Review: SARS-CoV-2 natural infection in animals

Revisión: Infección natural por SARS-CoV-2 en animales

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ABSTRACT

The objective of this study was to evaluate epidemiological and pathological reports of confirmed outbreaks and cases of zoo, farm, and pet animals naturally infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Confirmed reports of outbreaks and cases of SARS-CoV-2 infected animals were obtained by systematically researching and analyzing information available in open access databases. The reports were evaluated, incorporated into a database, classified, and integrated to estimate average morbidity and mortality values and characteristic clinical manifestations of SARS-CoV-2 in animals. Post-mortem lesions and microscopic alterations are also included. Diagnostic and therapeutic alternatives to confirm or mitigate infection in animals are outlined. Finally, control methods include isolation, culling of affected populations, and the development of the first available vaccines for animals. Available information suggests that domestic and zoo animals have become accidental hosts of SARS-CoV-2, becoming infected primarily through contact with COVID-19 affected humans; although there is concern that animals could become a risk for maintaining and spreading new mutant variants of the virus, which could eventually return to human populations.
Keywords: SARS-CoV-2, COVID-19, zoonosis, animal infection.

RESUMEN

El objetivo de este estudio fue evaluar los informes epidemiológicos y patológicos de brotes y casos confirmados de la enfermedad por SARS-CoV-2 en animales de zoológico, granja y mascota infectados naturalmente. Se obtuvieron informes de brotes y casos de animales infectados por SARS-CoV-2 mediante búsqueda, análisis y clasificación sistemática de información disponible en bases de datos de libre acceso. Los informes se evaluaron e incorporaron a una base de datos, se clasificaron e integraron para identificar los valores característicos de morbilidad, mortalidad y manifestaciones clínicas del SARS-CoV-2 en animales; además de lesiones post mortem y alteraciones microscópicas. Se indican alternativas diagnósticas y terapéuticas para confirmar o mitigar la infección en animales; métodos de control como el aislamiento, sacrificio de poblaciones afectadas y las primeras vacunas disponibles para animales. La

información disponible sugiere que los animales se han convertido en huéspedes accidentales del SARS-CoV-2, infectándose principalmente a través del contacto con personas afectadas por COVID-19; aunque existe la preocupación de que los animales podrían convertirse en un riesgo de mantenimiento y propagación de nuevas variantes virales, que eventualmente podrían volver a las poblaciones humanas.
Palabras clave: SARS-CoV-2, COVID-19, zoonosis, infección animal.

Introduction

In December 2019, in Wuhan, Hubei province, China, the first cases of sick patients with pneumonia of unknown origin were epidemiologically linked to the Huanan Seafood Market (Ciotti *et al.*, 2020; Xie & Guangzhou, 2020), where more than one hundred different species of animals were sold, including mammals (civets, koalas, bats, foxes), birds (ostriches, pheasants, ducks, peacocks), reptiles, and amphibians (crocodiles, snakes, frogs) in overcrowded conditions, poor hygiene, and inadequate handling of water, waste, and cadavers (Fasina, 2020; Jalava, 2020; Ji *et al.*, 2020b).

It was quickly identified that this disease was caused by a new ß-coronavirus initially named new coronavirus disease (2019-nCoV). On January 12, 2020, it was officially named coronavirus disease 2019 (COVID-19) by the WHO (World Health Organization) or SARS-CoV-2 by the International Committee on Viral Taxonomy (Ahn *et al.*, 2020).

The first reports in humans indicate that they were in contact with civets (*Paguma larvata*) sold in the Huanan Seafood Market before manifesting the first clinical signs of the disease, establishing a possible zoonotic origin of the disease. However, several studies indicate that this civet species is only an intermediate host because the genetic sequence of SARS-CoV-2 showed a 96.2% homology with the bat coronavirus CoV-RaTG13, bats being the species responsible for the outbreak of this new disease Salata *et al.,* 2019; Ye *et al.*, 2020).

This is not the first time that a species of β-coronavirus of animal origin has affected humans; in 2003, in the province of Guangdong, China, a coronavirus originating in bats affected humans through an intermediate host (palm civet; *Paguma larvata*). This virus is called severe acute respiratory syndrome (SARS) and caused 916 deaths and affected 8,422 people with a mortality of 10.9% (Singhal, 2020). In 2012, in Saudi Arabia, another virus originated in bats called Middle East respiratory syndrome coronavirus (MERS-CoV) affecting 2,494 people. It caused 858 deaths with a mortality of 34% (Shereen *et al.*, 2020). Reports of SARSCoV-2 outbreaks in animals are scarce, but their geographical distribution is very diverse. This coincides with a worldwide spread of the virus. Therefore, this paper aims to review the presence of the infection in pets, farm animals and zoos. Information on the origin and parallel spread between humans and animals, the mechanisms of infection and its impact on animal health are reviewed. Viable alternatives for diagnosis and therapy of SARSCoV-2 in animals are presented, and control of the pandemic with available vaccines is highlighted. The objective of this study was to

evaluate reports of outbreaks and confirmed cases of animals naturally infected with SARS-CoV-2 about epidemiological and pathogenic patterns in zoo, farm, and domestic animals.

Methods

This review was conducted by establishing a research objective, search strategies, and relevant research articles and reports; selection of bibliographic material, data extraction, data mapping, and summary of results were performed. The literature for this review was identified by searching online databases (World Organization for Animal Health, OIE, and World Health Organization, WHO, Google scholar, PubMed, and Web of Science). We searched for scientific publications from 2019 to 2022. The search terms were 'CORONAVIRUS', 'SARS', 'ANIMAL' and "COVID-19". All relevant scientific publications and official reports were included in the review, but other types of information (congresses, theses, etc.) were excluded from the analysis. Two investigators independently evaluated each bibliographic source. The two sets of selected literature were then compared; disagreements about the inclusion of the literature were resolved by group discussion to make the decision. Data on design, objectives, animal population, instrumental methodology, main results, and conclusions were extracted. Articles were categorized into the following areas "Origin", "Host species", "SARS-CoV-2", "Pathogenesis", "Clinical findings", "Lesions", "Therapeutic strategies", "Control" and "Vaccines". Quantitative data reported in the outbreaks were summarized and averages by animal species were estimated. All conclusions and statements in this review are based on published information, as indicated in the references.

Distribution of the new coronavirus

On December 30, 2019 (Chowdhury & Oommen, 2020; Rothan & Byrareddy, 2020) an outbreak of pneumonia of unknown etiology was reported in the city of Wuhan (Fig. 1). On January 7, 2020, the isolation and identification of the genome of a new coronavirus was performed (Bulut & Kato, 2020). On January 13, 2020, an increase in the propagation of the virus associated with nosocomial infections and direct contact with infected relatives was detected. On the same day, the first case of the novel coronavirus was confirmed in Thailand, and on January 19, the first cases were reported in Beijing, which indicated the spread of the virus within China and across the surrounding region (Sun *et al.*, 2020). By January 22, the National Health Commission of China reported 17 deaths and 571 infected people in 25 provinces of China (Rothan & Byrareddy, 2020), which is why the government of Wuhan implemented a total closure of activities inside and outside the city. Unfortunately, these measures coincided with the beginning of the Chinese New Year, which meant that more than five million people left the city to return to their homes. This caused an increase in the number of confirmed cases; therefore, on January 30, 2020, the WHO declared the disease caused by SARS-CoV-2 a "Public Health Emergency of International Concern" (WHO, 2020).

