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## **Coronaviridae - old friends, new enemy!**

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**Abstract:**

Coronaviridae is a family of single-stranded positive enveloped RNA viruses. This article aimed to review the history of these viruses in the last 60 years since their discovery to understand what lessons can be learned from the past. A review of the PubMed database was carried out, describing

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taxonomy, classification, virology, genetic recombination, host adaptation, and main symptoms related to each type of virus. SARS-CoV-2 is responsible for the ongoing global pandemic, SARS-CoV and MERS-CoV were responsible for causing severe respiratory illness and regional epidemics in the past while the four other strains of CoVs (229-E OC43, NL63, and HKU1) circulate worldwide and normally only cause mild upper respiratory tract infections. Given the enormous diversity of coronavirus viruses in wildlife and their continuous evolution and adaptation to humans, future outbreaks would undoubtedly occur. Restricting or banning all trade in wild animals in wet markets would be a necessary measure to reduce future zoonotic infections.

## Introduction

Coronaviruses (CoVs) are zoonotic viruses that belong to the Coronaviridae family with a simple positive-sense RNA genome (Ksiazek et al., 2003). CoVs are similar in the organization and expression of their genome, and are maintained simultaneously in nature, which allows for their constant genetic recombination, resulting in new viruses (Su et al., 2016). The viruses, known since 1960, can infect and cause disease in both animals and humans (Siddel et al, 1983; Ksiazek et al., 2003). The types known to cause disease in animals include; infectious bronchitis virus (IBV) (Lin & Chen, 2017), canine respiratory coronavirus (CRCoV) (Priestnall, Brownlie, Dubovi & Erles, 2006), mouse hepatitis virus (MHV) (Weiss & Leibowitz, 2011), bovine coronavirus (BCV), turkey coronavirus (TCV) and transmissible gastroenteritis virus (TGEV) (Szczepanski, Owczrek & Bzowska, 2019). Viruses of this family were first identified in humans from the nasal secretions of patients with the common cold (Tyrrel & Byone, 1965). Since Four CoVs are known to produce mild infections in individuals with normal immunity similar to the common 'flu, they are 229-E OC43, NL63, and HKU1 (Esper et al., 2006; Su et al., 2016).

However, in recent years, coronaviruses have given rise to significant diseases such as severe acute respiratory syndrome (SARS-CoV) and Middle Eastern respiratory syndrome coronavirus (MERS-CoV) SARS-CoV infected 8,000 people, from 2002 to 2003 and had a mortality rate of approximately 10% (Marra et al., 2003). Ten years later, in 2012, MERS-CoV, emerged, and infected more than 1,700 people, with a mortality rate of approximately 36% (Zaki et al., 2012). In 2013, it attacked animals again, with a coronavirus epidemic of porcine diarrhea (PEDV) in the United States, causing a mortality rate of almost 100% in piglets and wiping out more than 10% of the swine population in less than a year (Mole, 2013). More recently, a new coronavirus (SARS-CoV-2) has emerged that is responsible for the current COVID-19 global pandemic. This virus was first identified in the Chinese province of Hubei in December 2019 (Gudi & Twari, 2020) with possible transmission being suspected to have been from animal to human as the first case was detected from a person working in the local fish and wild animals market – with later transmission from human to human via respiratory droplets or direct contact

It is important to appreciate the ecology of CoVs, its propensity for viral recombination with different CoVs in animal populations, resulting in new CoVs that are transmissible and

pathogenic to humans. It is possible that the early cases of the infection went unnoticed as the disease may have been mild, there may have been other comorbidities that would fit with a respiratory infection and/or the initial sporadic distribution of affected individuals may have hidden the insidious nature of this infection. This early period of enigmatic transmission may have allowed SARS-CoV-2 to acquire the facilities to be both easily acquired by humans and to induce disease that aids its own survival.

