

EMERGING CORONAVIRUSES IN NEOTROPICAL PRIMATES: A NEW THREAT?

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ABSTRACT

Anthropogenic activities are the main reason for the current alarming conservation status of non-human primates (NHP) worldwide, and also lead to habitat-sharing, facilitating human-NHP (interspecific) viral transmission. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the ongoing COVID-19 pandemic, is well-known for its large genome plasticity and spike proteins (S proteins) highly adaptable to human receptor angiotensin-converting enzyme-2 (ACE2). NHP have been used as models for clinical, diagnostic, and therapeutic studies on SARS-CoV-2 and their correlates. However, the lack of systematic sanitary surveillance in NHP in the Neotropics, as well as the limited capacity to detect infections in their populations, challenge the implementation of consistent epidemiological connections regarding the potential interspecific transmission in the natural environment. Although the natural cross-transmission of SARS-CoV-2 between humans and NHP has not been demonstrated, the global spread of the virus represents a potential threat. Thus, establishing preventive, surveillance, and control measures for viruses of the family *Coronaviridae* in Neotropical NHP populations is crucial for their conservation.

Keywords: conservation, COVID-19, emerging infectious diseases, New World Monkeys, SARS-CoV-2.

Non-human primates (NHP) occur in 90 countries across the African, Asian, and American continents. Two thirds of the overall NHP species richness, in a decreasing scale of abundance, is found in Brazil, Madagascar, Indonesia and the Democratic Republic of Congo (ESTRADA et al., 2018). NHP are essential for the regeneration of tropical forests due to their irreplaceable role of seed dispersers (CHAPMAN et al., 2013), thus contributing to carbon retention and indirect mitigation of global warming (PERES et al., 2016). Furthermore, NHP are part of the cultural heritage and constitute an important food source of Indigenous people (CORMIER, 2006).

Recently, Estrada et al. (2017) showed that 75% of the NHP species present declining population trends, and that 36% of the Neotropical NHP species (also known as New World monkeys, infraorder Platyrrhini) are listed as threatened by the International Union for

Conservation of Nature (IUCN). Six out of the 25 most endangered NHP species are Neotropical (SCHWITZER et al., 2019). The factors that contribute to this scenario are essentially the fragmentation of American tropical forests and conversion of forests into monocultures and livestock pastures (TILMAN and CLARK, 2014; ESTRADA et al., 2017; SCHWITZER et al., 2019). Given the fast pace of agricultural expansion, a significant loss of NHP habitat is estimated by the end of this century, as high as 78% in Brazilian territory (ESTRADA et al., 2018).

In this context, primates are compelled to occupy forest fragments near anthropized areas, which are unfeasible for the long-term maintenance of most species (ESTRADA et al., 2012). Consequently, accidents due to roadkill or electrocution, predation by dogs, conflicts in crop areas, and capture for maintenance as pets have become a reality for periurban NHP species (JERUSALINSKY et al., 2017). The interaction between humans and NHP also occurs in illegal trade (SHANEE et al., 2017; NORCONK, 2019), and poaching, with the latter affecting approximately 35% of the Brazilian primate species (IUCN, 2020). Last but not least, primates are consumed by humans, as observed for Old World monkeys (infraorder Catarrhini) in Southeast Asia and in some African countries (DEVAUX et al., 2019; FUASHI et al., 2019; KAZABA, 2019).

This scenario of joint habitats, resources, and pre-existing and/or acquired pathogens facilitates the emergence of zoonotic diseases (SMITH et al., 2012). From an epidemiological perspective, the transfer of pathogens between wild animals and humans is generally more concerning than between domestic animals and humans (DEVAUX et al., 2019). On account of the historically close relationship and contact between people and domestic animals, our shared pathogens have potentially co-evolved and adapted; which explains why the large-scale epidemics faced by humanity in the last decades originated in wild fauna (e.g., Ebola virus, human immunodeficiency virus [HIV], severe acute respiratory syndrome coronavirus 1 [SARS-CoV-1], Middle Eastern respiratory syndrome [MERS-CoV], and more recently, acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) (AFELT et al., 2018; YE et al., 2020).