Animals   **2019**   **Humans**

December — ▶ 30 Disease (Wuhan, China)

2020

January — ▶ 7th Isolation of the virus
12th Identification of the genome and first dead
13th Outbreak outside China
20th America
21th Western Pacific
24th Europe
29th Eastern Mediterranean
30th Public health emergency of international concern

29th Domestic dogs (Hong Kong, China) ◀ — **February** — ▶ 11th Renamed COVID-19 or SARS-CoV-2
25th Africa

28th Domestic cats ◀ — **March**

6th Zoo big cats ◀ — **April** — ▶ 4th 1.0 million cases
26th Farms minks

September — ▶ 19th 1.0 million people dead

5th 17 MM minks slaughtered ◀ — **November**

December — ▶ 8th First person vaccinated (United Kingdom)

2021

11th Zoo big primate ◀ — **January** — ▶ 16th 2.0 million people dead
20th Establishes the SARS-CoV-2 risk
assessment manual in animals used for
fur farming (OIE)

28h Zoo otter ◀ — **April** — ▶ 18th 3.0 million people dead
30th Starts vaccination in animals
(Russia)

June — ▶ 2th 1.6 billon vaccine doses administered
4th 171 million confirmed cases
3.6 million people dead

17th Wild deer ◀ — **August** — ▶ 18th 4.5 billon vaccine doses administered
208 million confirmed cases
4.5 million people dead

14h Zoo binturong ◀ — **October**
Zoo coati

10th 1850 confirmed cases ◀ — **December** — ▶ 10th 8.1 billon vaccine doses administered
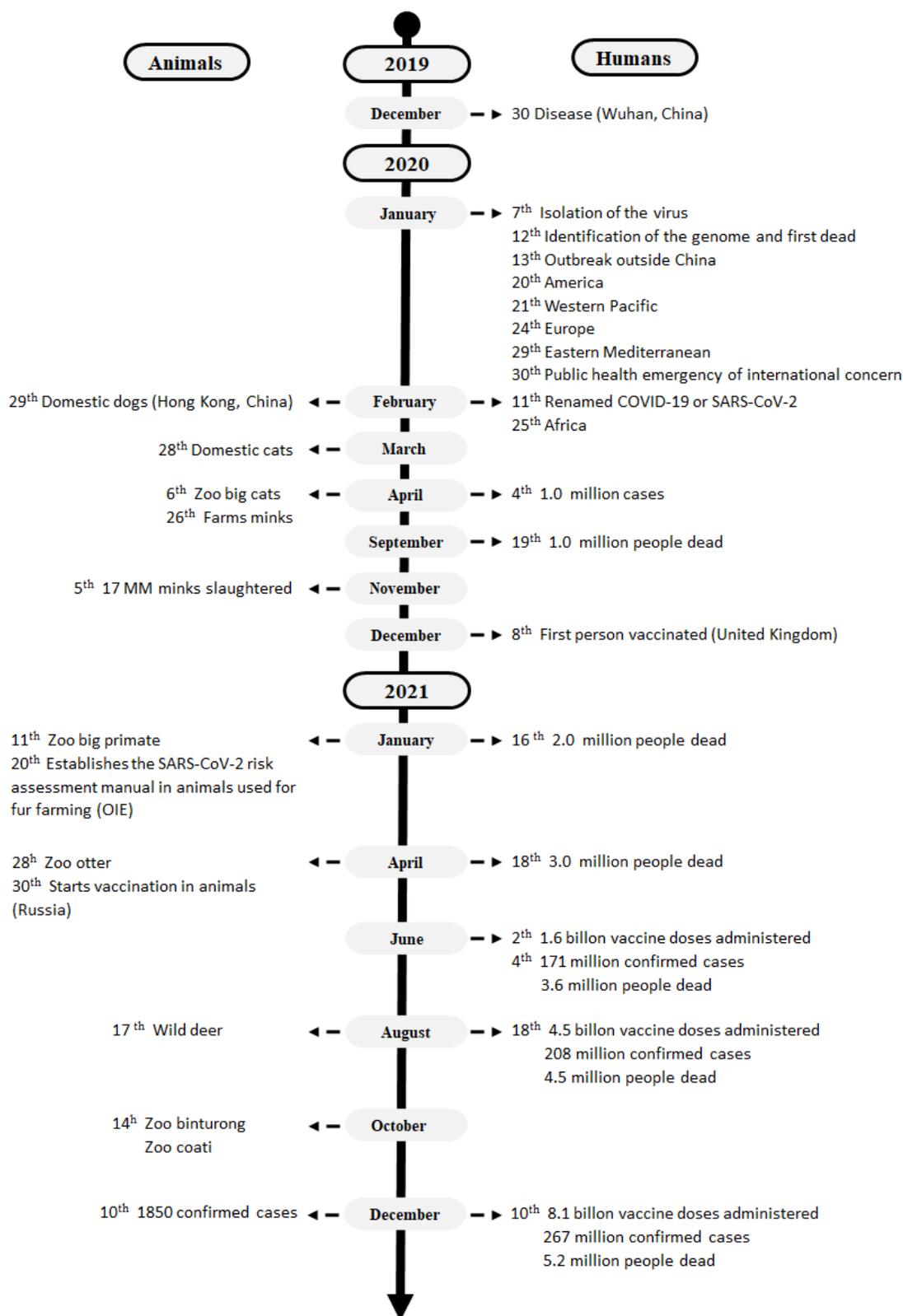267 million confirmed cases
5.2 million people dead

Figure 1. Timeline of the epidemiological spread of SARS-CoV-2 in humans and animals. Source: Own elaboration with data from: (OIE-WAHIS, 2021; WHO, 2021).

During the first week of February in Wuhan, a turning point in the epidemic was observed, where the daily number of confirmed cases began to decrease; however, it is not known whether the reduction in virus transmission was due to the established blockade, the public health measures implemented or other factors (Sun *et al.*, 2020). Since its onset in China, the disease spread rapidly. The number of cases increased exponentially worldwide, and in a couple of months, it extended to all continents except Antarctica (Bulut & Kato, 2020; Chowdhury & Oommen, 2020; Rothan & Byrareddy, 2020; Sun *et al.*, 2020; WHO, 2021).

Although there is extensive documentation on the progress of COVID-19 in humans, there are few studies related to the epidemiological distribution of SARS-CoV-2 in animals. In outbreaks in animals, the presence of clinical respiratory signs has been reported, in addition to low mortality and morbidity. It should be noted that contact with previously infected owners or workers has been identified as a source of infection for animals (OIE-WAHIS, 2021).

