



Review

COVID-19 and One Health: potential role of human and animals in SARS-CoV-2 life cycle



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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) in humans has zoonotic tendencies, which can potentially provoke cross-species transmission, including human-to-animal and animal-to-human infection. Consequently, the objective was to analyze the scientific evidence regarding SARS-CoV-2 animal infections from potential human transmission. A systematic review was executed following the PRISMA guidelines, in the PubMed/MEDLINE, Google Scholar and LILACS, using the descriptors combined in the following way: (“SARS-CoV-2” OR “COVID-19” OR “2019-nCoV”) AND (animals OR zoonosis). The results contemplated the viral susceptibility of about thirty animal species when induced naturally and/or experimentally. The mink & hamster species demonstrated ostensible animal-to-human transmission. Overall, there have been more reports of human contamination by other species than human retransmission from the pathogen. The natural infection of the virus was discovered in domestic dogs & cats, wild cats, deer, minks, rabbits and hamsters. Several animals, including the African green monkeys and rabbits, manifested high levels of viremia, respiratory secretions and fecal excretions of infectious virus conducive to environmental/aerosol transmission. It is still inadequately documented the intrinsic role of such processes, such as the animals' involvement in viral mutations, the emergence of new variants/lineages and the role of the animal host species. Accordingly, this research model type, natural and experimental analysis on varying animal species, corroborates the link between the two aforementioned forms of transmission. Epidemiological surveillance through extensive sequencing of the viral genomes of infected animals and humans can reveal the SARS-CoV-2 transmission routes and anticipate appropriate prophylactic strategies.

1. Introduction

The current coronavirus disease 2019 (COVID-19) pandemic, derived from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has triggered global repercussions in the social and economic sectors, notwithstanding, reported diagnoses in both humans and other animal species. It is well known that each type of coronavirus possesses a delimited range of hosts, with cross-species

transmission (CST) being conceivable. Nevertheless, the process solely depends on the internalization of the virus to specific cell membrane receptors in the host cell, which requires meticulous analysis of the cell receptor diversity of various species and the subsequent probability of CST [1,2].

There are still several uncertainties surrounding the first diagnosed cases of COVID-19. The most probable and accepted hypothesis is that the SARS-CoV-2 originated from an unknown animal species (initial

Abbreviations: SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; CST, cross-species transmission; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; MeSH, Medical Subject Headings; PICOS, Population, Interventions, Comparison, Outcomes and Study design; RT-PCR, Reverse Transcription-Polymerase Chain Reaction; ECLA, electrochemiluminescence assay; ICS, intracellular cytokine staining; TCID₅₀, median tissue culture infectious dose.

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host), possibly wild, residing in the ‘Wet Markets’. The deplorable and stressful conditions of this marketplace substantiated the rapid viral mutation and consequent human contamination, which in turn incited zoonotic spillover/overflow [3,4]. To corroborate this hypothesis, varying animal species underwent viral susceptibility testing, correlating the predictive models of the animal host susceptibility through gene expression. A thorough examination was executed on the mutations and emerging variants and how these alterations can influence the transmission of the SARS-CoV-2 [5,6].

Coronaviruses have cross-species infectivity potential. As the pandemic evolves, the tendency of zoonotic transmission of SARS-CoV-2 from human to animals and vice versa increases. The phase designated zoonotic spillback is the transmission of a pathogen from one species to another, returning to host species. Although it is not possible to ascertain the real dimension of this phenomenon, due to the quandary of diagnosing cases, it is a much greater threat than speculated upon in current literature. Spillback is a complex process, which necessitates specific viral adaptations to facilitate infection of a new host. Moreover, the resultant variants permit the recognition and internalization of the virus in the animal cells, while evading the immune system and allowing the creation of new viral copies [7].

There are several documented cases of spillover from infected humans to wildlife and domestic animals, followed by the spillback of the SARS-CoV-2 to humans. The biological conjecture deduces that after a period in the animal host the virus undergoes other modifications, denoting changes in the virulence patterns. Some scientists theorize that the SARS-CoV-2 variants may have endured the aforementioned process, which stimulated the variations of their original genetic material. The principal factors that can influence the process are the genotype of the species and environmental factors. Additionally, stressful ambience such as zoos and commercial breeders may pose immunological alterations inherent to these conditions, prompting similar results [3,7].

The mutations in the specific regions of the SARS-CoV-2, as observed in the structural spike glycoprotein, promote infection while generating virulent variants as they propitiate selective and survival advantages. The benefits include increased receptor affinity in the human cell (augmenting viral infectivity/transmissibility), and amelioration of viral replication and/or antibody resistance (enabling immune escape; reinfection) [1,8]. However, after molecular intersection analyses among the most common coronaviruses of domestic animals and humans, it is concluded that similarities in host enzymes and receptors did not always explain natural cross-infections [9]. Constant epidemiological surveillance and studies during the pandemic are vital to mitigate the foreseen threat of spillover to ‘One Health’ globally. The present study aims to investigate the occurrence of SARS-CoV-2 in humans and animals and analyze the scientific evidence of the virus in animal infections from potential human transmission.

2. Methodology

2.1. Main question

The main queries interpreted in this systematic review were, is there SARS-CoV-2 human-to-animal transmission and vice versa? Which species are more susceptible to the virus? Of those, which are the primary culprits of CST?

2.2. Search strategy

All included studies were classified in concordance with the standardized guidelines, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [10] (Fig. 1).

PubMed/MEDLINE, Google Scholar and LILACS electronic databases were employed to research original articles. Initially, the recuperation of indexed registries was based on filters of structured

searches on the PubMed platform combined with the hierarchical distribution of MeSH terms – Medical Subject Headings (<http://www.ncbi.nlm.nih.gov/mesh>) as well as the Boolean Operator, AND, utilizing the descriptors “SARS-CoV-2 AND animals”; from the last 2 years with “clinical trial” selected as the search filter/article type. No language restrictions were applied.

2.3. Selection criteria

The inclusion of articles was based on well-defined criteria, as follows: (i) original articles, (ii) studies that associated the occurrence of SARS-CoV-2 in humans and animals, (iii) be published in the last 2 years, and (iv) clinical trial; case report/case series and *ex vivo* studies.

Following the PICOS (Population, Interventions, Comparison, Outcomes and Study design) strategy, the articles that adhered to the criteria were included in the systematic review. Two reviewers (ANDF & GSBM) executed the bibliographic research, removed duplicate articles and selected Titles and Abstracts in accordance with the inclusion criteria. After the initial screening process, two reviewers (PAMS & SSP) evaluated potentially relevant full-text articles for their eligibility.