Pathogenic pollution is the introduction process of an exotic pathogen in a population, that can render such population potentially vulnerable (DASZAK et al., 2000). Interspecific transmission of infectious agents usually manifests as outbreaks (LONGA et al., 2011). The phylogenetic proximity between NHP and humans favors the cross-transmission of infectious agents and poses an additional threat (COOPER and NUNN, 2013). One should also consider that, unlike most mammal species, NHP are highly social and form complex and heterogeneous groups, which exponentially increases the intra-specific dissemination of diseases (CAPITANIO, 2012). Among the diseases shared between humans and NHP, one of great relevance is yellow fever. The yellow fever outbreak in NHP that took place in southeastern Brazil, between 2016 and 2018, resulted from a spillover of the virus from humans, which in turn maintained the infection in the urban environment through its vector (*Aedes aegypti*) (POSSAS et al., 2018). Once introduced in the wild environment, the disease decimated individuals of the *Alouatta* genus (DEVAUX et al., 2019). Moreover, Neotropical NHP species can be naturally infected by other infectious agents that have humans as reservoirs or main hosts, such as Zika virus (TERZIAN et al., 2018), human alphaherpesvirus 1 (CASAGRANDE et al., 2014), measles morbillivirus (LOWENSTINE, 1993) and *Mycobacterium tuberculosis* (ROCHA et al., 2011; ROSENBAUM et al., 2015).

SARS-CoV-1 is among the pathogens with potential cross-species transmission between humans and NHP, previously associated with respiratory disorders in Old World primates upon experimental inoculation (ROWE et al., 2004; SMITS et al., 2010; 2011). SARS-CoV-1 is phylogenetically close to SARS-CoV-2 - the strain of coronavirus that triggered the ongoing COVID-19 pandemic, first reported in the Chinese city of Wuhan in December 2019.

This is the second pandemic of the 21st century, predated by the H1N1 influenza pandemic of 2009 (CHAN, 2009; GHEBREYESUS and SWAMINATHAN, 2020). However, unlike H1N1, COVID-19 has prompted an unprecedented sanitary and socio-economic challenge (UNITED NATIONS, 2020). The estimated basic reproduction number (R_0) of COVID-19 ranges from 2.24 to 3.58 (ZHAO et al., 2020), an indication of moderate transmissibility. The disease is characterized by mild to severe respiratory illness, including pneumonia (PETROSILLO et al., 2020), and has caused the death of 445,535 people worldwide as of June 18th, 2020 (WHO, 2020a).

Coronaviruses (CoV, order *Nidovirales*, family *Coronaviridae*, subfamily *Orthoroconavirinae*), named after their solar corona-like spike-covered envelopes (ICTV, 2020), are positive single-stranded RNA viruses of about 120 – 160 nm in diameter, distributed in the genera *Alpha-*, *Beta-*, *Gamma-* and *Deltacoronavirus* (ICTV, 2020). The *Coronaviridae* family is known to infect mammals and birds, and is mainly related to respiratory and gastrointestinal imbalances (MASTERS and PERLMAN, 2013). The first isolation of a CoV was in the 1930s, in chickens with bronchitis, followed in the next decades by descriptions in pigs with transmissible gastroenteritis, and mice with hepatitis and neurological disease (MCINTOSH, 1974; MASTERS and PERLMAN, 2013). In spite of this, related coronavirus - human coronavirus 229E (HCoV- 229E) and human coronavirus OC43 (HCoV- OC43) - were reported in humans only thirty years after the first identification in chickens (KAHN and MCINTOSH, 2005). Other human CoVs have been discovered in the 21st century, specifically in 2002 – 2003 (SARS-CoV-1), 2004 (human coronavirus NL-63 [HCoV-NL63]), 2005 (human coronavirus HKU1[HCoV-HKU1]), 2012 (MERS-CoV), and 2019 (SARS-CoV-2) (VAN DER HOEK et al., 2004; WOO et al., 2005; SMITH et al., 2006; GRAHAM et al., 2013; GORBALENYA et al., 2020).