## Taxonomy

The *Coronaviridae* Study Group (CSG) of the International Virus Taxonomy Committee (ICTV), is responsible for the classification and taxonomy of coronaviruses (Gorbalenya et al., 2020). The *Coronaviridae* family is composed of 2 subfamilies, 5 genera, 26 subgenera, and 46 species that are part of the, belonging to the suborder *Cornidovirinae*, order *Nidovirales*, Phylum *Incertae sedis*, and realm *Riboviria*. CoVs belong to the subfamily *Orthocoronavirinae* covers four genera, namely *Alphacoronavirus*, *Betacoronavirus*, *Deltacoronavirus*, and *Gammacoronavirus* (<https://talk.ictvonline.org/taxonomy/> - accessed on April 26, 2020). The *Alphacoronaviruses* has 4 subgenera and 19 species, affecting only mammals, such as *Porcine Transmissible Gastroenteritis Coronavirus* (TGEV), *Porcine Epidemic Diarrhea Coronavirus* (PEDV) and humans are infected with HCoV-229E and HCoV-NL63. The *Betacoronavirus* has 5 subgenera and 14 species among them HCoV-OC43, HKU1, MERS-CoV, SARS-CoV, and SARS-CoV-2 (Gaunt, Hardie, Claas, Simmonds & Templeton, 2010; Gorbalenya et al., 2020). The genera *Deltacoronavirus* and *Gammacoronavirus* have do not infect humans, but cause infections in birds (Woo et al., 2012).

The CoVs in humans HCoV-NL63, HCoV-229E, HCoV-OC43, and HKU1 are associated with mild respiratory tract infections (Gaunt et al., 2010; Forni, Cagliani, Clerici & Sironi, 2017). HCoV-229E is associated with infections in immunocompromised individuals (Pene et al., 2003). SARS-CoV and MERS-CoV are highly pathogenic CoVs for humans and have caused two major epidemics (Cui, Li & Shi, 2019). There is still no consensus on a taxonomic position for SARS-CoV-2, but it belongs to a species related to acute respiratory viruses, based on genetic characteristics, but it is a virus independent of SARS-CoV (Gorbalenya et al., 2020) Figures 1a and 1b summarizes the main characteristics of human coronaviruses.

## Virology

Coronaviruses are viruses enveloped with positive, non-segmented, single-stranded RNA genomes approximately 26 to 32 kilobases in size. They have phenotypic and genotypic variety, due to recombinant RNA and large genomes, facilitating, unfortunately, the ability to adapt to new hosts (Woo et al., 2012; Zaki et al., 2012). The activation of S proteins of SARS-CoV-2 occurs through binding with angiotensin-converting enzyme 2 (ACE-2) of the host cells that can be found greatly expressed in nasal epithelial cells, allowing the entry of the virus into the host cells, releasing mRNA for translation of proteins (Guo et al., 2020). The initial portion of the CoVs genome encodes 16 non-structural proteins while the remaining portion encodes 4 essential structural proteins namely small envelope protein (E), spike glycoprotein (S), matrix (M) protein and nucleocapsid (N) protein (Liu et al., 2020).

The bat is suspected to be a natural host and origin for SARS-CoV-2. The present virus may have been transmitted to man via intermediate hosts, such as pangolins. (Zhou et al., 2020), Phylogenetic analysis has shown that SARS-CoV-2 is approximately 89% similar to two bat-derived SARS coronaviruses: bat-SL-CoVZC45 (GenBank MG772933.1) and bat-SL-CoVZXC2 (GenBank MG772934. 1); and is approximately 79% similar to SARS-CoV and 50% similar to the Middle Eastern respiratory syndrome (MERS-CoV) coronavirus (Chen et al., 2020). On the other hand, evolutionary analysis based on the ORF1a / 1b, S and N genes suggests that SARS-CoV-2 is more likely to be a new coronavirus that has been introduced independently from animals to humans due to the inherent mutation property of coronaviruses in nature (Lam et al., 2020). Considering genetic investigations and the presence of some bats and other live wild animals in the Wuhan market, the virus may have originated from bats or bat droppings associated with contaminated materials (Cui, Li & Shi, 2019).

