Humans infected with SARS-CoV-2 have clinical signs such as fever, non-productive cough, shortness of breath, and may progress to pneumonia, acute respiratory syndrome, and kidney failure, although a few other signs, symptoms, and clinical forms may be observed less frequently (SAXENA et al., 2020). The evolution of the infection to severe acute respiratory syndrome can lead to death from COVID-19. These patients have a strong inflammatory response, like that of cytokine release syndrome, and increased migration of neutrophils to lung tissue triggered by inflammatory mediators released by epithelial, endothelial cells of infected tissue and by immune system cells attracted to the site of infection

(MANGIAVACCHI et al., 2020; MERAD et al. 2022; BHARDWAJ et al., 2022; LI & LI, 2022).

Coronaviruses generally infect various animal species and cause respiratory, enteric, hepatic, renal, neurological, and in some cases, systemic diseases. Most coronaviruses have specificity for one type of host (WANG & YOO, 2022), but some may acquire the ability to infect a wider range of animal species from mutations (CAVANAGH & BRITTON, 2021).

Coronaviruses were not considered highly pathogenic among immunocompetent humans until the emergence of SARS-CoV-1 in China in 2002. quickly spread around the world (LEE et al., 2003; PEIRIS et al., 2003), but no cases of disease were reported after 2004 (MANN et al., 2020). MERS was a coronavirus reported in 2012, with the isolation of the previously unknown virus from respiratory samples from a patient in Jeddah, Saudi Arabia. The dynamics of MERS virus infection are still poorly known, but research indicates dromedary bats and camels as intermediate reservoirs (PEIRIS & PERELMAN, 2022). The virus is still circulating in the Middle East, with more than 2600 cases reported in 27 countries as of July 2022 (EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL, 2022). SARS-CoV-2 emerged in Wuhan, China, in December 2019, and by March 2020 had established itself as a pandemic, being the coronavirus with the greatest impact on global public health to date.

The SARS, MERS, and COVID-19 outbreaks share many similarities in clinical presentation and form of transmission. Although acute respiratory tract infections are the most common clinical manifestations, other organs can be affected, and systemic diseases are not uncommon in these viruses. Another striking feature is the zoonotic origin. According to Su et al. (2016) and Forni et al. (2017), analyses of genetic similarities allow us to affirm that all coronaviruses that affect humans have their origin in viruses that originally affected animals. The emergence of SARS-CoV-2 as a human pathogen is no exception, since more than 60% of emerging infectious diseases originate in wild animals (JONES et al., 2008). Zoonoses do not occur in a single sense in the dynamics of infection, from animals to humans. Like other diseases, the ability of animals to be infected by SARS-CoV-2 from contact with humans has already been demonstrated.

The objective of this work is to perform an analysis of the current scientific literature, regarding the possibility of zoonosis and zooanthroponosis of SARS-CoV-2 from the perspective of Single Health and possible implications for the future of the evolution of the virus.

2 METHODOLOGIES

The present work has the methodological design of a narrative review of the literature on the incidence of SARS-CoV-2 in animals and the impacts of the virus as an agent of zoonosis and reverse zoonosis. The review evaluated scientific articles available in the PubMed, SciELO and Google

Scholar databases, as well as medical and veterinary microbiology books. The descriptors used, in various combinations, were: "SARS-CoV-2"; " animals", "zoonosis", "reverse zoonosis”, “spillover", "spillback", "One Health", "interspecies transmission". Due to the theme addressed, the time frame of the literature review was established between the years 2019 and 2022. The inclusion criterion of articles was the verification of results consistent with the objective of the research. Of these studies, studies that presented laboratory confirmation by PCR, serology and equivalent diagnostic resources were selected. Articles that did not meet the criteria for evaluation were excluded, such as deficient or inadequate methodology, inconsistent data, and lack of laboratory confirmation. After reading the title and abstract, the material that presented consistency with the researched theme and the articles and reports read in full were selected. Then, the analysis of the material was performed, distribution of the results by related taxonomic groups, considerations on aspects of Single Health and writing of the critical review.

3 DISCUSSIONS

The identification of virus receptors contributes significantly to the understanding of cellular and tissue tropism and the ability to infect hosts, in addition to explaining aspects of the pathogenesis of the virus (EVANS, 2008). Like the first coronavirus (SARS-CoV) of greater pathogenicity for humans, SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to primarily enter hair cells of the bronchial epithelium and pneumocytes (XAVIER et al., 2020; SHANG et al. 2020; ZHOU et al., 2020). Diverses mammals have compatible ACE2 receptors in their cells, and the degree of affinity between these receptors and the SARS-CoV-2 spike protein is a predictor of the possibility of infection (ALEXANDER et al., 2020; BOURICHA et al., 2020; LAM et al., 2020; KUMAR et al., 2020; SHEN et al. 2020; DEVAUX et al., 2021). The possible presence of other relevant factors in the interaction of SARS-CoV-2 with the host cell, such as compatible receptors for type C lecithin, heparan sulfate, and sialic acid (CLAYTON et al., 2022; KUCHIPUDI et al., 2022) may or may not contribute to the success of viral infection capacity according to the physiology of each animal species.