Human CoVs are classified in the genera *Alphacoronavirus* (HCoV-229E and HCoV-NL63) or *Betacoronavirus* (HCoV-HKU1, HCoV-OC43, MERS-CoV, SARS-CoV-1 and SARS-CoV-2) (GORBALENYA et al., 2020; ICTV, 2020). These *Alphacoronavirus* and the former two *Betacoronavirus* have low pathogenicity, causing only mild upper and lower respiratory tract disorders similar to the common cold (CORMAN et al., 2018). Conversely, SARS-CoV-1, MERS-CoV and SARS-CoV-2 have been associated with severe respiratory diseases, severe acute respiratory syndrome (SARS), Middle Eastern respiratory syndrome (MERS) and coronavirus disease 2019 (COVID-19), respectively (PETROSILLO et al., 2020).

Bats are the most likely source of *Alpha-* and *Betacoronavirus* (WOO et al., 2012), including those infecting humans, thus deemed zoonotic (FORNI et al., 2017; ANDERSEN et al., 2020). Coronaviruses are generally airborne-transmitted via droplets of saliva and nasal discharges, and hardly ever via direct contact with contaminated surfaces (CONTINI et al., 2020). Some CoVs have required adaptation to intermediate hosts before spreading to humans, as observed with masked palm civets (*Paguma larvata*) for SARS-CoV-1 and dromedary camels (*Camelus dromedarius*) for MERS-CoV (AZHAR et al., 2014; CUI et al., 2018). The same mechanism of adaptation is believed to have taken place with SARS-CoV-2 prior to human infection (ANDERSEN et al., 2020), but its specific intermediate host species is yet to be determined. Two factors may have promoted CoVs host shifts and emergence: their large genome plasticity and highly adaptable spike proteins (S proteins) (FORNI et al., 2017). The S proteins of CoVs are crucial structures for viral infection as they mediate attachment and entry to host cells (SONG et al., 2019). The S proteins of HCoV-NL63, SARS-CoV-1, and SARS-CoV-2 bind predominately to the cellular receptor angiotensin-converting enzyme 2 (ACE2) (SONG et al., 2019; HOFFMANN et al., 2020; ICTV, 2020). Aside from being a fundamental regulator of cardiac function (CRACKOWER et al., 2002), ACE2 receptors are expressed by human pneumocytes, which favors the respiratory pathogenesis and epidemiology of SARS (MÜLLER et al., 2012).

The CD13 molecule also serves as a receptor in feline and swine CoVs, as well as human HCoV-229E (DELMAS et al., 1994). Despite resembling the ACE-2 receptor's functions, CD13 differ in morphology, which implies that some characteristics of this class of proteases may contribute to viral replication (LI et al., 2004). Today, we know that even in human cells expressing low concentrations of ACE-2, other receptors may intermediate the entry of SARS-CoV-2 (e.g., CD147, present on the surface of T lymphocytes) (WANG et al., 2020).

SARS-CoV-2 studies using NHP model are still incipient. However, a comparative approach can be used with other highly pathogenic human coronaviruses. For instance, the discoveries that support current clinical, diagnostic, and therapeutic approaches for SARS-CoV have arisen from studies conducted on animal models, mostly NHP (CORTI et al., 2015). As evidenced by several research groups (HAAGMANS and OSTERHAUS, 2006; LAWLER et al., 2006; CHEN et al., 2011; VERGARA-ALERT et al., 2017), high SARS-CoV-1 loads are found in the upper respiratory tract of a wide variety of animal species, albeit with notable differences on cellular tropism. In spite of the absence of an ideal animal model for SARS-CoV-1, the data raised from multiple experimental protocols so far can help clarifying the reasons for the devastating clinical evolution observed with SARS-CoV-1 in some particular human cases (SUBBARAO and ROBERTS, 2006; SUTTON and SUBBARAO, 2015).