Epidemiological information worldwide indicates a greater number of outbreaks in domestic animals, with morbidity and mortality rates of 52.5% and 2.6%, respectively. Cats are the species with the most reported outbreaks (OIE-WAHIS, 2021). In zoo animals, the disease has been identified in gorillas, cougars, lions, leopards, and tigers, with a presence of respiratory signs in 83.7% of the outbreaks (OIE-WAHIS, 2021).

One year after the beginning of the pandemic, on December 8, 2020, the first person worldwide was vaccinated against SARS-CoV-2, and a new viral variant was identified in the United Kingdom. By January 2021, two million deaths and more than 100 million infected people were counted worldwide; the OIE established a risk manual for farm animals due to the great losses in the production of minks (OIE-WAHIS, 2021). By April, the number of deaths in humans increased to three million, and the application of the first vaccines against COVID-19 in animals began. In August and October, the first reports of COVID-19 in wild deer, otters, and binturong were presented, reporting a total of 1,850 confirmed cases in animals and 267 million in humans. A possible animal-to-human transmission of SARS-CoV-2 was documented on January 31, 2022, in Hong Kong, where the Delta variant was detected in hamsters as well as in a pet store employee (OIE-WAHIS, 2021) .

Possible hosts of the virus

In China, there are established farms dedicated to the breeding of exotic animals for human consumption (civets, bats, pangolins, snakes), which distribute their products to various restaurants. Consequently, it has been assumed that farms, restaurants, and wet markets were probably responsible for the zoonotic origin of the new coronavirus (Tiwari

et al., 2020). Different authors point to four possible animal species as the initial hosts-bats, pangolins, civets, and snakes (Fig. 2) due to the high similarity in their genome and in some surface proteins that the coronaviruses of these animal species have in relation to SARS-CoV-2 (Anand *et al.*, 2020; Ji & Li, 2020; Lau *et al.*, 2020; Zheng, 2020).
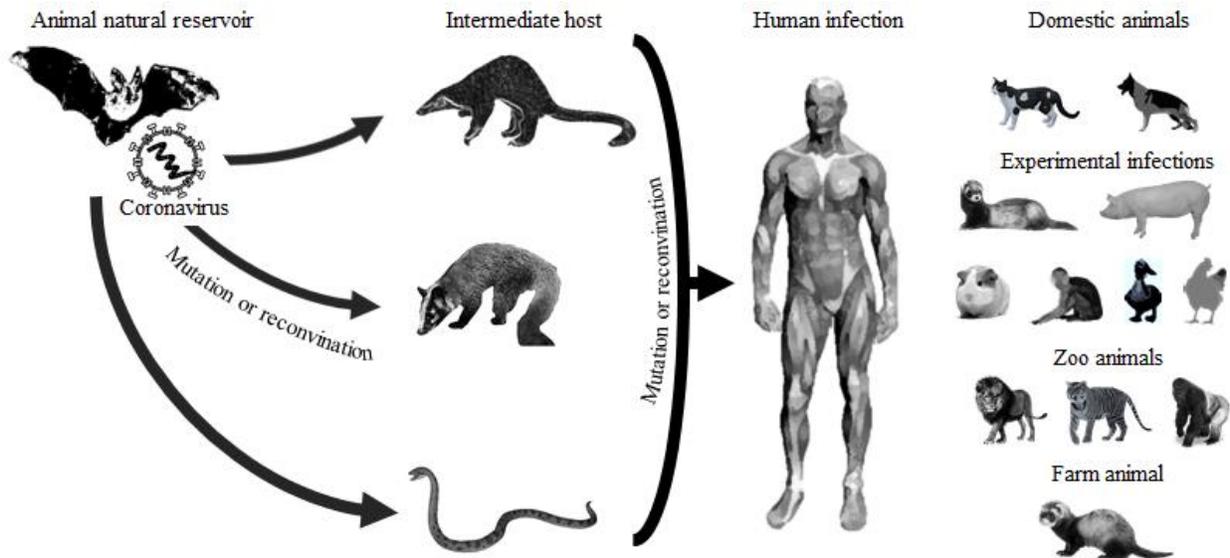

Figure 2. There is a possible origin, transmission, and infection of SARS-CoV-2. The natural reservoir is bats, and the possible intermediate hosts are pangolins, civets, and snakes. Species infected with SARS-CoV-2 include humans, domestic animals (dogs and cats); animals with experimental infections (ferrets, pigs, macaques, ducks, and chickens), zoo animals (lions, tigers, and gorilla), and farm animals (minks). Source: Own elaboration with data from: **(Anand *et al.*, 2020; Ji & Li, 2020; Lau *et al.*, 2020; Zheng, 2020).**

It has been described those bats are reservoirs for different species of coronavirus due to because when the carry the virus, it remains latent and asymptomatic. As well, the great distances they must travel to obtain food allows them to infect other animal species (Tiwari *et al.*, 2020). Laboratory findings reported that SARS-CoV-2 has a genetic identity of 87.6%, 87.8%, and 96.1% with SARSr-Rp-BatCoV-ZXC21, SARSr-Rp-BatCoV-ZC45, and SARSr-Ra-BatCoV-RaTG13, respectively, which are viruses identified in bats (*Rhinolophus pusillus, R affinis*) captured in China (Lau *et al.*, 2020).

Although SARS-CoV-2 appears to have originated initially in bats, it is probably that it used pangolins as intermediate hosts. Analysis of pangolin samples revealed several viral sub-lineages related to SARS-CoV-2 (Table 1) (Hu *et al.*, 2021; Zheng, 2020). Several studies point to the Malayan pangolin (*Manis javanica*) as a possible natural reservoir or intermediate host of COVID-19 (Zhang *et al.*, 2020). Genomic analyses suggest that GD Pangolin CoV has a nucleotide sequence similarity of 90.32% and 90.24% with SARS-CoV-2 and Bat-CoV-RaTG13, respectively. However, the similarity in some viral protein

sequences could be 100% (Liu *et al.*, 2020). These results could consider pangolins as an intermediate host of SARS-CoV-2 (Xiao *et al.*, 2020), referring that it probably could have originated from a genetic recombination between bat and pangolin coronaviruses (Wong *et al.*, 2020).