The origin of SARS-CoV-2 is uncertain, but many studies point to evidence that bats of the species *Rhinolophus lepidus* were the original hosts of the virus that gave rise to the pathogen that caused the pandemic in humans, with the possibility of an intermediate host (ZHOU et al., 2020). Studies analyzing the genetic composition propose that coronaviruses originating from bats are the basis of all other types of coronaviruses that infect mammals (VIJAYKRISHNA et al., 2007; WOO et al., 2012). Thus, the search for reverse zoonosis of SARS-CoV-2 in bats is a very plausible hypothesis (OLIVAL et al., 2020; COX-WITTON et al., 2021), although virus replication in lab-grown renal cells of *Rhinolophus lepidus* bat is considered limited (AUERSWALD et al., 2022). A survey of 129 bats in Italy revealed no positivity for SARS-CoV-2 (DAKROUB et al., 2022). The dynamics of interaction between humans and bats may not be favorable for the spillover of SARS-CoV-2 between species, however, they do not exclude the hypothesis of reverse zoonosis. One factor to consider is that bats have a great diversity of species and the structure of ACE2 receptors varies substantially among chiropractor species (YAN et al., 2021). And in an experimental study, Schlottau et al. (2020) intentionally infected nine bats of the species Rousettus aegyptiacus, of which et (78%) developed transient infections with viruses detectable by PCR, in the nasal cavity, trachea and lung, presenting Symptoms of rhinitis. Among three bats not inoculated and put in contact with the infected animals, one individual acquired the virus by contagion.

Rats' ACE2 receptors are poorly matched with the SARS-CoV-2 virus spike. For this reason, genetically modified acts using the CRISPR/Cas9 technique with the addition of the human ACE2 receptor expression gene have been used as a model for studying the pathogenesis and transmission of SARS-CoV-2 (SUN et al., 2020; STOLP et al. 2022). There is little affinity of the rat natural ACE2 receptor for the SARS-CoV-2 spike protein (KOLEY et al., 2021; SHOU et al., 2021). This low compatibility of the receptor in the genus Rattus explains the result of Miot et al. (2022), that among 217 rats of the species Rattus *norvegicus and Rattus tanezumi* found negative results in all PCR tests. These authors, however, verified that in one of the rats the serological test for detection of antibodies against SARS-CoV-2 was positive, indicating that this individual came into contact with the virus and obtained an immune response. Some emerging variants of SARS-CoV-2 have mutations that have the potential for greater adaptability to the murine ACE2 receptor, with the possibility of evolving to a greater tropism for this group of animals (SHUAI et al., 2021). The possible adaptation of SARS-CoV-2 with the acquisition of infective capacity for domestic rats could have a major impact on global public health.

The analysis performed by Preziuso (2020) of ACE2 receptors in rodents of the Order Lagomorfa, which include rabbits and hares, pointed to a high compatibility for the spike protein of SARS-CoV-2 and the possibility of susceptibility of these animals to the virus. Mykytyn et al. (2021) conducted experimental infection tests on three rabbits (*Oryctolagus cuniculus*) in the Netherlands to verify the feasibility of developing SARS-CoV-2 in these animals. The tests demonstrated the susceptibility of this species to the virus. The following year, Fritz et al. (2022) examined blood samples from 144 rabbits raised as pets in France and reported positivity in one animal (4.86%), based on the results of detecting both antigens and antibodies. These authors assess that the low prevalence may be an indication that rabbits are little susceptible to natural infection by SARS-CoV-2 and that, at least in relation to the currently circulating strains, they do not represent a risk of becoming reservoirs for the virus.

Golden hamsters (Mesocricetus auratus) are animals of the family Cricetidae widely used in laboratory experimentation and as pets. It was already known that this species demonstrated susceptibility to SARS-CoV-1 by the natural compatibility of ACE2 receptors (ROBERTS et al., 2003). Sai et al. (2020) infected golden hamsters via intranasal spray to evaluate the replication capacity of SARS-CoV-2 in this species. The virus replicated in cells of the nasal mucosa, bronchial epithelium, and areas of the lung. Viral antigens were found in the epithelial cells of the duodenum and viral RNA detected in the feces. The researchers reported that infected hamsters were able to transmit SARS-CoV-2 to other individuals of the species occupying the same cages, mainly by direct contact and through droplets, a result like that of the experiment conducted by Dowall et al. (2021) regarding transmission between animals in the same environment. Song et al. (2021), in a similar experiment, further found that SARS-CoV-2 infected hamsters systemically, with diffuse alveolar damage, and damage to the spleen, lymph nodes, different parts of the digestive system, liver adrenal gland, ovary, vesicular gland and prostate. Blaurock et al. (2022) state that the high susceptibility of golden hamsters to SARS-CoV-2 and the development of the virus in these rodents from viral loads considered small are indicative that these animals can be considered as potential sources of transmission to humans.