Two other reviewers (TAC & TMF) were consulted to compare and solve any inconsistencies in the selections. All the studies that investigate the occurrence of SARS-CoV-2 in humans and animals and analyze the scientific evidence of the SARS-CoV-2 animal infections from potential human transmission were included in the search. *In vivo*, *in vitro* and *in situ* studies were excluded. Subsidiary studies (literature reviews, letters to the editor, theses, dissertations, comments, and editorials) were also excluded. After screening, all relevant studies were retrieved in full text. There was a consensus reached to determine which eligible articles met the inclusion criteria. The reference lists of each included study were assayed to widen the strategic scope of the research. If additional documents were included, their reference list was also revised at the end of the cycle, in the system called ‘snow balling’.

2.4. Data extraction

Four independent reviewers (ANDF, GSBM, PAMS & SSP) extracted the essential data and grouped it into five descriptive levels, as follows.

- i. Publication characteristics: author, year, and country.
- ii. Sample characteristics: size and species.
- iii. Intervention: samples collected, and tests performed.
- iv. Principal results/highlights.
- v. Secondary outcomes or possibilities of human-to-animal transmission or vice versa.

Any discordances and subjectivity about the extracted data were resolved by general agreement during the discussion of the three additional reviewers (TAC, NAJM & MCC).

3. Results

3.1. PRISMA guideline

The search strategy resulted in the recuperation of 102 studies (40 on PubMed/MEDLINE; 42 on Google Scholar; 20 on LILACS), out of which 36 were duplicates. After deliberation on the Title and Abstract, 27 studies that had no direct relation to animal-to-human transmission and vice versa were excluded; another 16 were excluded considering they were review or update articles. The reference lists of all (26) selected articles were analyzed and one conformed to the inclusion criteria, totaling 27 studies in the systematic review (Fig. 1).

The following information was extracted from the 27 selected articles, including: the assayed animal, type of infection, the number of animals analyzed, the type of sample collected, and the type of examination

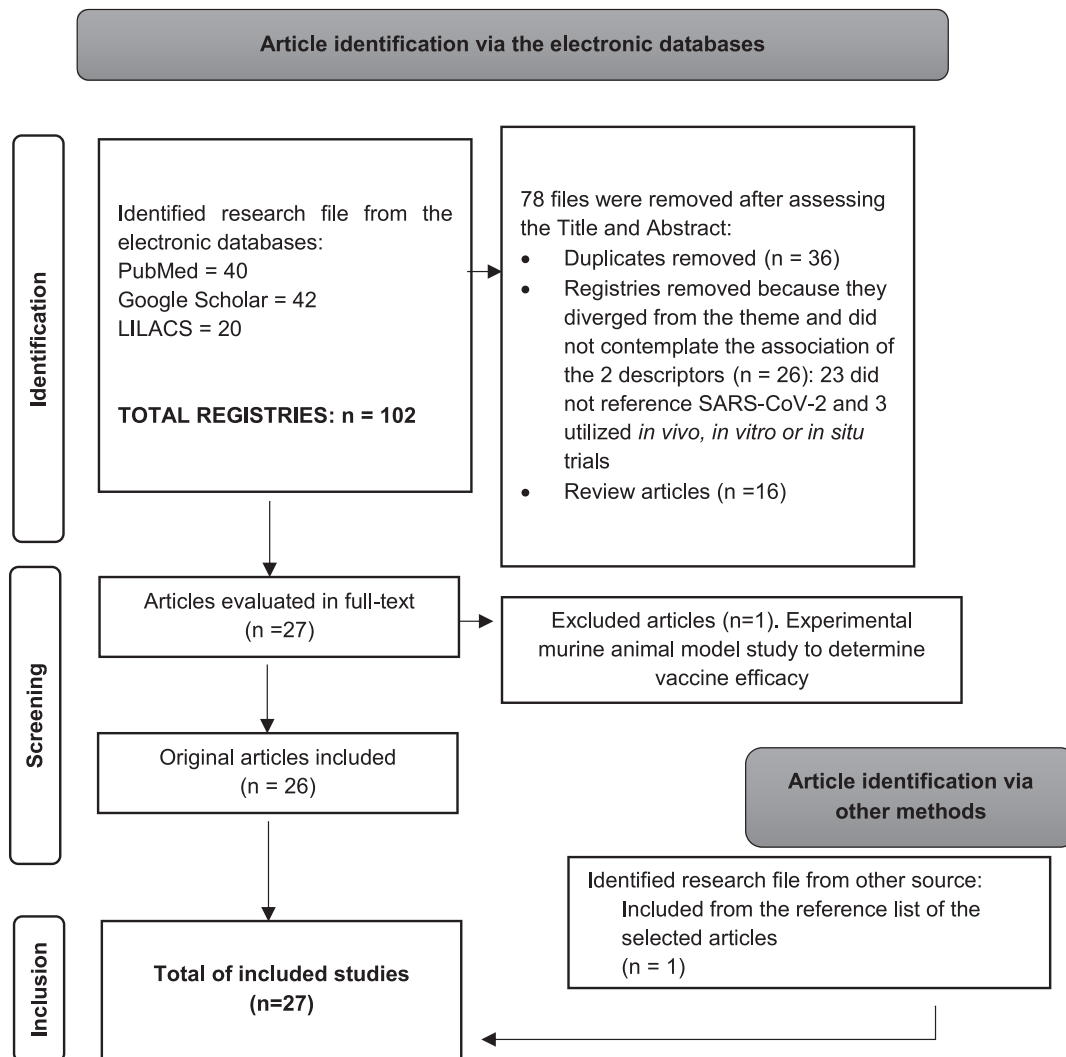


Fig. 1. Research flowchart of the SARS-CoV-2, classifying the animal infection and the human cycle of COVID-19. Source: Author 2022. Adapted from: [10]

methodology utilized in the research (Table 1). Emphasis was placed on those studies where human-to-animal or animal-to-human transmission occurred. Additionally, the characteristics of the experimental infection were observed: whether it was capable of triggering infection (clinical signs and positive SARS-CoV-2 tests), as well as the principal symptomatology evidenced in the animals (Table 2).

From the selected articles, 59% (16 articles) documented natural infections (Table 1). The experimental infection method was utilized in 33% (9 articles) of the selected. The remaining 8% (2 articles) employed both strategies of infection (natural and experimental). Overall, there have been more reports of human contamination to other species than human retransmission from the pathogen. Moreover, SARS-CoV-2 was documented in diverse animal species.