Table 1. SARS-CoV-2-related coronaviruses and their lineages in Sarbecovirus-infected animals

Related linage	Animal species infected by *Sarbecovirus*		
	Bat	**Pangolin**	**Human**
SARS-CoV	Bat SARSr-CoV Rs4231		SARS-CoV GZ02
	Bat SARSr-CoV SHC014		SARS-CoV Tor2
	Bat SARSr-CoV WIV1		SARS-CoV BJ01
	Bat SARSr-CoV Rp3		
	Bat SARSr-CoV HKU3-1		
SARS-CoV-2	Bat coronavirus ZXC21	GD_Pangolin-CoV	*Alpha variant (United Kingdom)*
	Bat coronavirus ZC45	GX_Pangolin-CoV_P2V	SARS-CoV-2 B.1.1.7
	Bat coronavirus RmYN02	GX_Pangolin-CoV_P5E	*Beta variant (South Africa)*
	Bat coronavirus RaTG13	GX_Pangolin-CoV_P1E	SARS-CoV-2 B.1.351
		GX_Pangolin-CoV_P5L	SARS-CoV-2 B.1.351.2
		GX_Pangolin-CoV_P4L	SARS-CoV-2 B.1.351.3
		GX_Pangolin-CoV_P3B	*Gamma variant (Brazil)*
			SARS-CoV-2 P.1
			SARS-CoV-2 P.1.1
			SARS-CoV-2 P.1.2
			Delta variant (India)
			SARS-CoV-2 B.1.617.2
			SARS-CoV-2 AY.1
			SARS-CoV-2 AY.2
			Omicron variant (South Africa)
			SARS-CoV-2 B.1.1.529

Source: Own elaboration with data from: (Hu *et al.*, 2021).

However, other researchers consider civets as a possible intermediate host and transmitter of the new coronavirus due to seroepidemiological results that identified antibodies against SARS-CoV-2 in people previously exposed to contact with these animals (Salata *et al.*, 2019). Phylogenetic analysis of SARS-CoV-2 showed a genome similarity of 78.6% with Civet-SARSr-CoVs. The ability of SARS-CoV-2 to emerge and infect humans could be caused by the genetic similarity between SARSr-BatCoV and Civet-SARSr-CoV from Yunnan, China (Lau *et al.*, 2020).

Similarly, there is a theory that the snake can serve as a natural reservoir of SARS-CoV-2 and participate in its transmission between animals and humans (Ji & Li, 2020), due to the similarity of the codons of SARS-CoV-2, bat-SL-CoVZC45, and snake coronavirus. However, SARS-CoV-2 has not been isolated in snakes so far (Zheng, 2020). These investigations suggest that COVID-19 possesses similar genetic information to bat and snake coronaviruses, and thus, recombination in its viral binding proteins could be responsible for cross-species transmission (Ji et al., 2020a).

Infected animal species

The identification of reservoir animals as infectious agents with zoonotic potential is essential for the establishment of sanitary measures to mitigate the adverse effects of the disease. However, this type of infectious agent can infect a wide variety of domestic or wild animals (OIE-WAHIS, 2021). Because coronaviruses have a wide diversity of animal species they can infect, there is the possibility they can cross the barrier between species by means of genetic recombination mechanisms that allow them to infect other animal species and even humans (Abdel-Moneim & Abdelwhab, 2020).

This process has been previously identified in SARS and MERS outbreaks. Like SARS-CoV-2, these were caused by a coronavirus that jumped the species barrier. Although the true origin of SARS-CoV-2 is currently unknown, the phylogenetic identity has served as a basis for suspicions that it was initially transmitted by bats, where this virus, in addition to infecting humans, has infected other animal species (Tiwari et al., 2020). Other research detected probable SARS-CoV-2 deer-to-deer transmission that demonstrates the possibility of opening new evolutionary pathways (Hale et al., 2022).

Pet animals

The first reported case was identified in Hong Kong on February 29, 2020, in a domestic dog belonging to a family infected with coronavirus, whereas in domestic and zoo felids, the first outbreaks of this disease were reported on March 28 and April 6, 2020 (OIE-WAHIS, 2021), respectively. The first reports of COVID-19 in dogs and cats in China were diagnosed by using polymerase chain reaction (PCR) for the isolation and sequencing of the viral genome (Ruiz-Arrondo et al., 2020; Sit et al., 2020). Studies showed that after a local outbreak in humans, antibodies to SARS-CoV-2 were detected in dogs and cats (Abdel-Moneim & Abdelwhab, 2020). After the outbreak in China, cases of COVID-19 were reported in domestic animals in different countries of the world (OIE-WAHIS, 2021). In all the outbreaks, the animals belonged to people previously ill with COVID-19. This evidence suggests a possible origin of the infection: the transmission from human to animal as well as the transmission from infected animals to humans, which has not been identified until now (Sit et al., 2020).

Farm animals

The first official report on SARS-CoV-2 in farm animals comes from mink farms located in the Netherlands. On April 19, 2020, some animals began to manifest clinical respiratory signs ranging from a slight nasal discharge to severe respiratory distress. Subsequently, outbreaks have occurred in other mink farms, affecting a population of 736,257 animals. The possible cause of infection was contact with sick workers with COVID-19. Due to the growing number of infected animals and the discovery of a new mutation of SARS-CoV-2, several countries of the European Union proceeded to slaughter more than 17 million minks, thus preventing the propagation and dispersion of a new viral variant (OIE-WAHIS, 2021; Oreshkova *et al.*, 2020).

Zoo animals

There have been reports of lions, tigers, cougars, leopards, lynx, otters, coati, binturong and gorillas diagnosed by PCR and genetic sequencing as SARS-CoV-2-positive. Most of these animals presented respiratory clinical signs where the possible cause of infection was previously infected zookeepers (OIE-WAHIS, 2021).

Experimental infections

Experimental infections in various animal species have been developed in the laboratory to understand the pathogenesis and development of the disease. For this reason, species such as hamsters, ferrets, macaques, shrews, and mice have been inoculated by different routes (intratracheal, intranasal, ocular, and oral), where the immunopathology, transmission and development of COVID-19 treatments have been established (Abdel-Moneim & Abdelwhab, 2020; Shi *et al.*, 2020). Experimentally infected swine and poultry (quails, geese, ducks, turkeys, and chickens) showed no clinical signs or pathological lesions, and it was not possible to identify the presence of viral RNA or antibodies. These results indicate that none of these animal species are susceptible to SARS-CoV-2, and they do not play an important role in its transmission (Shi *et al.*, 2020; Suarez *et al.*, 2020).

Characteristics of SARS-CoV-2

Until recently, coronaviruses in humans were not considered to cause anything more serious than the common cold. However, before advent of the COVID-19 pandemic, these viruses have had a higher profile in veterinary medicine (Table 2). SARS-CoV-2 is a β-coronavirus of the subgenus *Sarbecovirus*, subfamily *Orthocoronavirinae*, whose members primarily infect bats (Wrobel *et al.*, 2020). The *Coronaviridae* family consists of four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* (Chen *et al.*, 2021).

SARS-CoV-2 is an enveloped, capsid-bound, non-segmented, single-stranded RNA virus with a series of spikes on its surface, which are known as "S" proteins and are responsible for its binding to cellular epithelia (Majumder & Minko, 2021).