Yen et al. (2022) sequenced the SARS-CoV-2 genome obtained from golden hamsters and humans caring for these animals in pet shops. These authors presented evidence that pet hamsters can be naturally infected with SARS-CoV-2 and transmit the virus to humans. Comparison of coronavirus genetic sequences shows strong evidence of transmission of the Delta variety of SARS-CoV-2 from hamsters to humans, followed by human-to-human transmission of this virus. The movement of animals imported from one country to another, as observed by testing in Hong Kong among hamsters from the Netherlands, can be a means of diffusion of new strains (KOK et al., 2022), contaminating other animals and humans.

Other species in the family Cricetidae were also susceptible to experimental SARS-CoV-2 infections. Fagre et al. (2021) demonstrated that the deer rat (Peromyscus maniculatus) and the desert rat (Neotoma lepida) are susceptible to infection and can transmit the virus between individuals through direct contact or by aerosols. Unlike the golden hamsters investigated in the other studies, these are native species in North America, and the possible spread of the virus to wild deer rats poses a risk to the populations of these species and to the balance of the environment.

Ferrets (Mustela putorius) are mustelids highly prized as companion animals in several countries of the world and are susceptible to SARS-CoV-2. Giner et al. (2021) investigated the prevalence of SARS-CoV-2 in 127 ferrets kept in captivity in Spain. Dois individuals (1.57%) presented anti-SARS-CoV-2 antibodies, which remained detectable in the ELISA test for the following

129 days, demonstrating the exposure of these animals to the virus. Gortázar et al. (2021) performed quantitative PCR tests on 71 ferrets belonging to seven owners of these animals in the same country and detected SARS-CoV-2 in six individuals (8.4%), with viral loads indicative of infection. The authors concluded that ferret infection occurs in circumstances where the viral load to which they are exposed is high. Račnik et al. (2021) also presented a case report of SARS-CoV-2 transmission from an owner to the pet in Slovenia, in which the animal was hospitalized with gastroenteritis, vomiting, anorexia, and profuse diarrhea. For the diagnosis of infections in humans and animals, PCR and genotyping tests were performed, which confirmed that the viruses belonged to the same lineage. There is evidence that ferrets exhibit some resistance to infection when exposed to low viral load (SHI et al., 2020; Ryan et al., 2021; MONCHATRE- LEROY et al., 2021), confirming the hypothesis of Gortáz ar et al. (2021). However, after experimental infections become effectively established, these animals are highly susceptible, developing acute broncheolitis, presenting high levels of viral replication and contamination among individuals who share the same environment through direct contact, or through urine, feces and aerosols (KIM et al., 2020; Kutter et al., 2021; Richard et al., 2021; SAWATZKI et al., 2021) The contamination of ferrets by SARS-CoV-2 through viral particles dispersed by aerosols in the air by infected animals can exceed one meter away (RICHARD et al., 2021).

The mink anduropeum (Mustela mink) and the mink american (Neovison mink) are mammals of the family Mustelidae widely bred in various countries for the use of the skin as a material for clothing. In April 2020, Oreshkova et al. (2020) investigated the first outbreak of SARS-CoV-2 in mink on two breeding farms in the Netherlands. At least 18 animals died from the infection, most of them from interstitial pneumonia. In the following months, several other mink farms recorded outbreaks of SARS-CoV-2 in the same country (MOLENAAR et al., 2020; LU et al., 2021; MUNNINK et al., 2021) and in other countries such as Denmark, Poland, Spain, United States, Sweden, Italy, France, Lithuania, and Canada (HAMMER et al., 2021; Rabalski et al., 2020; ECKSTRAND et al., 2021; SHARUN et al., 2021). The rapid expansion of SARS-CoV-2 in mink from commercial breeding is linked to an adaptive mutation of the virus, which has made the spike protein more compatible with these animals' ACE2 receptors (STATENS SERUM INSTITUT, 2020; DYER, 2020; FRUITS & DEVAUX, 2020; LARSEN & PALUDAN, 2020; BARUA et al. 2022). Cases of SARS-CoV-2 transmission from mink to humans have been reported in Denmark and the Netherlands (STATENS SERUM INSTITUT, 2020; DYER, 2020; HAMMER et al., 2021; Munnink et al., 2021). Authorities in the European Union have declared that all mink farms are considered at risk and active monitoring should be carried out for the early detection of infection and the elimination of herds in which cases of SARS-CoV-2 infection are verified (EUROPEAN FOOD

SAFETY AUTHORITY AND EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL et al., 2021). Harrington et al. (2021) warned of the possible risk of extravasation of the strains most adapted to wild mink populations, a hypothesis confirmed by Aguiló-Gisbert et al. (2021) a few months later, when they found two free-living mink carrying SARS-CoV-2 in Spain. The rapid transmission of species-adapted SARS-CoV-2 and high mortality rates in confined animals make the consequences of the spread of the novel coronavirus in wild mink populations alarming and unpredictable. Manes et al. (2020) suggest that the rapid adaptation of ASRS-CoV-2 in mustelids may initiate panzoonosis.