Table 2 describes companion animals (domestic cats & dogs) as potential terminal hosts of the SARS-CoV-2 when infected by humans, without spillback [34,35]. Similarly, the white-tailed deer (*Odocoileus virginianus*) native to the USA manifested viral infection, presenting high levels of viremia and excretion conducive to environmental/aerosol transmission [32]; the omicron sequences of both species validated the human-to-animal zoonotic overflow [22]. However, to date, there are no confirmed cases of viral retransmission from deer as analogously emphasized in the examination of cats & dogs. Notwithstanding, the transmission of the virus from minks to farmers (animal-to-humans) is the most consistently documented case of SARS-CoV-2 zoonotic

spillback. The viral replication in ferrets resembled the subclinical infection in humans, with similarly efficient dissemination [31]. Sheep and shrews manifested low susceptibility to the SARS-CoV-2 infection [14,31]. The results from the natural infection of cats (domestic and wild/exotic) revealed their noteworthy propensity to contract the virus [26–29,33,34]. Even though birds and reptiles were exposed to the virus under natural and experimental circumstances, they presented no signs of infection [12,16]. Pigs and chickens could not be infected via their nasal tracts, while fruit bats exhibited features of a reservoir host [31].

Of the 27 selected articles, there were 11 European studies, being divided as such: Italy (2), one of the countries greatly affected by the initial onset of the virus, Denmark (1), Germany (1), Portugal (1), and Holland & Spain (3) respectively. Only one African study was included, from the country of South Africa. The Americas provided 11 studies as well, including, Brazil (1) and the United States of America (10). There were 4 Asian studies in total, the People's Republic of China (3) and India (1).

There were varying types of material/sample collection employed. The utilization of the upper airway swab prevailed in 25 of the studies and the rectal swab in 13 of the selected studies. Only 3 of the selected studies did not use the swab technique, in these cases blood & tissue samples and bronchoalveolar lavage were used. Most of the studies applied varying collection techniques, including blood samples (9), feces (9), tissue samples (3), milk (1) and organ culture (1) was utilized in the *ex vivo* test (Table 1 and Fig. 2).

Table 1
Description of the main characteristics examined in each selected study.

Animal	Infection	n	Sample/Exam
Minks [11]	N (+)	36	Nasal and rectal swab/PCR.
Buffalos, goats/sheep, horses, cows, carrier pigeons, rabbits, chickens, snakes and pigs [12]	B (-)	236	Nasal and pharyngeal swab; milk and feces/PCR.
African green monkey [13]	E (+)	6	Blood and bronchoalveolar lavage/PCR.
Tree shrew (<i>Tupaia belangeri chinensis</i>) [14]	E (+/-)	38	Nasal, throat and anal swab; blood; tissue samples/Histopathological/PCR.
Ferrets (<i>Mustela putorius furo</i>) [15]	N (-)	29	Oral swabs/PCR/ELISA.
Chickens, turkeys, geese, Chinese White Peking ducks and quails [16]	E (-)	50 (5 × 10)	Oropharyngeal and cloacal swabs/PCR.
Cats, pigs, rabbits and dogs [17]	N (-); (+)	23	Nasopharyngeal and rectal swabs/PCR.
Mink [18]	E (+)	18	Nasal, oral and anal swabs/PCR.
Feral American mink (<i>Neovison vison</i>) [19]	N (+)	13	Mesenteric lymph nodes/Necropsy/PCR.
Cynomolgus monkey [20]	E (+)	30	Nasal swabs and bronchoalveolar lavage/ELISA, ECLA, ICS, B cell immunophenotyping; PCR; TCID ₅₀ test; Histopathological/immunohistochemistry.
Cats (3), tiger (1), dog (1) [21]	N (-)	5	Swabs nasais, traqueal, orofaríngeo retal e fecal/PCR; necropsy & radiography.
White-tailed deer (<i>Odocoileus virginianus</i>) [22]	N (+)	131	Nasal swab; Sangue; Indirect ELISA/N-Protein/PCR.
Sheep [23]	E (+/-)	10	Nasopharyngeal and rectal swab; tissues from euthanized animals/PCR; ELISA.
Mink [24]	E (+)	2150	Oropharyngeal swabs; blood/PCR.
Rabbit [25]	E (+)	12	Nasal, throat and rectal swabs; blood/PCR.
Pigs, oxen and sheep [26]	E (-)	9 (3 × 3)	Ex vivo and serum organ cultures/immunohistochemistry & immunofluorescence.
Mountain lion (1) and African lions (3) [27]	N (+)	4	Nasal swabs; fecal samples/PCR; viral IgG and RNA antibodies.
Asiatic lions (<i>Panthera leo persica</i>) [28]	N (+)	11	Nasal swab, rectal swab and fecal samples/PCR.
Tigers (2) and lions (3) (<i>Panthera tigris e Panthera leo</i>) [29]	N (+)	5	Nasopharyngeal swab/PCR; immunofluorescence.
Lions (<i>Panthera leo</i>) [30]	N (+)	4	Nasal fluids, feces and saliva/PCR.
Fruit bats, ferrets, pigs and chickens [31]	N (-); (+)	56	Nasal and rectal swabs; fecal samples/PCR.
White-tailed deer (<i>Odocoileus virginianus</i>) [32]	N (+)	360	Nasal swab/PCR.
Malayan tigers (<i>Panthera tigris jacksoni</i>) (2), Siberian tiger (<i>P. tigris altaica</i>) (2) and African lions (<i>Panthera leo krugeri</i>) [33]	N (+)	7	Oropharyngeal and nasal swabs; tracheal lavage fluid; fecal sample; PCR; chest x-ray and ultrasound.
Dogs (15) and cats (7) [34]	N (+)	22	Nasal, oral and rectal swabs; fecal sample; blood/PCR.
Dogs (29) and cats (10) [35]	N (+)	39	Rectal, naso- & oropharyngeal swabs; blood/PCR; plaque reduction neutralization
Syrian/Golden & Dwarf hamsters, rabbits, guinea pigs, chinchillas and mice [36]	B (+)	535	Nasal, oral swabs; saliva, fecal & blood samples/PCR; serological tests.
Dogs (148) and cats (69) [37]	N (+)	217	Rectal, naso- & oropharyngeal swabs; blood sample/PCR; serological tests.

N: Natural infection; E: Experimental infection; B: Mixed infection; (+) High susceptibility to SARS-CoV-2 infection; (-) No/without susceptibility to SARS-CoV-2 infection; (+/-) Low susceptibility to SARS-CoV-2 infection.

The following methods were applied to adequately diagnose the SARS-CoV-2 in the selected studies, such as: reverse transcription-polymerase chain reaction (RT-PCR) test (25), diagnostic imaging (3), histopathological test - immunohistochemistry & immunofluorescence (4), ELISA & IgG tests (11), plaque reduction neutralization test, electrochemiluminescence assay (ECLA), intracellular cytokine staining (ICS) assay B cell immunophenotyping, median tissue culture infectious dose (TCID₅₀) assay and N-protein assay.