As a member of the *Betacoronavirus* genus, SARS-CoV-2 shares a genomic similarity of 50% and 79% with MERS-CoV2 and SARS-CoV, respectively, and SARS-CoV-2 encoded proteins have a similar length to those corresponding to SARS-CoV (Hu *et al.*, 2021). Several authors point out the degree of molecular divergence between SARS-CoV-2 and other coronaviruses. The phylogenetic analysis of SARS-CoV-2 shows a relationship with SARS-CoV, and other SARS-related coronaviruses found in bats (Tang *et al.*, 2020). SARS- CoV-2 clusters in a distinct lineage along with four bat coronaviruses, RaTG13, RmYN02, ZC45, and ZXC21, as well as new coronaviruses recently identified in pangolins, which cluster similarly to SARS coronavirus (Hu *et al.*, 2021).

Table 2. Taxonomic classification of the coronaviruses

Subfamily	Genus	Subgenus	Species
Letovirinae	*Alphaletovirus*	*Milecovirus*	*Microhyla letovirus 1*
Orthocoronavirinae	*Alphacoronavirus*	*Duvinacovirus*	*Human coronavirus 229E*
		Minacovirus	*Mink coronavirus 1*
		Pedacovirus	*Porcine epidemic diarrhea virus*
		Setracovirus	*Human coronavirus NL63*
		Tegacovirus	*Alphacoronavirus 1 (Canine, feline and porcine coronavirus, Transmissible gastroenteritis virus)*
	Betacoronavirus	*Embecovirus*	*Human coronavirus HKU1*
		Merbecovirus	*Middle East respiratory syndrome-related coronavirus*
		Sarbecovirus	*Severe acute respiratory syndrome-related coronavirus*
	Deltacoronavirus	*Buldecovirus*	*Coronavirus HKU15* (Porcine)
	Gammacoronavirus	*Igacovirus*	*Avian coronavirus (infectious bronchitis)*

Source: Own elaboration with data from: (ICTV, 2021).

Pathogenesis

The routes of transmission identified in animals for infection caused by COVID-19 have been reported as the main cause of contact with infected persons as well as the inhalation of aerosol particles (OIE-WAHIS, 2021), which have the capacity to lodge in the respiratory tract (Rothan & Byrareddy, 2020; Woodby *et al.*, 2020). In animals, a incubation period has been described in experimental and natural SARS-CoV-2 infections (2 to 14 days; Fig. 3) (Munster *et al.*, 2020; Shi *et al.*, 2020; Tiwari *et al.*, 2020). It has been observed in most outbreaks that the onset of clinical manifestations and recovery is earlier, with the first clinical signs being observed as early as 0-10 days postexposure

(dpe) and ceasing between 9 or 17 dpe. However, the presence of viral RNA can be detected from 3-13 dpe, whereas the formation of antibodies is generated at 10 dpe or more. Furthermore, the presence of radiographic changes in the lungs and pathological lesions in various organs (1-3 dpe) has been described, which may persist after the end of the disease (Abdel-Moneim & Abdelwhab, 2020; Chan *et al.*, 2020; Lu *et al.*, 2020). Outbreaks with clinical manifestations have occurred mainly in animals with a history of cardiovascular, respiratory, neurological diseases, neoplasms, and obesity (OIE-WAHIS, 2021; Ruiz-Arrondo *et al.*, 2020).
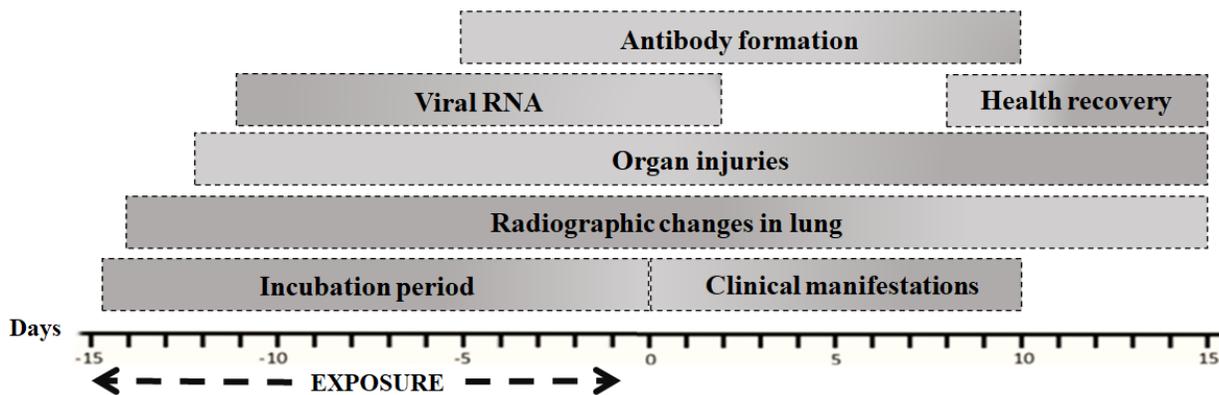

Figure 3. Natural history of SARS-CoV-2 in animals. Source: Own elaboration with data from**: (Abdel-Moneim & Abdelwhab, 2020; Chan *et al.*, 2020; Lu *et al.*, 2020)**

Nasal epithelial cells have been identified as the site of initiation of SARS-CoV-2 infection, where an increase in ACE2 levels has been observed due to a high binding affinity for the SARS-CoV-2 spike glycoprotein. Subsequently, through inspiration, the virus manages to colonize the respiratory tract, where it invades type II pneumocytes and initiates a phase of rapid viral replication, producing localized inflammation, increased vascular permeability, increased chemotaxis, and pulmonary edema (Chan *et al.*, 2020; Munster *et al.*, 2020).

The presence of edema in the lungs hinders them from filling with air, causing low oxygen saturation, pneumonia, lung damage, and death. Lung damage allows the virus to enter the bloodstream and initiate the activation of the coagulation cascade, thrombus formation, and damage to other organs such as the heart, kidney, brain, stomach, and intestine (Lotfi & Rezaei, 2020; Shi *et al.*, 2020).

In animals, reports of natural and laboratory infections have described the presence of histopathological lesions in the liver, heart, kidney, and intestine; respiratory failure; arrhythmias; and complication with opportunistic bacterial infections (Lu *et al.*, 2020; OIE-WAHIS, 2021). These reports demonstrate that if the organism is unable to control the early stages of viral replication, it can give rise to severe disease and cause death as a result of an impaired or delayed immune response (Woodby *et al.*, 2020).

Clinical manifestations in animals

During the development of this pandemic, the clinical symptomatology in humans has been described in detail; however, in animals, there are currently few reports of outbreaks describing the clinical manifestations, lesions, and pathological alterations associated with SARS-CoV-2 infection (OIE-WAHIS, 2021). It has been observed that the presentation of the disease in animals (Table 3, 4) is very similar to its presentation in humans. In animals, respiratory clinical signs include cough, dyspnea, nasal secretion, sneezing, fever, and inflammation in the anterior and posterior respiratory tract (Abdel-Moneim & Abdelwhab, 2020; OIE-WAHIS, 2021; Shi *et al.*, 2020).