Viral switching overcomes the innate immunity of each host specifically, and coronaviruses can overcome this natural barrier with some ease, as for example MERS-CoV uses Dipeptidyl peptidase 4 as a receptor in several hosts (Muller et al., 2003). Coronaviruses can acquire new genes that facilitate infection in different hosts through recombination between different viruses, as in the recombination of CoVs with feline FIPV type 1 and CCoV through different parts of the viral ORF1b (Herrewegh et al; 1998). This same type of viral recombination seems to have been involved in the emergence of SARS-CoV (Lau et al., 2010),

Another phenomenon supposedly associated with the adaptation of CoV to different hosts and cells is the variable deletions that cover more than 600 nucleotides in the S1 globular domain of the Spike gene, which is associated with a change in the enteric virus (TGEV) to respiratory tract virus (PRCV). Furthermore, the exclusion of 290 nucleotides from the Spike gene in HCoV-OC43 compared to its BCoV ancestor may have allowed it to adapt to the human host (Vijgen et al., 2005).

The pathogenesis of bat coronavirus is poorly understood when compared to other mammalian hosts and there is little evidence of the consequences of clinical infections in bats. In humans, HCoVs-NL63, -OC43, -HKU1, and -229E circulate constantly in the populations of the world. A comparison and main characteristics of these viruses are shown in Table 1 (Ogimi et al., 2020). SARS-CoV, on the other hand, disappeared a few years after the epidemic, while the new MERS-CoV seems to have remained. All HCoV mainly cause respiratory symptoms in humans (Hamre and Procknow, 1966; Peiris et al., 2003; Woo et al., 2005), although MERS-CoV has also been associated with severe renal complications (Zaki et al., 2012). HCoV is detected in feces (Liu et al., 2004), and there are sporadic reports of CoVs in humans with gastroenteritis, even though they are not consistently related to gastroenteritis in humans (Esper et al., 2010).

SARS-CoV-2 and SARS-CoV have different patterns of tropism and hence transmission profiles. This being due to mutations in NSP2 and NSP3 (Angeletti et al., 2020); this aspect greatly changed the clinical presentation and hence treatment strategies for each viral infection. Although these mutations were smaller when compared to H7N9 mutations, they significantly worsened the clinical landscape (Zhang, Shen, Chen & Lin, 2020). In the Chinese population, two prevalent types of SARS-CoV-2 evolution have now been observed; type L and type S. Type L strains derive from type S strains and are the more clinically aggressive and contagious (Lai et al., 2020); = hence demonstrating the showing notable adaptive biological capacity of this virus.

It is now recognized that mutations in SARS-CoV-2 have led to clusters of slightly different viruses in different parts of the globe. These clusters, termed A, B and C, vary in their geographic locale. They called the genetic root A; and from it, they identified two sub-clusters of A that are distinguished by the synonymous mutation T29095C. The two other phylogenetic clusters were called B and C. All but 19 of the 93 genomes of type B came from samples from Wuhan and other parts of eastern China and, sporadically, from samples from countries in the adjacent Asian region. Outside East Asia, cluster B was found in 10 viral genomes samples from the United States and Canada, one from Mexico, four from France, two from Germany, one from

Italy, and finally one from Australia. Cluster B is derived from A by two mutations: the mutation synonymous with T8782C and the non-synonymous mutation C28144T, changing a leucine to serine. Type C cluster, mainly found in the Americas and Europe, differs from type B by the non-synonymous G26144T mutation that alters a glycine in a valine. This genotype has been found in samples from France, Italy, Sweden, and England, also from California and Brazil, Singapore, Hong Kong, Taiwan, and South Korea but not in mainland China. This phylogenetic classification can be used to design treatment and, eventually, vaccines (Foster et al., 2020).