The natural infection of the SARS-CoV-2 was observed in dogs, cats, tigers, lions, deer, minks and hamsters. Additionally, the experimental infections were manifested in African green monkeys, shrews, minks, cynomolgus monkeys, sheep, rabbits, oxen and lions. Despite some animal populations coexisting with humans and other infected species and/or being exposed experimentally to the virus, their results returned negative. These animals included chickens, turkeys, geese, Chinese White Peking duck, quails, pigs, mountain lions, snakes, buffaloes and carrier pigeons. There were documented cases of animal-to-human transmission (hamsters and minks), while companion animals such as dogs and cats demonstrated naturally occurring overflow. Possible cat-to-human infection has been described in Thailand [38]. Natural human-to-animal spillover was also witnessed in rabbits, deer and lions (Fig. 3).

4. Discussion

The SARS-CoV-2 that causes COVID-19 in humans is potentially originated from animal species, a vital fact that emphasizes zoonotic tendencies and the potential for CST. Human/animal interaction was

responsible for most of the emerging and re-emerging zoonotic outbreaks. Accordingly, the discernment of animal welfare can play an important role in the cycle of human diseases (e.g. COVID-19), to present prophylactic approaches aimed at 'One Health' and not only human health [39]. Although there are some literatures describing the effects of natural and experimental viral infection in several animal species, the essential aspects of such, their involvement in viral mutations, the emergence of new variants/lineages and the role of the animal host species is still inadequately defined. Consequently, this review compiled and explored the given data to disclose the occurrence of CST to mitigate the potential threat it poses to the 'One Health' interface.

The review was limited in certain aspects. Most of the collated studies (natural and/or experimental cases) analyzed were realized in geographical regions with greater economic power, especially in research; the USA (10 studies) and Europe (11 studies). There was a negligible quantity (3) of suitable studies in regions with greater fauna biodiversity (tropical regions - South Africa, Brazil, India), environments adapted in favor of zoonotic overflow and spillback. Furthermore, these areas have experienced the emergence of significant variants of the virus with little deliberation on the relationship between the animal species and the viral mutation [10,40]. Consequently, recent studies affirm that the SARS-CoV-2 Omicron sub-lines/variants B.1.1.529 [40], BA.2.12.1, BA.4 and BA.5 [8] present a higher transmissibility, which is activated by several spike mutations, and consequently increases their receptor binding and immune evasion capacity, in addition to presenting partial escape to neutralizing antibodies.

The spread and proliferation of organisms into new regions is associated with ecosystem change, wildlife exploitation and global

Table 2

Correlation between the type of transmission and the observed SARS-CoV-2 symptomatology amongst animals.

Highlights	Clinical Signs
Mink infection from human contamination [11] High risk of zoonotic overflow amongst bred animals; low risk/non-existent animal-to-human transmission [12]	Respiratory signs; necropsy: congestion, edema, interstitial pneumonia/lung infection. Not applicable
There were notable similarities between the infections of the humans and the monkeys; the probability of human-to-animal transmission is high [13]. The tree shrew may not be a suitable model; however, it could be a potential intermediate host [14].	Loss of appetite, fever, high protein C activity, hypercapnia.
There was no naturally occurring human-to-ferret transmission in the high-exposure environment [15]. The virus was not detected in any of the analyzed bird samples [16]. Human-to-animal transmission due to their propinquity [17]	Fever Not applicable
The infected lung and inflammation pathology of minks were like that of the infected humans [18]. Negative PCR test, however, there were observed signs of infection during autopsy [19]. Omicron neutralizing antibodies were observed after booster immunization [20].	No clinical signs were manifested. Asymptomatic, digestive, and respiratory symptoms Cerebral, ocular, and alveolar damage; severe histological lesions in the respiratory system. Asymptomatic
Observed human-to-animal transmission in 3 cats and 1 tiger; The dog tested negative [21]. The clustering analysis of the Omicron sequences of the deer was equivalent to the observed human sequences, which is consistent with human-to-animal overflow [22].	Interstitial inflammation, septal expansion, syncytial & endothelial formation in the lungs of the animals infected with Omicron; the animals were vaccinated. Cats: clinical respiratory signs; dog: coughing, sneezing, oculonasal discharge and acute onset diarrhea; respiratory distress worsened and the dog was euthanized. It is not known whether infecting the deer with Omicron manifests clinical symptoms.
Documented viral replication in cell cultures and detection in nasal swabs; the species susceptibility to the virus was limited to the upper respiratory tract and regional lymph nodes [23]. Observed zoonotic spillover and spillback between the humans and minks [24] The animals were infected but cross-species transmission was improbable [25]. The <i>ex vivo</i> experiments demonstrated that the cattle & sheep respiratory tissues support viral replication, but there was no documented change in the pork tissue [26].	No observed clinical signs. Although some of the sheep were infected, it remained subclinical, which indicated that sheep are not good hosts. Respiratory damage Asymptomatic Additional <i>in vivo</i> tests involving varying ruminant species are required to determine the potential epidemiological role of the virus.
Observed delta variant transmission from zookeeper to 3 lions, similar to the human infections in South Africa [27] The source of the infection in lions may have been an asymptomatic individual [28]. Risk of contagion via handlers and shared provisions [29] Human-to-animal transmission [30] The pigs and chickens were not infected; the fruit bats manifested transient infection; only one ferret was not infected [31]. There were 6 documented cases of human-to-animal (deer) transmission [32].	One lion developed pneumonia, while the other cases manifested mild infection and remained positive for a period of 7 weeks. Loss of appetite, runny nose and occasional coughing. Respiratory signs Respiratory signs No animal presented clinical signs.
The 1 st known naturally occurring documented case of human-to-animal (non-domestic cats) transmission [33] It is still unclear whether infected dogs can transmit the virus to other animals and/or back to humans [34]. The cats and dogs tested positive; three dogs tested positive twice within a span of 14, 30 and 31 days; neutralizing antibodies were found in one of the dogs and in two of the cats [35]. The genetic and epidemiological evidence suggest that there were 2 independent transmission, one animal (hamster)-to-human and a possible human-to-animal; the likely source of the viral infection stemmed from the importation of infected hamsters [36]. Human-to-animal transmission was observed in half of the animal population while 33% of the cats were contaminated through animal-to-animal transmission [37]	Presented high levels of viremia and excretion, which is conducive to environmental/aerosol transmission. Coughing, wheezing, loss of appetite and minor signs of vomiting and epistaxis. Asymptomatic Six of the thirteen seropositive animals developed mild but reversible disease symptomatology. More than 50% of the Syrian hamsters tested positive; the Dwarf hamsters, rabbits, guinea pigs, chinchillas and mice all tested negative. Digestive, neurological, and respiratory symptoms; apathy and loss of appetite; fever

connectivity. This type of endemic distribution is referred to as biological invasion and is characterized by emergence, proliferation, and rapid dissemination with adaptation to new environments, and may be associated with large-scale geographic dispersal [41]. Notwithstanding, it is hypothesized that the viral infection pathway through different animal species and humans provides diverse and favorable physiological output that can elicit mutations. There are peculiar characteristics that regulate these events, such as: (i) tropical regions with agglomerations of domestic and wild animals species in close proximity to humans; (ii) impoverished regions that generate deprived ecosystems and populations (human & animal); (iii) the deplorable and stressful conditions encountered in some commercial animal farms, zoos and exotic animal markets; (iv) the consumption of exotic animal species, which normally are reservoirs of various etiological agents (bats) [3].