A fulfilled Koch's postulate for SARS-CoV-1 was first determined in the cynomolgus macaque (*Macaca fascicularis*), an Old World primate species (FOUCHIER et al., 2003). The virus was inoculated and isolated in pulmonary tissue and subsequently quantified by real-time RT-PCR. The individuals with macroscopic pulmonary lesions presented diffuse alveolar damage marked by necrosis of the alveolar and bronchiolar epithelia, associated with alveolar infiltrate composed of proteinaceous material, fibrin, erythrocytes, alveolar macrophages, and neutrophils. This model elicited further studies with *in vitro* cell cultures (either human or NHP), as well as inoculation of SARS-CoV-1 in live animals (McAULIFFE et al., 2004; ROWE et al., 2004; NAGATA et al., 2007; MÜLLER et al., 2012).

In the last two decades, the studies addressing SARS-CoV-1 pathogenesis, especially those focusing on the immunological aspects of the disease, have mainly used species of the infraorder Catarrhini (DEVAUX et al., 2019). Additionally, the rhesus macaque (*Macaca mulatta*), also a Catarrhini species, has also been a subject of MERS-CoV studies (MUNSTER et al., 2013), which observed that the ribavirin and interferon- α 2b (INF) co-therapy reduced viral replication, moderated host response (reduction on IL-6 and INF- γ levels) and improved clinical outcome (FALZARANO et al., 2013). It was also possible to verify in this same species, the efficacy of a human anti-MERS-CoV monoclonal antibody (3B11-N), and the anti-HIV antibody E410-N, which significantly reduced the MERS-CoV-induced pulmonary damage (JOHNSON et al., 2016).

Although coronavirus trials on Neotropical NHP are still recent, in the last years, black-tufted (*Callithrix penicillata*) and common marmosets (*C. jacchus*) have been used as animal models (CARRION and PATTERSON, 2012). Callitrichidae seem to be a suitable group of Neotropical NHP for medical experiments due to their early sexual maturity (mostly at 18 months of age) and production of offspring (at around 3 years of age), and because their susceptibility to infectious agents and immune system similar to that of humans (ABBOTT et al., 2003). In this context, callitrichids are elective for MERS-CoV studies both on the production of neutralizing monoclonal antibodies (LCA60, m336) (DE WIT et al., 2018; DE WIT et al., 2019) and on passive immunity (VAN DOREMALEN et al., 2017).

According to the World Health Organization (WHO) and the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), convalescent plasma transfusion potentially mitigates the clinical consequences of the MERS-CoV infection (WHO, 2020b). A recent meta-analysis study assessing passive immunity as therapy for severe acute respiratory infections caused by viruses has proposed that the appropriate use of blood products from

convalescent patients, especially the ones carrying neutralizing antibodies, could lead to lower mortality rates (MAIR-JENKINS et al., 2015). One major challenge for such treatment option, however, is tracing fully recovered patients that have responded to the viral infection with high levels of antibodies, thus justifying plasma donation (ARABI et al., 2016). In that regard, the common marmoset has also been evaluated for the feasibility of this treatment, with promising results; therapies with hyperimmune plasma and m336, respectively, reduced viral load and attenuated severe respiratory clinical signs in MERS-COV-infected common marmosets (VAN DOREMALEN et al., 2017). As previously discussed, NHP, including Neotropical species, have been used in studies on the emerging coronavirus SARS-CoV-1 and MERS-CoV. Nevertheless, reliable information regarding the use of Neotropical NHP as models for SARS-CoV-2 is still scarce.

CONCLUSION

In face of the monumental challenges and socioeconomic burdens so far caused by SARS-CoV-2, an immediate assessment of the epidemiology and pathology of this emerging virus in wild Neotropical NHP species is crucial to evaluate potential biodiversity losses and possible spillover of SARS-CoV-2 to this group. Up until the present moment, there is no current supporting evidence of cross-species transmission between humans and Neotropical NHP. Nevertheless, given their similar genetic and immunological machinery, as well as shared habitats, and the rapid spread of SARS-CoV-2, interspecific transmission should be considered. The limitations involving SARS-CoV-2 detection and lack of systematic sanitary surveillance in NHP in the Neotropics challenge the understanding of epidemiological connections in the event of a potential interspecific transmission. Thus, it is urgent to establish infection prevention and control strategies to protect wild Neotropical NHP populations, as well as implement and/or reinforce epizootics surveillance programs. Finally, the potential use of Neotropical NHP for research about SARS-CoV-2 and COVID-19 should be carefully assessed.

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