Padilla-Blanco et al. (2022) reported the presence of SARS-CoV-2 in a European otter in a water reservoir in Valencia, Spain. The researchers detected the virus through two PCR-type test kits and performed genotyping of the found virus. Analysis of the genetic sequence showed that much of the SARS-CoV-2 genetic material infecting the otter was common to strains circulating among humans, but other sequences were divergent from the known strains. This genetic arrangement constitutes a unique variety of the virus and suggests that SARS-CoV-2 mutations may be evolving in host populations of the family Mustelidae.

Species of the family Procyonidae have shown some susceptibility to SARS-CoV-2. Freuling et al. (2020) conducted an experimental study with infection induced by intranasal spray containing SARS-CoV-2 that demonstrated that raccoon (Procyon lotor) is susceptible to infection by the virus and can transmit to other individuals by direct contact. The infected raccoons showed subtle clinical signs. The histopathological study showed evidence of viral replication and tissue lesions only in the nasal turbinates. The study also demonstrated that experimentally infected animals can transmit SARS-CoV-2 to other uninfected animals through direct contact. Allender et al. (2022) performed PCR-type tests on nasopharyngeal samples in animals at the Chicago Zoo, United States of America, and found positivity for SARS-CoV-2 in a coati (Nasua nasua). The animal showed no clinical signs of the disease. Further studies on the possibility of infection in free-living Procyonidae are needed, since these animals often frequent anthropic environments in search of food (DEMENY et al., 2019; BARCELAR et al., 2022), with the possibility of direct or indirect contact and contamination by humans.

Domestic dogs (Canis familiaris) are the most popular companion animals in the world, in close contact with their owners, and for this reason much more studied than other species of animals regarding the possibility of infection by the new coronarivus. SARS-CoV-2 has been detected in domestic dogs (Canis familiaris) in several studies, but these animals are asymptomatic or with mild signs and symptoms during infection (SIT et al., 2020; HAMER et al., 2022; BARROSO-ARÉVALO et al., 2022; JAIRAK et al., 2022; Medkour et al., 2022; Rivero et al., 2022; ZAMBRANO-MILA et al., 2022). Although the affinity of the ACE2 receptor in dogs for SARS-CoV-2 is considered high (WU et al., 2020; Koley et al., 2021; MA & GONG, 2021; ZHANG et al, 2021), this factor is not the only predictor of susceptibility to the virus (WU et al., 2020; Koley et al., 2021; MA & GONG, 2021; PIPLANI et al., 2021). Patterson et al. (2020) examined 919 domestic dogs in Italy at the height of the pandemic in this country, finding antibodies against SARS-CoV-2 in 3.3% of these animals, but no dogs tested positive for viral particles. Barroso et al. (2022), in research with 22 dogs in Portugal whose owners were positive for SARS-CoV-2, found seropositivity in 50% of the animals, but PCR was reactive in only one dog. These results show that Canis familiaris does not constitute a good host or has efficient immune defense mechanisms for the virus strains circulating in those countries. To date, there is no evidence of transmission of SARS-CoV-2 from dogs to humans (NADERI et al., 2022; OLIVEIRA et al., 2022).

Zambrano-Mila et al. (2022) analyzed the oral and nasal smear samples of three dogs from Amazonian indigenous communities with high prevalence of COVID-19 among humans. Two PCR kits that analyzed different viral particles were used to confirm the presence of the virus. The result showed positivity for the three dogs examined. The authors point out that the occurrence of SARS-CoV-2 in dogs living in the Amazon rainforest is worrisome, due to the risk of transmission to other animals of the native fauna that interact with the pets, representing a risk from the perspective of unique health.

Domestic cats (Felis catus), like dogs, are pets exposed to contact with the SARS-CoV-2 virus by proximity to infected humans. Cats have susceptibility to the virus, verified both by experimental infections (GAUDREAULT et al., 2020; BOSCO-LAUTH et al., 2020; Halfmann et al., 2020; SHI et al., 2020; BRAUN et al. 2021; PATANIA et al., 2022) as well as by the discovery of animals that acquired the infection naturally (RUIZ-ARRONDO et al., 2020; AART et al., 2021; BARROSO-ARÉVALO et al., 2021; CURUKOGLU et al., 2021; BRANDÃO et al. 2021; HOSIE et al., 2021; Klaus et al., 2021; Natale et al., 2021; PAGANI et al., 2021; BARROSO et al., 2022; JAIRAK et al., 2022, MOHEBALI et al., 2022). Many cats have had clinical manifestations (GAUDREAULT et al., 2020; BOSCO-LAUTH et al., 2020; Halfmann et al., 2020; SHI et al., 2020; AART et al., 2021; BRANDÃO et al. 2021; BRAUN et al. 2021; HOSIE et al., 2021; Natale et al., 2021; PAGANI et al., 2021; PATANIA et al., 2022) with varying degrees of severity. Brandão et al. (2021) point out one of the most common characteristics in the domesticated cats examined: free access to the environment outside the home. This habit is particularly important for a potential increase in the viability of virus dispersal, since these cats in the circulation outside the home have contact with humans, cats and animals of other species. The possibilities of zoonotic and reverse zoonosis transmission of SARS-CoV-2 are even more plausible since research shows transmission of the virus directly between cats