### SARS-CoV

Severe acute respiratory syndrome (SARS) is a human disease associated with severe pneumonia and as noted above is caused by SARS-*Coronavirus* (SARS-CoV) (Drosten et al., 2003). The disease initially occurred in November 2002 in China, and by February 2003, more than 300 cases had reported (Zhong et al., 2003). During the outbreak in 2002-2003, a total of 8,096 cases were reported, including 774 deaths in 27 countries (Ksiazek, et al., 2003). The outbreak was contained, and since 2004 there have been no known cases of SARS-CoV.

SARS-CoV was initially detected in masked palm civets and a raccoon dog. Antibodies against the virus were detected in Chinese ferret badgers in a live-animal market in Shenzhen, China (Guan, 2003), but it is believed that bats were the reservoir (Drexler, Corman & Drosten, 2014). Most of the cases were the result of direct transmission by respiratory droplets during close personal contact, and adequate respiratory precautions taken proved to be effective (Seto et al., 2003).

Of note there was a relatively high incidence of infection in health care professionals managing patients with, or suspected to have SARS-CoV. Peiris et al, (2003) reported that 28% of those infected were health professionals, hospital transmission being a characteristic of the outbreak. The average incubation period depended on the route of transmission but was between 2 to 10 days (Donnelly et al., 2003).

The clinical course of SARS-CoV begins with a flu-like prodrome consisting of fever, chills, fatigue, and malaise. Towards the end of the first week, there is a deterioration of the clinical picture where the lower respiratory tract is involved, and the patient may present with a dry cough, shortness of breath, and possibly hypoxemia (Vijayanand, Wilkins & Woodhead, 2004). Less common symptoms include watery diarrhea, vomiting, and nausea (Peiris et al.,

2003). Laboratory findings include lymphopenia, thrombocytopenia, elevated lactate dehydrogenase (LDH), raised creatine kinase, and alanine aminotransferase (AAT). Infected patients have abnormal chest X-rays in 60-100% of cases, with predominant lower zone and peripheral lung involvement (Goh et al., 2003). Other common findings include lack of cavitation, lymphadenopathy, pleural effusion, mainly ground-glass opacification and sometimes consolidation, interlobular septal, and intralobular interstitial thickening (Wong et al., 2003). Only 20-30% of patients with SARS require intensive care (Peiris et al., 2003). Patients with advanced age and male sex are associated with poor disease outcomes, and the mortality rate is approximately 10% (Leung et al., 2004). Treatment is mainly symptomatic and supportive, no specific therapy (eg.: antivirals) have proven useful.

## MERS

A new coronavirus-related outbreak occurred again in 2012 in Saudi Arabia called Middle East Respiratory Syndrome (MERS), it is a severe respiratory illness caused by a variant of the Coronaviruses (CoV), the MERS-CoV, first case detected through sputum analysis in a 60-year-old man (Zaki et al.m 2012).

According to WHO (2019) to November 2019, 2494 cases were confirmed, with 858 related deaths. The spread of the outbreak occurred due to people who traveled to the Middle East, with most cases concentrated in Saudi Arabia (Alanazi et al., 2019).

Studies show that MERS-CoV transmission occurs through direct contact with camel dromedaries, such as the consumption of unpasteurized camel milk or undercooked camel meat. The routes of human to human transmission are not yet fully understood, but possible routes of transmission may occur via human respiratory droplets and contact transmission (Memish et al., 2014). Another characteristic of MERS-CoV was hospital transmission with 43.5% to 100% of outbreaks in different places associated with health care (Chowell et al., 2015). Among the independent risk factors associated with MERS infection are diabetes mellitus, heart disease, smoking, and chronic obstructive pulmonary disease (COPD) (Al-Tawfiq et al., 2014).