Although there are few documented cases of animal-to-human transmission of the virus, some regions have performed euthanasia events of specific animal populations. In 2021, thousands of minks

(*Mustela*; bred commercially to produce fur) were exterminated in the Netherlands due to their role in the retransmission (zoonotic spillback) of SARS-CoV-2 to humans. These animals had previously suffered contamination of the virus by humans (zoonotic overflow) and manifested COVID-19 symptomologies, even death [24]. Likewise, in January 2022, two thousand rodents (hamsters) were euthanized in Hong Kong after reports of the transmission and dissemination of the SARS-CoV-2 Delta variant amongst customers and employees of a local pet shop [36].

The predisposition of the various animal species studied, most notably mammals, to contract and transmit the virus is another concerning factor. The clinical tests have indicated that both the human and animal species that sustain viremia manifest similar respiratory symptomatology. Additionally, fever, gastrointestinal signs and loss of appetite can be observed. These factors can represent a major problem in an animal production chain, provoking considerable economic detriment in the given sector [42]. A featured study investigated the role of marine mammals and their potential to propagate the disease. According to the

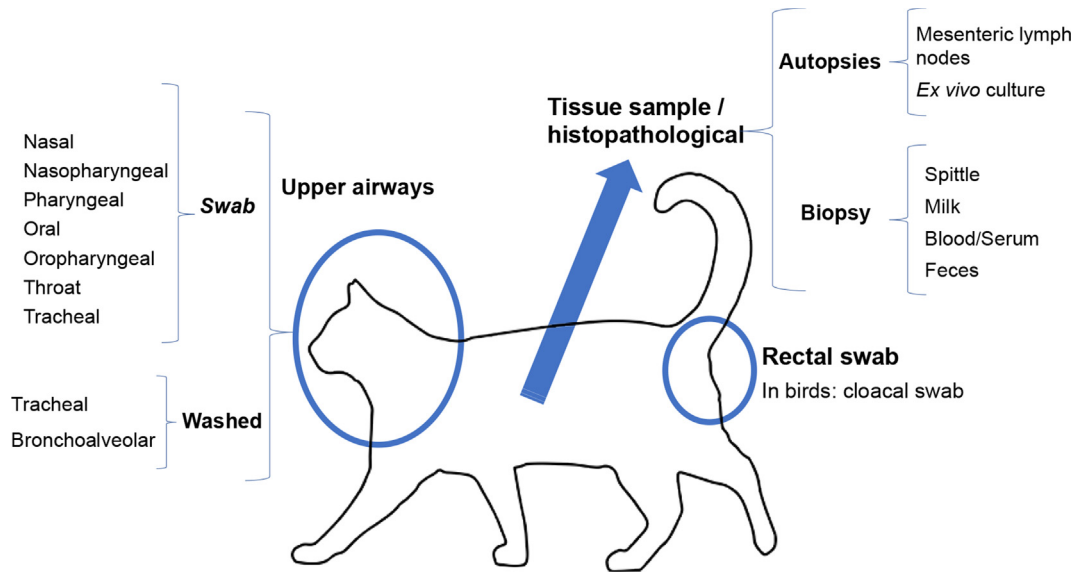


Fig. 2. The different types of material/sample collection techniques utilized for the SARS-CoV-2 infection analysis.

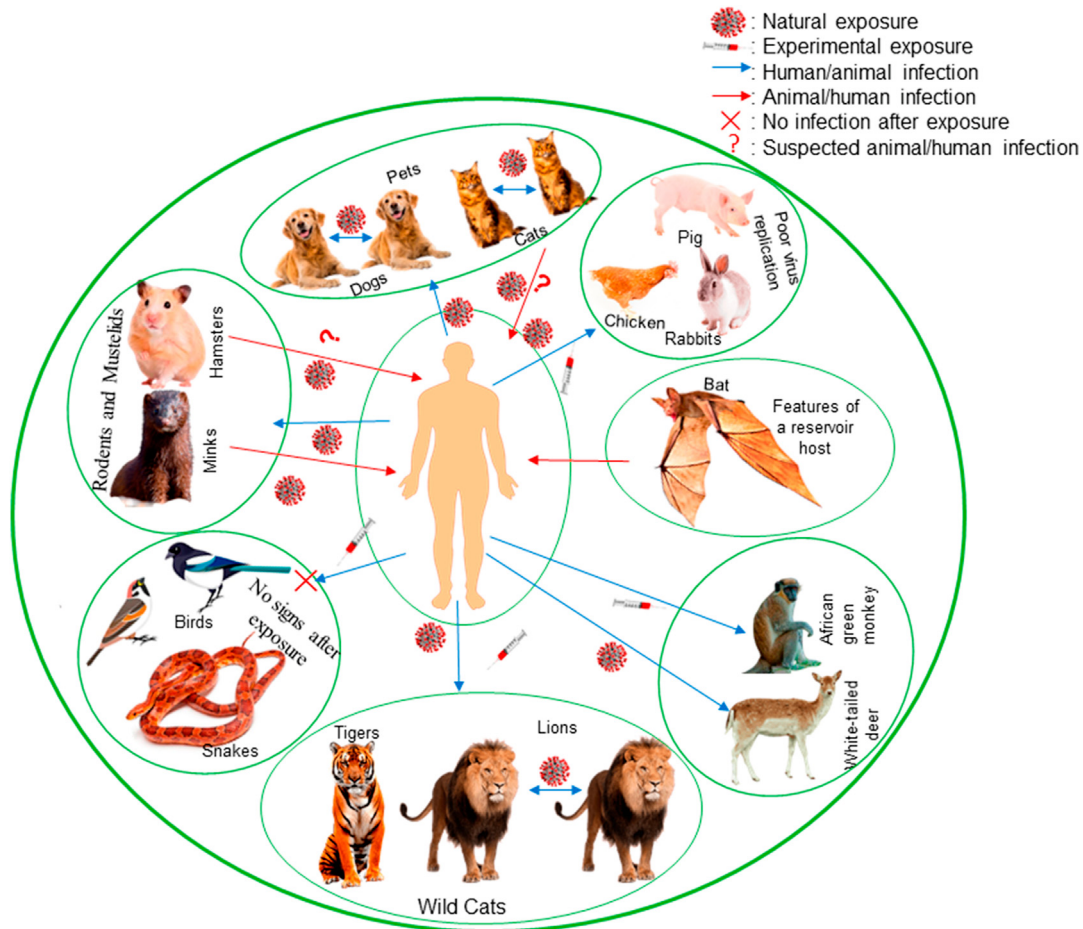


Fig. 3. The probable routes of human-to-animal and animal-to-human transmission.

research, around 15 marine species including whales, dolphins, seals and sea otters are conceivably susceptible to the SARS-CoV-2 via environmental exposure (wastewater discharge areas). Close monitoring of these vulnerable populations is imperative [43].