(GAUDREAULT et al., 2020; Halfmann et al., 2020; BRAUN et al., 2021; SHI et al., 2020; BARROSO et al., 2022), and among cats and other species, such as the acquisition of mink-borne viruses (AART et al., 2021). Although Chaintoutis et al. (2022) state that there is no record of adaptive mutations in SARS-CoV-2 strains found in cats when compared to strains circulating among humans, Braun et al. (2021) found that the Ômicron variety with mutation in the position of the amino acid H655Y sees rapid transmission between cats under experimental conditions, resulting in an affinity specific that calls for further investigation. The mutation in the position of the amino acid H655Y in the spike of the virus is found in many of the "subvariants of interest" according to the classification of the World Health Organization, with the potential to escape the immunity conferred by the vaccine antigens currently used (HARVEY et al., 2021; OU et al., 2022).

Big cats are susceptible to SARS-CoV-2 infections. Cases of natural infection have been recorded in cats of the genus Panthera, such as lions (Panthera leo) in the wild (MISHRA et al., 2021) and in zoos (BARTLETT et al., 2021; FERNÁNDEZ-BELLON et al., 2021; MCALOOSE et al., 2021; Karikalan et al., 2021; NAGY et al., 2022); captive tigers (Panthera tigris) (MCALOOSE et al., 2020; WANG et al., 2020; BARTLETT et al., 2021; CUSHING et al., 2021; GROME et al., 2022; NAGY et al., 2022); leopards (Panthera pardus) in the wild (MAHAJAN et al., 2022); and snow leopards (Panthera uncia) in zoo (WANG et al., 2022). SARS-CoV-2 infection has also been reported in suçuarana (Puma concolor) (GIRALDO-RAMÍREZ et al., 2021). As with domestic cats, some animals showed signs and symptoms with varying severity (MCALOOSE et al., 2020; BARTLETT et al., 2021; CUSHING et al., 2021; FERNÁNDEZ-BELLON et al., 2021; Karikalan et al., 2021; GROME et al., 2022). The incidence of SARS-CoV-2 of the Delta variety, with symptomatic individuals among wild Asian lions (MISHRA et al., 2021) is worrisome due to the threat to the population of only 523 remaining individuals of this subspecies in the wild, in a restricted region of the province of Gujarat, India, according to an estimate made in the year 2018 (SINGH, 2018).

White-tailed deer (Odocoileus virginianus) are the most common deer in North America. These animals are highly susceptible to SARS-CoV-2 infection. In a survey of 151 deer in Iowa, United States of A, Kuchipudi et al. (202 2) found genetic material of the virus in 33.2% of the animals, with an epidemic peak between November 23, 2020, and January 10, 2021, in which 82.5% of the individuals examined were positive for PCR tests for the detection of SARS-CoV-2. The genetic analysis identified 12 different strains of SARS-CoV-2, and the coincidence in the predominance of the circulating strains in deer and humans according to geographic distribution suggests that there were multiple events of spread by reverse zoonosis, in addition to the transmission of SARS-CoV-2 between deer. Hale et al. (2022) conducted a similar survey in the state of Ohio, and among 360 animals, 129 (35.8%) were positive for the detection of SARS-CoV-2 through the PCR technique, with records of three different strains of the virus. Vandegrift et al. (2022) detected SARS-CoV-2 through PCR testing using material obtained from nasal smears of white-tailed deer on Staten Island, New York, and found positivity in 7 of the 68 (10.29%) of the deer sampled. Viral genome sequencing identified that the Ômicron variety of SARS-CoV-2 circulating among deer is phylogenetically close to that prevalent in humans in New York City. Marques et al. (2022) conducted a survey in the state of Pennsylvania, United States of America, in which they examined 123 Odocoileus virginianus nasal smear samples analyzed by PCR, of which 20 (16.3%) were positive for SARS-CoV-2. Alpha and delta variants were found.

Chandler et al. (2021) investigated in four states of the same country that involved the serology analysis of 385 blood samples from white-tailed patients living in the vicinity of cities that revealed that 485 of the animals had antibodies against SARS-CoV-2, confirming exposure to the virus. The serology of white-tailed animals in free-living animals in Texas revealed that in the year 2020 no sample was found with positive serology for antibodies against SARS-CoV-2, but among the 54 samples collected in the year 2021, 20 (37%) were positive (PALERMO et al., 2021). These results point to a high prevalence rate of SARS-CoV-2 in populations of this species in a wide geographic distribution in the United States of America.