In addition to anorexia, fatigue, depression, and stooped posture (Chan *et al.*, 2020; Munster *et al.*, 2020), in farm animals, alterations in reproductive parameters, increased mortality, and development of secondary infections have been reported (Oreshkova *et al.*, 2020).

The principal postmortem lesions described in animals (Table 4) show acute interstitial pneumonia with the presence of edema, hemorrhages, and areas of pulmonary consolidation; epithelial necrosis in the anterior airways; decrease in the alveolar lumen; infiltration of inflammatory and immune cells; and hematological alterations and radiographic changes in the pulmonary pattern (Boudewijns *et al.*, 2020; Pruijssers *et al.*, 2020; Schlottau *et al.*, 2020).

Diagnostic techniques

Several diagnostic methods have been developed for clinical use or research. Their rationale is based mainly on the detection of nucleic acids or immunological and pathological changes. The WHO has established the importance of the use of SARS-CoV-2 diagnostic tests that allow surveillance of the disease, limit its spread, assess the epidemiological risk, trace positive cases, local control of outbreaks, and determine previously infected individuals. COVID-19 tests are divided into two groups based on their diagnostic foundation (Table 5): tests for the detection of viral nucleic acid and tests for the detection of antigens or antibodies (Jarrom *et al.*, 2020).

Molecular tests are based on the presence of nucleic acids in a sample to make a diagnosis. These tests can detect nucleic acids prior transcription and are therefore considered essential for the diagnosis of diseases of viral origin. Some of these tests use procedures to identify and amplify viral nucleic acid, such as real-time reverse transcriptase PCR, reverse transcriptase loop-mediated isothermal amplification and reverse transcriptase recombinase polymerase amplification (Jarrom *et al.*, 2020). These techniques have high sensitivity, specificity, and performance and are reliable and easy to implement. However, they have a disadvantage in their complex design of primers and alteration in sensitivity due to an insufficient viral load, in addition to not indicating whether

the disease has been present previously (Gao & Quan, 2020; Jarrom *et al.*, 2020; Li *et al.*, 2020).

Table 3. Analysis of SARS-COV-2 outbreaks in domestic, zoo, wild, and farm animals

Animal species	Report date		Outbreaks (No.)	Outbreaks with clinical respiratory signs (%)	Susceptible animals (No.)	Apparent morbidity (%)	Deaths (No.)	Apparent mortality (%)	Confirmed animals (No.)	Probable source of contagion
	First	Last								
Domestic	**02/29/20**	**12/06/21**	**85**	**43.5**	**270**	**52.5**	**7**	**2.6**	**142**	**Owner**
-Cat	03/28/20	12/06/21	43	46.5	140	55.0	3	2.1	77	Owner
-Dog	02/29/20	12/06/21	40	37.5	127	49.6	4	3.1	63	Owner
-Ferret	12/23/20	09/28/21	2	100	3	66.6	0	0.0	2	Owner
Zoo	**08/11/20**	**10/28/21**	**49**	**83.7**	**223**	**47.0**	**2**	**0.8**	**105**	**Staff**
-Binturong	10/14/21	10/14/21	1	100	1	100	0	0.0	1	Staff
-Cougar	08/11/20	03/18/21	4	25.0	16	18.7	0	0.0	3	Staff
-Fisher cat	10/14/21	10/14/21	1	100	1	100	0	0.0	1	Staff
-Gorilla	01/11/21	10/14/21	3	33.3	34	38.2	0	0.0	13	Staff
-Lion	01/11/21	12/02/21	15	92.3	68	54.4	1	1.4	37	Staff
-Otter	04/28/21	09/13/21	3	100	14	50	0	0.0	7	Staff
-Coati	10/14/21	10/14/21	1	100	1	100	0	0.0	1	Staff
-Snow leopard	12/18/20	10/28/21	5	100	13	76.9	1	7.6	10	Staff
-Tiger	12/23/20	12/07/21	15	93.3	75	41.3	0	0.0	31	Staff
-Lynx	01/12/21	01/12/21	1	100	1	100	0	0.0	1	Staff
Wild deer	**08/31/21**	**12/01/21**	**2**	**0.0**	**360**	**3.0**	**0**	**0.0**	**11**	**Wild**
Farm mink	**04/26/20**	**12/07/21**	**33**	**24.2**	**736257**	**0.2**	**8601**	**1.1**	**1592**	**Staff**
America	**04/6/20**	**10/28/21**	**93**	**72.0**	**56404**	**0.6**	**8062**	**14.2**	**391**	
-Domestic	04/22/20	09/21/21	50	60.0	210	45.7	7	3.3	96	Owner
-Farm	08/20/20	12/9/20	3	100	55657	0.36	8053	14.4	200	Staff
-Zoo	04/6/20	10/28/21	38	89.5	177	47.4	2	1.1	84	Staff
-Wild	08/31/21	12/01/21	2	0.0	360	3.0	0	0.0	11	Wild
Europe	**03/28/20**	**10/25/21**	**58**	**32.8**	**680656**	**0.2**	**548**	**0.1**	**1427**	
-Domestic	03/28/20	12/06/21	21	33.3	37	67.5	0	0.0	25	Owner
-Farm	04/26/20	12/07/21	30	16.7	680600	0.2	548	0.1	1392	Staff
-Zoo	12/8/20	12/07/21	7	100	19	52.6	0	0.0	10	Staff
Asia	**02/29/20**	**12/02/21**	**16**	**18.8**	**45**	**62.2**	**0**	**0.0**	**28**	
-Domestic	02/29/20	10/06/21	14	7.1	23	91.3	0	0.0	21	Owner
-Zoo	09/08/21	09/08/21	2	100	22	31.8	0	0.0	7	Staff
Africa										
-Zoo	08/11/20	07/27/21	2	100	5	80.0	0	0.0	4	Staff
Overall	**02/29/20**	**12/07/21**	**166**	**56.6**	**737110**	**0.25**	**8610**	**1.3**	**1850**	

Source: Own elaboration with data from: (OIE-WAHIS, 2021)