Common symptoms of people infected with MERS-CoV are fever, cough, shortness of breath, and diarrhea. Pneumonia is not always present and some people are asymptomatic, but test positive on laboratory tests (Chafekar & Fielding, 2018). It has an incubation period of

approximately 5 days. Abnormal such as chest X-rays and laboratory tests are common the latter include lymphopenia, thrombocytopenia, high elevated levels of lactate dehydrogenase, and liver enzymes. There are reports of some cases of disseminated intravascular coagulation and hemolysis (Al-Tawfiq et al., 2014). Up to 50 to 89% of patients require intensive care and mechanical ventilation due to acute respiratory distress syndrome (ARDS). The mortality rate of MERS is approximately 35%, higher when compared to SARS-CoV. There is no specific treatment for MERS, the mainstay of management include supportive, symptomatic measures, and the prevention and management of secondary complications (de Wit et al., 2016).

### SARS-CoV-2

Coronavirus disease (COVID-19) originated in December 2019 in Wuhan, Hubei province, China, spread rapidly through China and many other countries, being registered by WHO as the sixth public emergency of international interest. With alarming rates of spread of the disease in many countries outside China, WHO declared COVID-19 a pandemic in March, 2020. On February 11, 2020, WHO announced a new name for the 2019-nCoV epidemic-COVID-19 (WHO, 2020). The International Virus Taxonomy Committee renamed 2019-nCoV, as severe acute respiratory syndrome coronavirus-2 of the genus betacoronavirus (SARS-CoV-2). SARS-CoV-2 is effectively transmitted between humans, including via asymptomatic carriers (Rabi et al., 2020).

The risk factors associated with the worsening of the disease are patients in the seventh decade of life, male, with associated morbidities and late diagnosis. Laboratory confirmation of COVID-19 is based on detection of SARS COV-2 RNA by reverse-transcription polymerase chain reaction (RT-PCR) on upper respiratory specimens (nasopharyngeal/oropharyngeal swabs) or lower respiratory specimens (sputum, endotracheal aspirates or bronchoalveolar lavage (WHO, 2020: Laboratory testing for coronavirus disease (COVID-19) in suspected human cases interim guidance (WHO, 2020; <https://apps.who.int/iris/handle/10665/331329>).

Clinical characteristics and pathogenesis of COVID-19 are similar to SARS and MERS (Xie & Chen, 2020), with an incubation period of 4 to 7 days, however, this can be up to 14 days. There are reports of high rates of asymptomatic and subclinical infections (Yang et al., 2020). A comparison between these 3 viruses are shown in Table 2. In a study of 1099 patients with Covid-

19 confirmed in a laboratory in Mainland China, 5% of patients were admitted to the ICU, 41.3% needed oxygen therapy, 6.1% needed mechanical ventilation and 1.4% died. The average hospital stay was 12 days (Guan et al., 2020). Wang et al (2020) showed that as the number of transmission of COVID-19 cases increases, lethality decreases, this would explain the low mortality rate when comparing SARS and MERS.

The most common presentations in symptomatic patients are fever, dry cough, and shortness of breath. Other features include gastrointestinal symptoms, such as diarrhea, neurological symptoms (stroke, headache, altered mental status, GBS), cardiovascular events (myocarditis, arrhythmias, heart failure), and ocular manifestations (conjunctival hyperemia, chemosis), anosmia and dysgeusia. (Guan et al, 2020). In computed tomography of the chest of COVID-19 pneumonia, subpleural ground-glass opacities were initially observed, which increased, with changes in the paving pattern. In recovering patients, the lesions appeared absorbed with the presence of opacities and subpleural parenchymal bands. (Xie & Chen, 2020). Laboratory findings include leukopenia, lymphocytopenia (sometimes very notable), elevated neutrophilic ratio, C-reactive protein and serum proinflammatory cytokines, the last 3 findings mentioned being associated with more severe disease (Guan et al., 2020)

### Immune response in COVID-19

The initial response to CoV infection is carried out through the immune system (Frieman & Baric, 2008). Toll-type receptors, which are receptors for antigen-presenting cells that detect viral RNAs, inducing the signaling cascade of the immune system, consequently increasing cytokines (Alexopolou, Holt, Medzhitov & Flavell, 2001; Wu & Chen, 2014). To prevent recognition of the host's immune system, the virus forms double vesicles on the outside of the cell, it also has non-structural proteins inhibiting functions of the innate immune system, such as Nsp1 to block INF (Guo et al., 2020).