As with other infectious viruses, several animal species can disseminate the SARS-CoV-2 through respiratory secretions and fecal excretions.

Both African green monkeys and rabbits can excrete infectious viruses (SARS-CoV-2) via their upper respiratory tracts, as confirmed after experimental infection [13,25]. Consequently, to appropriately diagnose the virus the gold standard test (RT-PCR) was employed in 26 of the selected studies; 25 studies documented results from upper airway swab samples and 13 studies utilized rectal swab samples. The other specimens

gathered included blood, feces, tissue biopsy or necropsy (euthanasia/-death of the animals). This form of molecular diagnostic efficiently detects and quantifies viral infections, substantiating the need for greater epidemiological surveillance to facilitate the detection of alterations to the RNA (mutations) and/or of the viral genome (variants) of such infectious diseases. Moreover, this strategy enables the production of effective vaccines against the pathogen and consequent alterations (mutations and/or variants) [42,44].

Despite the 'One Health' approach having been increasingly highlighted in the international scientific community, prospects for tools to monitor single health, along with their technical protocols and databases, need to be established, to provide a reference for establishing public policies for identifying gaps and integrated analysis of animal, human and environmental health [45,46]. Vaccination of animal populations is a feasible and inexpensive prophylactic strategy when compared to the development of vaccines for humans, which requires expensive development programs and extensive clinical trials. Furthermore, the inoculation of domestic animals (companion animals & livestock) and specific wild animal populations (zoos; animal markets) that coexist with human populations is a socially and economically viable preventative measure to impede the resurgence of SARS-CoV-2 [44] and ensure the perpetuation of 'One Health'.

4.1. Final considerations

Mammals are more susceptible to the SARS-CoV-2 that causes COVID-19. Although there are over five thousand mammalian species worldwide, only about 30 have been studied to determine their predisposition to contract the virus.

Naturally, SARS-CoV-2 can infect dogs, cats, tigers, lions, deer, minks, rabbits and hamsters; from this group, dogs, cats & white-tailed deer are all terminal hosts of the virus when contaminated by humans (overflow), incapable of retransmission. In addition, among the examined and identified animal species, cats (domestic, wild/exotic) manifested greater levels of viral susceptibility to SARS-CoV-2. Pigs, birds and snakes can be neither naturally nor experimentally contaminated by the virus. Nonetheless, several animal species can present high levels of viremia, respiratory secretions and fecal excretions of infectious virus conducive to environmental/aerosol transmission. Animal-to-human transmission was evinced in minks and conceivably, in hamsters. In general, there are more reported cases of human-to-animal transmission, without pathogenic retransmission to host.

Most of the selected studies were descriptive (59%), however, an experimental approach was executed in the more developed countries. The scientific evidence demonstrates the need for greater investment in research that investigates and identifies the role of the animal species in the COVID-19 cycle, globally, especially in impoverished and/or developing regions. Epidemiological surveillance through extensive sequencing of the viral RNA (mutations) & viral genomes (variations) of infected animals and humans can reveal the SARS-CoV-2 transmission routes and anticipate appropriate prophylactic strategies. Nevertheless, vaccination of the animal species near human populations is the quintessential measure to contain the virus/disease and consequently facilitating social & economic growth, as well as perpetuating 'One Health'.

Author contributions

ANDF, GSBM, PAMS, and SSP: conceived the study, methodology, formal analysis, interpreted results, writing- original draft preparation, revised the manuscript; **MCC, TAC, NAJM, and MCC:** interpreted results and revised the manuscript. **RSB, and MCC:** supervision. All authors have read and agreed to the published version of the manuscript.