Table 4. Clinical manifestations in animals infected with SARS-CoV-2

Animal species	Clinical signs	Lesions and alterations	References
Domestic animals			
Cat	Ocular and nasal discharge, fever, dyspnea, sneezing, wheezing, hypothermia, lethargy, anorexy.	Inflamed and hemorrhagic nasal, tracheal and pulmonary mucosal epithelia.	(OIE-WAHIS, 2021; Oreshkova *et al.*, 2020)
Dog	Dry cough, nasal discharge, fever, dyspnea, abnormal lung sounds, positive palm percussion, pharyngitis, bronchitis, polypnea, tachycardia, fatigue, anorexy, depression, lymph adenomegaly.	NR	(OIE-WAHIS, 2021)
Zoo animals			
Lion	Dry cough, serous nasal discharge, dyspnea.	NR	(OIE-WAHIS, 2021)
Snow leopard	Dry cough, nasal discharge, wheezing, sneezing.	NR	(OIE-WAHIS, 2021)
Tiger	Dry cough, nasal discharge, dyspnea, anorexy, neurological alterations.	Trachea and bronchi with presence of bloody mucus.	(OIE-WAHIS, 2021)
Farm animals			
Mink	Cough, nasal discharge, severe dyspnea, sneezing, Bodyweight loss, inappetence, increase in mortality, reproductive failure.	Diffuse interstitial pneumonia with hyperemia, loss of alveolar lumina, sepsis, edema, diffusely dark lung lobes, dystocia, clinical alterations compatible with chronic Aleutian disease.	(Abdel-Moneim & Abdelwhab, 2020; OIE-WAHIS, 2021; Sit *et al.*, 2020)
Lab animals			
Monkey	Hyperthermia, Bodyweight loss.	Radiographic changes in lungs, macroscopic and inflammatory alterations in the lung, heart, liver and stomach, hematological alterations (lymphocytosis, monocytosis and increased cytokine activity).	(Munster *et al.*, 2020)
Macaque	Cough, fever, changes in respiratory pattern, tachypnea, asthenia, bodyweight loss, anorexy, piloerection, hunched posture, pale appearance and dehydration.	Interstitial pneumonia, radiographic changes in lungs, edema, hemorrhage, lung congestion and consolidation, hematological alterations (leukocytosis).	(Woodby *et al.*, 2020)
Ferret	Cough, fever, adynamic, anorexy.	Rhinitis with epithelial degeneration and necrosis, bronchiolitis, mixed cellular infiltrates in lungs, increase in alveolar macrophages, severe lymphoplasmacytic vasculitis and perivasculitis.	(Lu *et al.*, 2020; Oreshkova *et al.*, 2020)
Mice	Dyspnea, bodyweight loss, thin hair.	Pneumonia with infiltration of inflammatory and immune cells, peribronchiolar inflammation, hemorrhages in lungs and alveoli.	(Boudewijns *et al.*, 2020)
Hamster	Tachypnea, lethargy, anorexy, piloerection, hunched posture.	Pneumonia, hemorrhages in lungs and alveoli, Lungs with presence of edema, hemorrhage and severe consolidation, multifocal necrotizing bronchiolitis and leukocyte infiltration.	(Lotfi & Rezaei, 2020; Schlottau *et al.*, 2020)
Shrew	Fever.	Histopathological changes in liver, spleen, intestines, pancreas, kidney, heart, lung and brain.	(Pruijssers *et al.*, 2020)

Source: Own elaboration with data from: (Boudewijns *et al.*, 2020; OIE-WAHIS, 2021; Pruijssers *et al.*, 2020; Schlottau *et al.*, 2020; Shi *et al.*, 2020; Zhao *et al.*, 2020)

Serological tests focus on the detection of antigens or antibodies against SARS-CoV-2. These tests are easy to perform, have a high yield, and allow working many samples in a short time. However, they are less accurate and are likely to give false positives and negatives. Some of the techniques used on this basis are enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay, lateral flow immunoassay, serum virus neutralization assay, immunofluorescence test, dot blot/western blot, and virus neutralization test. These techniques allow a diagnosis to be made in the laboratory or in an environment close to the patient, allowing the identification of sick, healthy, convalescent, reinfected, or previously infected animals (Gao & Quan, 2020; Jarrom *et al.*, 2020).

Table 5. Diagnostic techniques for SARS-CoV-2

Test	Sample	Advantages	Disadvantages
Nucleic acid tests for viral			
RT-PCR	Nasopharyngeal or oropharyngeal swab, bronchoalveolar lavage, tracheal aspirates, saliva	High sensitivity, specificity, performance and reliable	Sensitivity may be affected by sampling errors or insufficient viral load
RT-LAMP	Blood	High sensitivity and specificity, easy to use	Complex primers, susceptible to amplification and false positives
RT-RPA	Blood	High sensitivity and specificity, easy to use	Complex primers, susceptible to amplification and false positives
CRISPR	Blood	High sensitivity and specificity, reliable, easy visual readability	Not tested for SARS-Cov-2.
Antigen or antibodies detection tests			
ELISA	Blood and saliva	Easy to use	Not as accurate as the RT-PCR test, with false positives and negatives.
EIA	Nasopharyngeal swab and saliva	Easy to use, high performance and availability	Lack of knowledge and inability to confirm the antibodies
LFIA	Blood and saliva	Independent of laboratory equipment	Questionable sensitivity and specificity
IFT	Blood	No analyzer is required but an IF microscope is needed.	Low throughput, requires experience, discrimination of other coronavirus antibodies, time consuming
DB/WB	Blood	Discrimination of other coronavirus antibodies	Not common, WB experience required
VNT	Blood	Functional information	Biosafety level 3 lab required

RT-PCR, real-time reverse transcriptase/polymerase chain reaction; RT-LAMP, reverse transcriptase loop-mediated isothermal amplification; RT-RPA, reverse transcriptase recombinase polymerase amplification; CRISPR, clustered regularly interspaced short palindromic repeats; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; LFIA, lateral flow immunoassay; SVNA, serum virus neutralization assay; IFT, immunofluorescence test; DB/WB, Dot blot/Western blot; VNT, virus neutralization test. Source: Own elaboration with data from from: (Abduljalil, 2020; D'Cruz *et al.*, 2020; Gao & Quan, 2020; Hu *et al.*, 2021; Özçürümez *et al.*, 2020; Ravi *et al.*, 2020).

ELISA detects the presence and concentration of immunoglobulin G or immunoglobulin M antibodies in the blood but have low specificity and cannot detect viral variables because the antibodies produced are very stable between species (Li *et al.*, 2020; Michel *et al.*, 2020; Sidiq *et al.*, 2020). The western blot technique is based on the presence of viral or immune proteins in blood serum, and it can identify the molecular weight of unknown proteins other than a virus. However, it is a very laborious and time-consuming technique and is recommended more for research than for diagnosis (Sidiq *et al.*, 2020). Techniques such as immunohistochemistry make it possible to demonstrate the damage caused by the virus in the various affected tissues and is used as a support for other diagnostic techniques. This technique provides physical evidence of the lesions caused by the virus in addition to being able to reveal its presence through high resolution microscopes (Gao & Quan, 2020; Nguyen *et al.*, 2021).