The increase in pro-inflammatory cytokines, including as IFN- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-12, IL-18, IL-33, TNF- $\alpha$ , TGF $\beta$  and CCL2, CCL3, CCL5 chemokines, CXCL8, CXCL9, CXCL10, is the first line of defense against infection Wu & Chen, 2014). However, the massive proliferation of immune cells can result in hyper inflammation of the lungs and other viscera causing acute respiratory distress syndrome (ARDS) and notable myocardial damage. (Huang et al., 2020)

### Asymptomatic cases

As noted above, there are reports of asymptomatic COVID-19 cases from several groups. For example, nearly 46% of positive cases in a quarantined cruise ship were asymptomatic. A study conducted in an Italian village revealed that 50- 75% of cases were asymptomatic. In children, 15-30% who tested positive may be asymptomatic. Notably, SARS-CoV-2 has been found in upper respiratory tract secretions of asymptomatic individuals (Zou et al., 2020), raising concerns that even asymptomatic patients can transmit COVID-19.

### Conclusions

SARS-CoV-2 has become the seventh Coronavirus disease in humans responsible for this current global pandemic. Once again, it demonstrated its ability to cross-species and adapt to the human host. Critically, Coronavirus surveillance in animals must include animals other than bats, as the role of intermediate hosts is likely to be of great importance, providing a more direct route for the virus to emerge in humans. Given the enormous diversity of coronavirus viruses in wildlife and their continuous evolution and adaptation to humans, mainly causing respiratory or gastrointestinal disorders it is not difficult to predict other outbreaks. Restricting or banning all trade in wild animals in wet markets would be a necessary measure to reduce future zoonotic infections.

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Table 1- Comparison between HCoV- 229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1  
(Ogimi et al., 2020).

Features	HCoV- 229E	HCoV-OC43	HCoV-NL63	HCoV-HKU1
Genus	Alpha	Beta	Alpha	Beta
First description (Year)	1966	1960s	2004	2005
Origin	Bats	Rats	Bats	Rats
Entry Receptors	Aminopeptidase N (APN)	Sialic acid residues	ACE2	Sialic acid residues
Transmission	<p style="text-align: center;">Droplet transmission</p> <p style="text-align: center;">Direct contact with infected secretion</p> <p style="text-align: center;">(Incubation Period : 3 days)</p>			
Clinical Disease	<p style="text-align: center;">Endemic , worldwide (HCoV-OC43 is the most common species)</p> <p style="text-align: center;">Normally mild upper respiratory infections</p> <p style="text-align: center;">(rhinorrhea, sore throat, cough, wheezing, and fever)</p> <p style="text-align: center;">Duration of illness : 6-7 days</p> <p style="text-align: center;">Occasionally in Older patients, immunocompromised: lower respiratory tract infections</p>			
Treatment	<p style="text-align: center;">Supportive</p> <p style="text-align: center;">No Specific antivirals; No vaccine</p>			

Table 2- Comparison between SARS-Cov-2, SARS and MERS

	SARS-CoV-2	SARS	MERS
Origin	Wuhan, China	Guangdong, China	Jeddah, Saudi Arabia
Incubation Period (days)	2-14 (Median=5.1)	2-7	5 (2-14)
Case Fatality Rate (%)	6.89	9.6	34
R <sub>0</sub>	5.8	2.0	<1
Total No. of Cases (Global)	4 million (to date)	8096	2229
Total No. of Deaths (Global)	277k (to date)	774	791

(Centre for Infectious Disease Epidemiology and Research-NUS. COVID-19 Situation Report 80 WHO 2020).