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References

- [1] A.A. Shehata, Y.A. Attia, Md.T. Rahman, S. Basiouni, H.R. El-Seedi, E.I. Azhar, et al., Diversity of coronaviruses with particular attention to the interspecies transmission of SARS-CoV-2, *Animals* 12 (3) (2022) 378, <https://doi.org/10.3390/ani12030378>.
- [2] C.J. Zeiss, S. Compton, R.T. Veenhuis, Animal models of COVID-19. I. Comparative virology and disease pathogenesis, *ILAR J.* 62 (1–2) (2021) 35–47, <https://doi.org/10.1093/ilar/ilab007>.
- [3] M.C. Cupertino, M.B. Resende, N.A. Mayer, L.M. Carvalho, R. Siqueira-Batista, Emerging and re-emerging human infectious diseases: a systematic review of the role of wild animals with a focus on public health impact, *Asian Pac. J. Tropical Med.* 13 (3) (2020) 99–106, <https://doi.org/10.4103/1995-7645.277535>.
- [4] K. Sharun, K. Dhama, A.M. Pawde, C. Gortázar, R. Tiwari, D.K. Bonilla-Aldana, et al., SARS-CoV-2 in animals: potential for unknown reservoir hosts and public health implications, *Vet. Q.* 41 (1) (2021) 181–201, <https://doi.org/10.1080/01652176.2021.1921311>.
- [5] J. Chen, R. Wang, G. Wei Wei, Review of the mechanisms of SARS-CoV-2 evolution and transmission, *ArXiv [Preprint]* (2021 Sep 15) arXiv:2109.08148v1. PMID: 34545334; PMCID: PMC8452100.
- [6] B. Colitti, L. Bertolotti, A. Mannelli, G. Ferrara, A. Vercelli, A. Grassi, et al., Cross-sectional serosurvey of companion animals housed with SARS-CoV-2-infected owners, Italy, *Emerg. Infect. Dis.* 27 (7) (2021) 1919–1922, <https://doi.org/10.3201/eid2707.203314>.
- [7] S.M. Hirabara, T.D.A. Serdan, R. Gorjao, L. N Masi, T.C. Pithon-Curi, D.T. Covas, et al., SARS-CoV-2 variants: differences and potential of immune evasion, *Front. Cell. Infect. Microbiol.* 11 (2022), 781429, <https://doi.org/10.3389/fcimb.2021.781429>.
- [8] Y. Cao, A. Yisimayi, F. Jian, W. Song, T. Xiao, L. Wang, et al., BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection, *Nature* 608 (2022) 593–602, <https://doi.org/10.1038/s41586-022-04980-y>.
- [9] K. Bentum, S. Shaddox, C. Ware, G. Reddy, W. Abebe, R. Foltse, et al., Molecular phylogeny of coronaviruses and host receptors among domestic and close-contact animals reveals subgenome-level conservation, crossover, and divergence, *BMC Vet. Res.* 18 (124) (2022), <https://doi.org/10.1186/s12917-022-03217-4>.
- [10] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, *BMJ* 71 (2021), <https://doi.org/10.1136/bmj.n71>.
- [11] N. Oreshkova, R.J. Molenaar, S. Vreman, F. Harders, B.B.O. Munnink, R.W. Hakzevan der Honing, et al., SARS-CoV-2 infection in farmed minks, The Netherlands, April and May 2020, *Euro Surveill.* 25 (2020) 23, <https://doi.org/10.2807/1560-7917.ES.2020.25.23.2001005>.
- [12] P. Cerino, C. Buonerba, G. Brambilla, L. Atripaldi, M. Tafuro, D. Di Concilio, et al., No detection of SARS-CoV-2 in animals exposed to infected keepers: results of a COVID-19 surveillance program, *Future Sci. OA* 7 (7) (2021) FSO711, <https://doi.org/10.2144/fsoa-2021-0038>.
- [13] C. Woolsey, V. Borisevich, A.N. Prasad, K.N. Agans, D.J. Deer, N.S. Dobias, et al., Establishment of an African green monkey model for COVID-19 and protection against re-infection, *Nat. Immunol.* 22 (1) (2021) 86–98, <https://doi.org/10.1038/s41590-020-00835-8>.
- [14] Y. Zhao, J. Wang, D. Kuang, J. Xu, M. Yang, C. Ma, et al., Susceptibility of tree shrew to SARS-CoV-2 infection, *Sci. Rep.* 10 (1) (2020), 16007, <https://doi.org/10.1038/s41598-020-72563-w>.
- [15] K. Sawatzki, N. Hill, W. Puryear, A. Foss, J. Stone, J. Runstadler, Ferrets not infected by SARS-CoV-2 in a high-exposure domestic setting, *bioRxiv* 8 (21) (2020), 254995, <https://doi.org/10.1101/2020.08.21.254995>.
- [16] D.L. Suarez, M.J. Pantin-Jackwood, D.E. Swayne, S.A. Lee, S.M. DeBlois, E. Spackman, Lack of susceptibility to SARS-CoV-2 and MERS-CoV in poultry, *Emerg. Infect. Dis.* 26 (12) (2020) 3074–3076, <https://doi.org/10.3201/eid2612.202989>.
- [17] I. Ruiz-Arroondo, A. Portillo, A.M. Palomar, S. Santibáñez, P. Santibáñez, C. Cervera, et al., Detection of SARS-CoV-2 in pets living with COVID-19 owners diagnosed during the COVID-19 lockdown in Spain: a case of an asymptomatic cat with SARS-CoV-2 in Europe, *Transbound. Emerg. Dis.* 68 (2) (2021) 973–976, <https://doi.org/10.1111/tbed.13803>.
- [18] Z. Song, L. Bao, W. Deng, J. Liu, E. Ren, Q. Lv, et al., Integrated histopathological, lipidomic, and metabolomic profiles reveal mink is a useful animal model to mimic the pathogenicity of severe COVID-19 patients, *Signal Transduct. Targeted Ther.* 7 (29) (2022), <https://doi.org/10.1038/s41392-022-00891-6>.
- [19] J. Aguiló-Gisbert, M. Padilla-Blanco, V. Lizana, E. Maiques, M. Muñoz-Baquero, E. Chillida-Martínez, et al., First description of SARS-CoV-2 infection in two feral American mink (*Neovison vison*) caught in the wild, *Animals (Basel)* 11 (5) (Mar 25 2021) 1422, <https://doi.org/10.3390/ani11051422>.
- [20] A. Chandrashekar, J. Yu, K. McMahan, C. Jacob-Dolan, J. Liu, X. He, et al., Vaccine protection against the SARS-CoV-2 Omicron variant in macaques, *Cell* 185 (9) (Apr 28 2022) 1549–1555, <https://doi.org/10.1016/j.cell.2022.03.024>.
- [21] D.S. Rotstein, S. Peloquin, K. Proia, E. Hart, J. Lee, K. K Vyhna, et al., Investigation of SARS-CoV-2 infection and associated lesions in exotic and companion animals, *Vet. Pathol.* 59 (4) (2022) 707–711, <https://doi.org/10.1177/03009858211067467>.
- [22] K.J. Vandegriff, M. Yon, M. Surendran-Nair, A. Gontu, S. Amirthalingam, R. H Nissly, et al., Detection of SARS-CoV-2 Omicron variant (B.1.1.529) infection of