Experimental infections of white-tailed deer individuals confirmed a high rate of transmission of the virus among the animals, as well as tropism and multiplication of SARS-CoV-2 in several organic tissues of this species. The infections were considered subclinical, but the viral load dispersed through the nasal secretion and feces of the infected animals was considered high, as well as the transmission rates among individuals of Odocoileus virginianus (PALMER et al., 2021; MARTINS et al., 2022).

In addition to the high incidence rate, an important feature for the epidemiological course of SARS-CoV-2 in white-tailed deer is the multiplicity of strains circulating among these animals, as verified by Chandler et al. (2021), Marques et al. (2022) and Kuchipudi et al. (2022). Marques et al. (2022) found that the alpha strain persisted in the deer population after replacing the prevalence in humans with the delta variety, and the genotype of the alpha variants obtained from deer diverged significantly from those infecting humans, presenting mutations consistent with adaptability to the new host species. Hale et al. (2021) indicated that deer-to-deer viral transmission of viruses B.1.2, B.1.582, and B.1.596 allowed the virus to exhibit changes in the spike protein, including the receptor binding domain, and other infrequent mutations in strains circulating between humans. Pickering et al. (2022) have identified a new highly divergent strain of SARS-CoV-2 in a white-tailed deer in Ontario, Canada. This lineage has the highest number of genotype changes identified to date, with 76 mutations, including 37 changes in the viral genotype previously associated with non-human hosts.

Although there is no evidence of contamination of humans by contact with white-tailed deer (HALE et al., 2022), there is great potential for eventual transmission, including new variants of SARS-CoV-2, since these animals frequent peri-urban environments (CHANDLER et al., 2021; HALE et al., 2021; KUCHIPUDI et al., 2022). White-tailed deer are appreciated as game meat (BRICEÑO-MÉNDEZ et al., 2021), and the consumption of this animal in human food offers an atypical, but not unlikely, risk of infection due to the multiplication of the virus in a wide variety of tissues and organs in this deer species (PALMER et al., 2021; MARTINS et al., 2022).

The structural characteristics of the ACE2 receptor of old-world primates are predictors of a high susceptibility of these animals to SARS-CoV-2, as they bear up to 99% similarity to the human ACE2 protein (DAMAS et al., 2020; MELIN et al., 2020; SHI et al., 2020). Great apes are susceptible to many of the diseases that affect humans by genetic affinity, especially respiratory viruses (SPELMAN et al., 2013; Negrey et al., 2019). Experimental infections have verified the susceptibility of rhesus monkeys (Macaca mulatta and Macaca fascicularis), with signs, symptoms, and evolution of pathogenesis similar to that of COVID-19 in humans (LU et al., 2020; MUNSTER et al., 2020; ROCKX et al., 2020; SHAN et al., 2020; ZHENG et al., 2020). Contact with humans has been the source of gorilla contamination in zoos (NAGY et al., 2022; ISLAM et al., 2021; GIBBONS, 2021), with mild symptoms of respiratory infection. The possibility of reverse zoonosis for great apes, including chimpanzees and gorillas, has prompted the implementation of protective measures in wildlife reserves across Africa and Asia (GIBBONS, 2021). Non-primate New World monkeys have low susceptibility to SARS-CoV-2 (LU et al., 2020; LIU et al., 2020), possibly due to the lower affinity of the ACE2 receptor, which has a similarity of 92% in relation to the human os cellular receptor, with four differences between the twelve binding sites considered essential for the coupling of SARS-CoV-2 (MELIN et al. 2020; BHATTACHARJEE et al. 2021; ABREU et al., 2021). Research conducted in Brazil with free-living monkeysfound no signs of infection in these animals (SACCHETTO et al, 2020; ABREU et al., 2021).

Other captive animal species have tested positive for SARS-CoV-2, such as hippos (Hippopotamus amphibius) (BBC, 2021), Asian cat bear (Arctictis binturong), spotted hyena (Crocuta crocuta) and mandrill (Mandrillus sphinx) (USDA APHIS, 2022), demonstrating the possibility of a greater number of hosts for the pandemic virus.

According to the Food and Agriculture Organization of the United Nations, One Health is an integrated and unifying approach that aims to balance and sustainably optimize the health of people, animals, and ecosystems. It recognizes that the health of humans, domestic and wild animals, plants, and the environment in general (including ecosystems) are closely linked and interdependent (ONE HEALTH HIGH-LEVEL EXPERT PANEL, 2022). It is a comprehensive approach to understanding the risks to human and animal health, including domestic animals and wildlife, and the health of the ecosystem. These principles are fundamental to a critical analysis of collaborative and interdisciplinary approaches to responding to emerging and emerging diseases. A key factor in this analysis is the inclusion of animal health and the balance of the environment as a component of the prevention, surveillance, control, and mitigation of global diseases. The analysis of the pandemic through the perspective of Single Health is, therefore, the most appropriate approach due to the zoonotic origin and possible reverse zoonosis of the dynamics of transmission of SARS-CoV-2. According to Winck et al. (2022), outbreaks of zoonotic diseases are the result of an ecological, socioeconomic and demographic interconnection that determine conditions for greater contact between the vulnerable human population and wildlife in areas in environmental degradation and for the rapid geographical spread of infections. These circumstances are verified both in the hypotheses of the emergence of SARS-CoV-2 as a human pathogen and in the possible perpetuation of the virus through reverse zoonosis, characterizing the pandemic as an event inseparable from environmental conditions.