Treatment

Therapeutic strategies to combat SARS-CoV-2 infection focus on reducing the severity of the disease because there are no specific drugs for treatment in animals. Even some of the most used drugs in humans (paracetamol and naproxen) are not recommended for use in dogs and cats (Papich, 2015); however, it has been recommended that the therapeutic protocol used in humans be adapted for animals according to the drugs approved for veterinary use (Ahn *et al.*, 2020; Guo *et al.*, 2020; Izda *et al.*, 2020). Therapeutic indications have been established in dogs and cats with acute respiratory problems applicable to the alterations induced by SARS-CoV-2 (Nelson & Couto, 2019; Papich, 2015; Plumb, 2018). These are aimed at controlling each of the different clinical manifestations present in this disease (Table 6), reducing inflammation, edema and lack of pulmonary oxygenation through the use of drugs such as ibuprofen, acepromazine and oxygen administration respectively, as well as cough control (dextromethorphan, butorphanol) and bronchoconstriction (terbutaline, aminophylline). The use of antiviral drugs that inhibit viral replication processes (acyclovir, oseltamivir, ribavirin) is also suggested, as well as the administration of antibiotics that prevent the development of secondary infections of the respiratory tract that could be originated as a consequence of the alterations and lesions caused by SARS-CoV-2 (Ahn *et al.*, 2020; Das *et al.*, 2021; Nelson & Couto, 2019; Papich, 2015; Plumb, 2018).

Control

The OIE has emitted a series of recommendations focused on the control of SARS-CoV-2 in animals and in the workers in charge of their care and handling. These measures seek to minimize the spread of the disease and to avoid the appearance of viral mutations. However, the capacity to reduce the risk of the introduction and spread of SARS-CoV-2 in farm, domestic, and zoo animals varies greatly among countries because they apply different biosecurity, zoosanitary surveillance, and public health measures (OIE, 2021b).

To mitigate the risk of introduction and spread in fur farms and zoo animals, it is recommended to reinforce biosecurity measures in the facilities, to guarantee the use of personal protective equipment for workers and visitors, and to promote handwashing and disinfection after working with animals (OIE, 2021b). For workers who are in contact with animals, some of the control measures recommended by the OIE include respecting personal distance, avoiding large concentrations of people in common areas, not rotating workers between farms, informing workers about the pathways of spread of SARS-CoV-2 in animals, and preventing workers with symptoms compatible with COVID-19 or living with someone with such symptoms from entering work facilities (OIE, 2021a).

Table 6. Suggested therapy for SARS-CoV-2-infected dogs and cats

Therapeutic Indications	Optional drugs	Animal species/ Dosage		Administration via	Usual Interval (h/d)
		Dog	Cat		
Pain alleviation	Butorphanol (mg/kg)	0.2-0.4	0.2-0.8	IV, IM	8-12/5
	Buprenorphine (mg/kg)	0.005	0.005	IV, IM	4-8/3
Inflammation	Ibuprofen (mg/kg)	5.0	NR	PO	12/5
	Prednisolone (mg/kg)	0.5-1	0.5-1	IV, IM, PO	12-24/5
Pulmonary edema	Acepromazine (mg/kg)	0.05	0.05	IV, SC	6-8/3
Bronchospasm	Terbutaline (mg/kg)	1.25-5	0.1	PO	8-12/5
	Aminophylline (mg/kg)	11	5	PO	8-12/5
	Oxtriphylline (mg/kg)	14-47	NR	PO	8/5
Nonproductive cough	Dextromethorphan (mg/kg)	1-2	0.5-2	PO	6-8/5
	Butorphanol (mg/kg)	0.5	NR	PO	6-12/5
	Hydrocodone (mg/kg)	0.2-0.5	NR	PO	8-12/5
	Nebulization with SSF+O_2 (L/min)	4-10	4-10	IN	4-12/5
Lower oxygen saturation	Oxygen 50-60% (L/min)	8-12	8-12	Mask	Q.S.
	Oxygen 60% (L/min)	2-3	2-3	Oxygen cage	Q.S.
	Oxygen 100% (L/kg/min)	0.2	0.2	Endotracheal tube	Q.S.
Secondary infections	Azithromycin (mg/kg)	5-10	5-10	PO	24/7
Viral sepsis	Acyclovir (mg/kg)	5-10	5-10	PO	6/10
	Oseltamivir (mg/kg)	2.2	NR	PO	12/7
	Ribavirin (mg/kg)	5-10	5.0-5-5	PO	12-24/7

NR, Not reported. Source; IV, intravenous; IM, intramuscular; PO, *per os*; IN, intranasal; SC, subcutaneous; Q.S., *quantum satis*. Source: Own elaboration with data from: (Ahn *et al.*, 2020; Das *et al.*, 2021; Nelson & Couto, 2019; Papich, 2015; Plumb, 2018).

In the case of an outbreak of SARS-CoV-2 in animals and workers, it is recommended to perform the sequencing, phylogenetic analysis, and comparison of genetic sequences of the viruses in all positive cases. Doing so allows the identification of mutations in the viral genome. Uninfected workers should inspect all animals for clinical respiratory or gastrointestinal signs, increase the level of personal protective equipment when handling sick or dead animals, immediately isolate animals positive in screening tests, and reduce the number of people interacting with these animals (OIE, 2021a).

Vaccines against SARS-CoV-2 in animals

The WHO has reported the importance of the use of vaccines in animals to protect against infection and prevent the spread of viral mutations to humans. To combat the possible threat of transmission from animals to humans and the increase in viral variants, an inactivated vaccine against COVID-19 called Karnivak-Kov or Carnivac-Cov was developed in Russia for use in carnivorous animals, and it is a safe, innocuous, highly immunogenic vaccine capable of producing immunity for at least six months after vaccination (Chavda et al., 2021). For the development of this vaccine, the SARS-CoV-2 virus was inactivated, causing the virus to be deficient in viral replication but with the capacity to be recognized by the host immune system and to provoke humoral and cellular immune responses against viral antigens (de Andrade et al., 2021). In the United States, the EvviVax laboratory conducted tests in felines vaccinated with DNA-Evvivax LinearDNA™ producing neutralizing antibodies in 100% of the cases (Evvivax, 2021). Similarly, Zoetis Laboratories developed a vaccine against SARS-CoV-2 for great apes and ferrets and a new vaccine for zoo animals (Sharun et al., 2021; Zoetis, 2021).

Conclusion

The destruction of natural habitats, globalization, and the flow of travelers throughout the world contributed greatly to SARS-CoV-2, causing a pandemic in a relatively short time since December 2019, when it began to spread. On January 30, it was declared a worldwide emergency, and in a short time, the first cases occurred in America on April 6 and in Europe on April 28. As a result, protocols began to be applied worldwide to curb the pandemic, some with greater success than others, based on previous pandemics. The purpose of identifying the animal origin of SARS-CoV-2 and the way in which the virus is transmitted between different animal species is to establish strategies for a diagnostic and therapeutic approach and to establish control measures to help predict and prevent the future diffusion of the pandemic.

The various studies suggest that ferrets, minks, and felines are considered highly susceptible species to SARS-CoV-2, whereas dogs have a low susceptibility, and farm animals (cattle, pigs, and poultry) are not naturally susceptible. The above information suggests that domestic and zoo animals have become accidental hosts of SARS-CoV-2, becoming infected by contact with affected humans with whom them coexist. The concern

remains that domestic and zoo animals could become a risk for maintaining mutant variants of the virus, which could eventually return to human populations.

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Errata Erratum
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