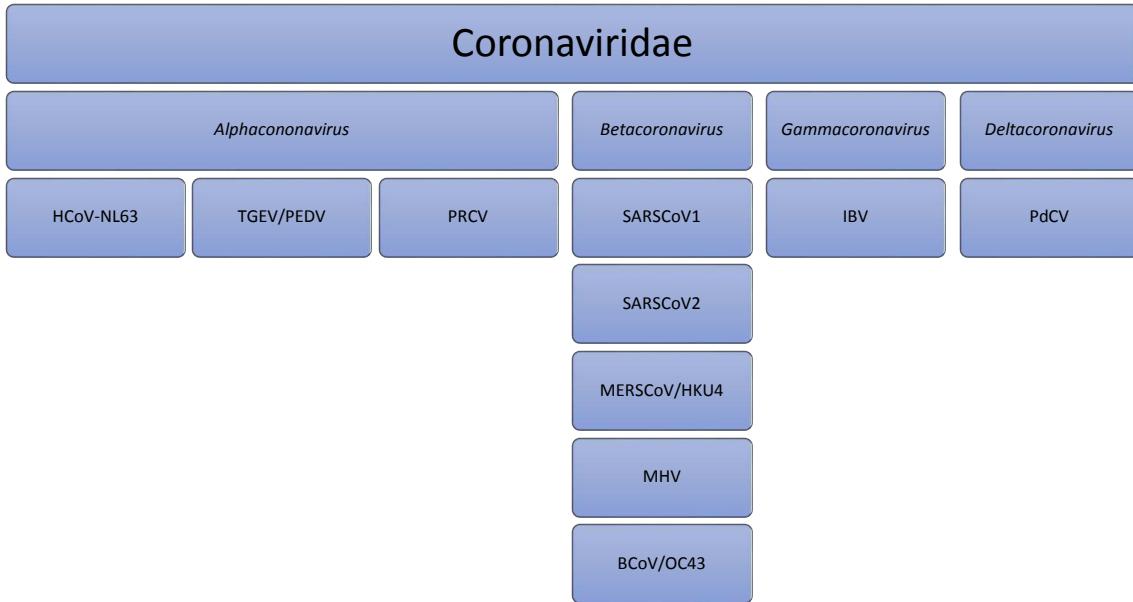


Figure 1a. *Coronavirus*: genera and species.

Figure 1b - Human *Coronavirus*

Strain name	Evolutionary origin	Disease	Year of virus discovery
HCoV-229E	The human coronavirus 229E diverged from the alpaca coronavirus before 1960 (Crossley, Mock, Callison & Hietala, 2012)	Common cold.	1960 (Crossley et al., 2012)
SARS-CoV	The human coronavirus SARS diverged from the bat coronavirus in 1986 (Vijaykrishna et al., 2007)	SARS disease.	2002 (Hu, Ge, Wang & Shi 2015)
HCoV-OC43	The human coronavirus OC43 diverged from the bovine coronavirus in 1890 (Vijgen et al., 2005)	Common cold.	2004 (Vijgen et al., 2005)
HCoV-NL63	Human coronavirus NL63 diverged from bat coronavirus 822 years ago (Huynh et al., 2012)	Common cold.	2004 (Hu et al., 2015)
HCoV-HKU1	The human coronavirus HKU1 diverged from the bat coronavirus (Woo et al., 2009)	Common cold.	2005 (Esper et al., 2009)
MERS-CoV	The human coronavirus MERS diverged from the bat coronavirus before the 1990s and was transmitted to humans by camels (Coman et al., 2016)	MERS disease.	2012 (Hu et al., 2016)
SARS-CoV-2	Studies have suggested that the SARS-CoV-2 virus diverged from the version that parasites bats (Zhou et al., 2020; Lu, 2020) and transmitted to humans by an intermediate animal. Recent studies indicate that the virus has diverged from the version that parasites pangolins (Lam et al., 2020) as it has genetic material 99% equal to the virus found in this animal.	Covid-19 disease	2019 (WHO,2020)