- white-tailed deer, *bioRxiv* 7 (2022), 479189, <https://doi.org/10.1101/2022.02.04.479189>, 02.04.
- [23] N.N. Gaudreault, K. Cool, J.D. Trujillo, I. Morozov, D.A. Meekins, C. McDowell, et al., Susceptibility of sheep to experimental co-infection with the ancestral lineage of SARS-CoV-2 and its alpha variant, *bioRxiv* 11 (15) (2021), 468720, <https://doi.org/10.1101/2021.11.15.468720>.
- [24] A. Boklund, A.S. Hammer, M.L. Quaade, T.B. Rasmussen, L. Lohse, B. Strandbygaard, et al., SARS-CoV-2 in Danish mink farms: course of the epidemic and a descriptive analysis of the outbreaks in 2020, *Animals (Basel)* 11 (1) (2021) 164, <https://doi.org/10.3390/ani11010164>.
- [25] A.Z. Mykytyn, M.M. Lamers, N.M.A. Okba, T. I. Breugem, D. Schipper, P. B van den Doel, et al., Susceptibility of rabbits to SARS-CoV-2, *Emerg. Microb. Infect.* 10 (1) (2021) 1–7, <https://doi.org/10.1080/22221751.2020.1868951>.
- [26] G. Di Teodoro, F. Valleriani, I. Puglia, F. Monaco, C. Di Pancrazio, M. Luciani, et al., SARS-CoV-2 replicates in respiratory ex vivo organ cultures of domestic ruminant species, *Vet. Microbiol.* 252 (2021), 108933, <https://doi.org/10.1016/j.vetmic.2020.108933>.
- [27] K.N. Koeppel, A. Mendes, A. Strydom, L. Rotherham, M. Mulumba, M. Venter, SARS-CoV-2 reverse zoonoses to pumas and lions, South Africa, *Viruses* 14 (1) (2022) 120, <https://doi.org/10.3390/v14010120>.
- [28] A. Mishra, N. Kumar, S. Bhatia, A. Aasdev, S. Kannappan, A.T. Sekhar, et al., SARS-CoV-2 delta variant among Asiatic lions, India, *Emerg. Infect. Dis.* 27 (10) (2021) 2723–2725, <https://doi.org/10.3201/eid2710.211500>.
- [29] D. McAloose, M. Laverack, L. Wang, M.L. Killian, L.C. Caserta, F. Yuan, et al., From People to Panthera: natural SARS-CoV-2 infection in tigers and lions at the Bronx zoo, *Am. Soc. Microbiol.* 11 (5) (2020), <https://doi.org/10.1128/mBio.02220-20>.
- [30] H. Fernández-Bellón, J. Rodon, L. Fernández-Bastit, V. Almagro, P. Padilla-Solé, C. Lorca-Oró, et al., Monitoring natural SARS-CoV-2 infection in lions (*Panthera leo*) at the Barcelona zoo: viral dynamics and host responses, *Viruses* 13 (9) (2021) 1683, <https://doi.org/10.3390/v13091683>.
- [31] K. Schlottau, M. Rissmann, A. Graaf, J. Schön, J. Sehl, Claudia Wylezich, *etal. SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens: an experimental transmission study*, *Lancet Microbe* 1 (5) (2020) e218–e225, [https://doi.org/10.1016/S2666-5247\(20\)30089-6](https://doi.org/10.1016/S2666-5247(20)30089-6).
- [32] V.L. Hale, P.M. Dennis, D.S. McBride, J.M. Nolting, C. Madden, D. Huey, et al., SARS-CoV-2 infection in free-ranging white-tailed deer, *Nature* 602 (48) (2022) 481, <https://doi.org/10.1038/s41586-021-04353-x>.
- [33] S.L. Bartlett, D.G. Diel, L. Wang, S. Zec, M. Laverack, M. Martins, et al., SARS-CoV-2 infection and longitudinal fecal screening in Malayan Tigers (*Panthera tigris jacksoni*), Amur Tigers (*Panthera tigris altaica*), and African Lions (*Panthera leo krugeri*) at the Bronx zoo, New York, USA, *J. Zoo Wildl. Med.* 51 (4) (2021) 733–744, <https://doi.org/10.1638/2020-0171>.
- [34] T.H.C. Sit, C.J. Brackman, S.M. Ip, K.W.S. Tam, P.Y.T. Law, E.M.W. To, et al., Infection of dogs with SARS-CoV-2, *Nature* 586 (2020) 776–778, <https://doi.org/10.1038/s41586-020-2334-5>.
- [35] G.A. Calvet, S.A. Pereira, M. Ogrzewalska, A. Pauvolid-Corrêa, P.C. Resende, W.S. Tassinari, et al., Investigation of SARS-CoV-2 infection in dogs and cats of humans diagnosed with COVID-19 in Rio de Janeiro, Brazil, *PLoS One* 28 (2021), e0250853, <https://doi.org/10.1371/journal.pone.0250853>.
- [36] H.L. Yen, T.H.C. Sit, C.J. Brackman, S.S.Y. Chuk, H. Gu, K.W.S. Tam, et al., Transmission of SARS-CoV-2 delta variant (AY.127) from pet hamsters to humans, leading to onward human-to-human transmission: a case study, *Lancet* 399 (10329) (2022) 1070–1078, [https://doi.org/10.1016/S0140-6736\(22\)00326-9](https://doi.org/10.1016/S0140-6736(22)00326-9).
- [37] R. Barroso, A.V. Pires, A. Antunes, I.F. Carvalho, Susceptibility of pets to SARS-CoV-2 infection: lessons from a seroepidemiologic survey of cats and dogs in Portugal, *Microorganisms* 10 (2) (2022) p345, <https://doi.org/10.3390/microorganisms10020345>.
- [38] T. Sila, J. Sunghan, W. Laochareonsuk, S. Surasombatpattana, C. Kongkamol, T. Ingviya, et al., Suspected cat-to-human transmission of SARS-CoV-2, Thailand, July–September 2021, *Emerg. Infect. Dis.* 28 (7) (2022) 1485–1488, <https://doi.org/10.3201/eid2807.212605>.
- [39] Q. Li, R. Bergquist, L. Grant, J.X. Song, X.Y. Feng, X.N. Zhou, Consideration of COVID-19 beyond the human-centred approach of prevention and control: the ONE-HEALTH perspective, *Emerg. Microb. Infect.* 11 (1) (2022) 2520–2528, <https://doi.org/10.1080/22221751.2022.2125343>.
- [40] C.J. Reynolds, C. Pade, J. M. Gibbons, A.D. Otter, K. Lin, D.M. Sandoval, et al., Immune boosting by B.1.1.529 (Omicron) depends on previous SARS-CoV-2 exposure, *Science* 377 (6603) (2022), <https://doi.org/10.1126/science.abq1841>.
- [41] M.A. Nuñez, A. Pauchard, A. Ricciardi, Invasion science and the global spread of SARS-CoV-2, *Trends Ecol. Evol.* 35 (8) (2020) 642–645, <https://doi.org/10.1016/j.tree.2020.05.004>.
- [42] P. Zhou, Z.L. Shi, SARS-CoV-2 spillover events, *Science* 371 (6525) (2021) 120–122, <https://doi.org/10.1126/science.abf6097>.
- [43] S. Mathavarajah, A.K. Stoddart, G.A. Gagnon, G. Dellaire, Pandemic danger to the deep: the risk of marine mammals contracting SARS-CoV-2 from wastewater, *Sci. Total Environ.* 760 (2021), 143346, <https://doi.org/10.1016/j.scitotenv.2020.143346>.
- [44] K. Sharun, R. Tiwari, A.R.A. Saied, K. Dhama, SARS-CoV-2 vaccine for domestic and captive animals: an effort to counter COVID-19 pandemic at the human-animal interface, *Vaccine* 39 (49) (2021) 7119–7122, <https://doi.org/10.1016/j.vaccine.2021.10.053>.
- [45] T. Lefrançois, D. Malvy, L. Atlani-Duault, D. Benamouzig, P.-L. Druais, Y. Yazdanpanah, et al., After 2 years of the COVID-19 pandemic, translating One Health into action is urgent, *Lancet (London, England)* 6736 (22) (2022) 1840–1842, [https://doi.org/10.1016/S0140-6736\(22\)01840-2](https://doi.org/10.1016/S0140-6736(22)01840-2). S0140.
- [46] X.X. Zhang, J.-S. Liu, L.-F. Han, S. Xia, S.-Z. Li, O.Y. Li, et al., Towards a global One Health index: a potential assessment tool for One Health performance, *Infect. Dis. Poverty* 11 (2022) 57, <https://doi.org/10.1186/s40249-022-00979-9>.