The evolution of the various variants of the virus may be related to the continuous spillover between species. Wei et al. (2021) and Sun et al. (2021) analyzed the genetic sequencing of the Ô micron variant and found that this strain had mutations adapted to rodents, which suggests that the Ômicron may have evolved from these hosts. Mutations in the cell receptor-binding protein of Ômicron have potential implications for the progression of the pandemic and for the possible escape of some types of vaccines that use the virus spike as an antigen in immunization (SUN et al., 2021; SHRESTHA et al., 2022; KONISHI, 2022). The variant adapted to mink, with mutations in cluster 5, infected up to 68% of those employed on farms breeding these animals (MOLENAAR et al., 2020; ORESHKOVA et al., 2020; HAMMER et al., 2021).

Cui et al. (2022) points out that the Delta variant was the predominant among infections in animals, but infections were detected by all other variants of greater circulation in the different species investigated, indicating that there are few barriers to transmission between species. According to Bashor et al. (2021), as of October 2021, 14 emerging variants of the SARS-CoV-2 virus had been detected in animals, with mutations in the structure of the capsid, spike and in non-structural genes. These researchers warn that the rapid selection of SARS-CoV-2 variants in animals illustrates that the spillover of infection to new hosts accelerates the evolution of new viral strains, revealing the adaptive plasticity of this coronavirus. A worrying aspect is the great capacity of coronaviruses in general to recombine RNA, expanding the genetic diversity of this pathogen through new strains (GOLDSTEIN et al., 2021). Genetic combination is the process by which nucleic acid molecules of viral RNA exchange fragments, generating a new molecule, with differences in gene expression with possible changes in viral structure or infective capacity. Recombination processes are, together with mutations, the main means of increasing genetic variability. The evolution of the virus by natural selection in different species, with diversity in biochemical and immunological characteristics, selects more adapted varieties that guarantee the perpetuation of viruses with new characteristics. New varieties may exhibit abilities in terms of infectivity and transmission different from the varieties that originated them, including the development of capacities for the jump between species that characterize the zoonotic process. In this sense, the adaptation of SARS-CoV-2 as a viable pathogen in animals poses multiple risks in the evolution of the virus to other mammalian species, including those not yet susceptible to the virus, and to humans.

Animals can become reservoirs of strains that are no longer prevalent in humans, so they can be reintroduced into the population by zoonotic route. The multiplicity of hosts also reflects in the variety of adaptations by mutational pathway, generating a greater number of variants and increasing the possibilities of new epidemic waves between animals and humans. The greater abundance of mutations may also have consequences in the escape of the immune response induced by vaccines that use viral proteins from strains with different structural characteristics from those existing in new variants.

The introduction of new pathogens into sensitive populations can have dramatic impacts on the environment. Yellow fever epidemics, for example, have resulted in the drastic reduction or local extinction of monkey species in Brazil and Argentina, (ALMEIDA et al., 2012; Moreno et al., 2015; ANDRADE et al., 2021; POSSAMAI et al., 2022), in addition to zoonotic transmission with reflexes in the human population. The consequences of the circulation of SARS-CoV-2 among animals susceptible and likely to develop the disease in wild environments goes beyond the issue of damage to a single animal species: the population reduction or extinction of a species affects the entire balance of the ecosystem, with results that can compromise even species not subject to infection by the new coronavirus due to environmental imbalance in food chains, seed dispersal, pollination and other regulatory mechanisms and interactions between biotic components.

In addition to the transmission of the virus through direct contact between humans and animals, SARS-CoV-2 has the potential to be transmitted indirectly, by environmental contamination. Several studies demonstrate the presence of viable viral particles in wastewater and sewage (BARCELO, 2020; BIVINS et al., 2020; LEE et al., 2020; MARTIN et al., 2020; Westhaus et al., 2021; ZANETI et al., 2021). Environmental pressure, with the exposure of animals to high loads of pathogens continuously, is a source of infection and maintenance of pathogens in animals that frequent aquatic environments contaminated by domestic sewage, especially regarding microorganisms with zoonotic potential (FENG and XIAO, 2011; ARMON and CHERUTI, 2012; NORBERG et al., 2020). Franklin and Bevins (2020) draw attention to the potential for perpetuation of SARS-COV-2 through wastewater contamination and consequent colonization or infection of animals. The contamination of a European otter in a water reservoir in Spain (PADILLA-BLANCO et al.; 2022) may be related to this type of indirect contamination. Mustelids are among the animals most susceptible to SARS-CoV-2 and several species of this family have aquatic habits. We did not find in the current scientific literature investigations on the presence of SARS-CoV-2 amonglontras and otters in South America, animals potentially capable of sustaining an infection by the virus. Marine mammals, such as seals and whales, have ACE2 receptors with high compatibility for the SARS-CoV-2 spike, and represent a high-risk group for contamination by the virus circulating in contaminated waters (DAMAS et al., 2002; MATHAVARAJAH et al., 2021; GAO et al., 2021; LI et al., 2022).

Places with agglomeration of animals in contact with humans facilitate the transmission of the virus between species. Outbreaks on mink farms were facilitated by the accumulation of adjacent cages. These facilities allow both free airflow and contact with animals within facilities with a high density of individuals, which combined with poor hygienic conditions and stress factors resulting from the overpopulation of mink, have fostered the spread of SARS-CoV-2 and created opportunities for viral variants (DÍAZ et al., 2021). Zoos may have the same conditions as animal husbandry farms, and the greater circulation of visitors and keepers may reflect in a greater number of human-to-animal transmission events (MCALOOSE et al., 2020) and, consequently, infections by different strains, increasing the potential for adaptation of the virus to the most diverse species of animals confined in these establishments.

While monitoring on farms, zoos, and pets is relatively easier, with access to veterinary diagnosis and constant surveillance for possible signs and symptoms, research on free-living animals is basically fortuitous and relatively scarce. of susceptible species already affected by the incidence of SARS-CoV-2 may be underestimated. The finding of the incidence of SARS-CoV-2 in white-tailed deer in several parts of the United States of America shortly after the warning of the research conducted by Chandler et al. (2021) illustrates that the detection of the novel coronavirus as reverse zoonosis can be carried out late, when a population has already been widely affected. The lack of knowledge of the magnitude of the reverse zoonosis of SARS-CoV-2 in megadiverse countries such as Brazil represents a risk both for the mast fauna and for the ecosystem and human populations in a broader context under the prism of Single Health.

4 CONCLUSIONS

SARS-CoV-2 is a virus of zoonotic origin. Recent research indicates that the virus has shown potential for reverse zoonosis, infecting mammals in various parts of the planet. Mustelids, hamsters, felines, and old-world primates are the animals that showed the greatest susceptibility to SARS-CoV-

2. The reverse zoonosis of SARS-COV-2 favored the emergence of variants whose mutations were adapted to the various physiological characteristics particular to the affected species. The infection of many mammalian species with varied strains increases the risk of adaptability of the virus, as well as the potential for mutability and circulation of strains that can return to humans, with new characteristics and with the possibility of escape from vaccine immunization with antigens of different strains of the new variant. The process of evolution of the virus points out that SARS-CoV-2 is likely to be persistent among mammals after the pandemic wave that has affected humanity. Transmission events of SARS-CoV-2 from animals to humans have already been recorded, proving the interspecific infecting capacity of the virus. The spillover of SARS-CoV-2 to free-living animals sensitive to the virus may have consequences for the population of these species, with unpredictable morbidity and mortality aspects.

Actions to mitigate the processes of zoonosis and reverse zoonosis of SARS-CoV-2 require actions at three levels. The first level is that of the human population, as human-to-human transmission is arguably the main driver of the spread of the novel coronavirus. The intensification of prevention and immunization mechanisms for the entire population is essential to accelerate the decrease in the incidence of the virus. Updating vaccine antigens with viral proteins from emerging strains before they are prevalent is an important step in trying to stop the advance of new variants that can adapt to new hosts. The second level is in the relationship between humans and animals of direct contact. Social isolation of humans along with their pets and periodic testing to ensure that there will be no viral transmission after the lockdown period are measures that should be adopted in public health protocols. Testing for the presence of SARS-CoV-2 among humans dealing with animals or zoo visitors is also a type of measure that would help decrease interspecies transmission. The third level refers to animal populations in the environment. Control measures are challenging in free-living animals. The intensification of the number of samples and the increase of epidemiological surveillance for a larger number of species may be important for the recognition of new variants, threats to the health of the local fauna and possible control measures related to the dynamics in the relationship between animals and the environment that may cause zoonotic or interspecies transmission. Cui et al. (2022) suggests the use of commercially available veterinary vaccines against SARS-CoV-2, or the development of vaccines either for dispersal in water or environment, an experimental strategy used to control rabies in wildlife. An example of using this strategy was the vaccination of birds with the H5/H7 influenza virus vaccine, which not only successfully prevented influenza in birds, but also prevented human infection with the H7N9 virus in China (XIANG et al., 2022). These strategies, feasible in domestic and extensively farmed animals, would be effective only in small populations of free-living animals and require great efforts and costs. Comprehensive effects of the expansion of SARS-CoV-2 to other species indicate that the adoption of measures to prevent reverse zoonosis are the most indicated to reduce the damage resulting from the evolution of viruses in relation to the number of hosts.

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