COVID-19 PANDEMIC

# THE VIROLOGY OF SARS-CoV-2

http://www.lebanesemedicaljournal.org/articles/68(1-2)/pandemic2.pdf

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Bizri AR, Moghnieh R. The virology of SARS-CoV-2. J Med Liban 2020; 68 (1-2) : 9-15.

## INTRODUCTION TO CORONAVIRUSES

Coronaviruses are positive sense RNA viruses that belong to the Nidovirales order and Coronaviridae family. The name is derived from their appearance as a crown under electron microscopy [1]. Small, with diameter ranging between 65-125 nm, they are enveloped with a positive sense single-strand RNA genome that varies from 26 to 32 kbs in length [2,3]. In the Coronaviridae family, some members are known to produce disease among a wide range of humans and vertebrates. Their disease spectrum includes respiratory, gastrointestinal and central nervous system infections. They have varying manifestations from symptoms associated with upper and lower respiratory symptoms, affecting several organ systems including renal disease [1,2].

Prior to the severe acute respiratory syndrome (SARS-CoV) outbreak in 2002 in Guangdong Province of China, it was believed that coronaviruses produced enzootic infections and were not highly pathogenic to humans, causing mild infections in immuno-compromised hosts. This belief was debunked with the subsequent discovery of the Middle East Respiratory Syndrome virus (MERS-CoV), which plagued mainly the Arabian Peninsula ten years later [4]. Coronaviruses have bypassed the human-animal barrier and have become zoonotic diseases [5].

In December 2019, a novel coronavirus dubbed SARS-CoV-2 caused an outbreak, COVID-19, in the city of Wuhan, China, leading to the death of one thousand eight hundred individuals and affecting around seventy thousand individuals within the first fifty days [3]. As of March 2020, more than two million individuals have been infected with a death toll of around one hundred and forty thousand individuals. COVID-19 has truly taken the world by storm becoming one of the worst pandemics in modern times.

The Coronaviridae family is divided into four main genera, classified based on their genomic characteristics: Alphacoronavirus (α-CoV), Betacoronavirus (ß-CoV), deltacoronavirus (∂-CoV) and gammacoronavirus (γ-CoV) [4].

The genus Beta coronavirus is subdivided further into 4 lineages: A, B, C and D [1]. The first two genera infect only mammals. They can also cause severe infection to livestock. The latter two genera mainly target birds and certain mammalian species [4]. Both intra- and inter-species transmission of the virus as well as genetic recombinant events contribute to the appearance of new coronavirus strains (Table I).

As a result of two large overlapping reading frames (ORFs), coronaviruses have many similarities, particularly in their genome organization and expression. At the 5' end terminus, is ORF1a/b which encodes 16 non-structural proteins (Nsp1 to Nsp16), followed by the ORFs at the 3' end which encode for the 4 main structural proteins: spike (S), envelope (E), membrane (M) and nucleocapsid (N) [1].

Some coronaviruses do not require all the structural proteins to produce an infectious virion. This suggests that the virus might not require all the structural proteins, or it encodes additional proteins that have overlapping compensatory functions [6]. The S protein is required for fusion of the virus to membrane cells of the host by attaching to surface receptors on the host cell, enabling

**TABLE I**

CORONAVIRUSES AND THEIR GENERA DISTRIBUTION

| | |
|---|---|
| **Order** | Nidovirales |
| **Family** | Coronaviridae |
| **Sub-Family** | Coronavirinae |
| **Genera** (according to genome characteristics) | Alpha coronavirus<br>Beta coronavirus<br>Delta coronavirus<br>Gamma coronavirus<br><br>#Several subgenera, lineages & species |

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infection. It was also revealed that the S protein has a role in cell-cell fusion forming large syncytia, which is another proposed mechanism of intercellular spread.

The N protein is primarily engaged in binding the RNA genome. M protein is a major protein found in and defines the envelope. It requires interaction with all other structural proteins; homotypic interactions are the driving force for envelope development but alone it is not enough for virion formation.

The E protein is the smallest among the structural proteins, yet it has an important role in viral assembly and release of the virions [5].

## HUMAN CORONAVIRUSES

There are currently seven different human coronavirus (HCoVs) belonging to the alpha and beta genera. The HCoV-229E (229E) and HCoV-NL63 (NL63) belong to the genus Alphacoronaviruses. Meanwhile HCoV-OC43 (OC43), HCoV-HKU1 (HKU1), SARS-CoV, MERS-CoV and SARS-CoV-2 belong to the genus Betacoronaviruses [7] (Table II).

229E is the prototypical virus that has a global distribution and exhibits peaks in transmission during the winter period in temperate climates. It was discovered in 1966 by a group of researchers trying to characterize agents leading to the common cold. Presenting symptoms include malaise, nasal discharge, sore throat, headache and sneezing. In around 10 to 20% of cases the patient will exhibit fever and a cough. 229E has an incubation period of 2 to 5 days preceding an illness of approximately 2 to18 days in duration [1,8].

The second HCoV is NL63 which is associated with mild respiratory illnesses in the immunocompromised as well as young children and elderly individuals [9]. It has a global distribution, an incubation period of 2-4 days and phylogenetically it is similar to HKU1. Presenting symptoms include cough, rhinorrhea, hypoxia, fever, tachypnea and croup (obstructive laryngitis) [1,10].

The Betacoronavirus genera is further subdivided into lineages, each with its own HCoV: OC43 and HKU1 (lineage A, subgenus Embecovirus), SARS-CoV (lineage B, subgenous Sarbevirus) and MERS-CoV (lineage C, subgenous Merbecovirus).

OC43 is the prototype virus for this genus. It was isolated in 1967 from a patient with the common cold. It has a global distribution and an incubation period of 2-5 days. Clinical symptoms are very similar to those of 229E, with no serological cross-reactivity. HKU1 has global distribution with a short incubation period ranging between 2-4 days. Symptoms depend on the location of the infection. In the upper respiratory tract, patients have fever, runny nose, and cough. Whereas, in the lower respiratory tract they complain of fever, dyspnea and productive cough. There is also a high association for the development of seizures and meningitis. [1,11]

SARS-CoV was first detected in the Guangdong province of China, spreading to surrounding Asian countries and several other regions, affecting a total of thirty-seven countries worldwide. Originally found in bats, it then spread to civets before eventually reaching humans. The incubation period ranges between 2 to 11 days with a fatality rate of 9.7%, reaching up to 50% in elderly patients. Initial presenting symptoms include fever and chills, headache, myalgia, and malaise to be followed by respiratory distress, cough, and dyspnea. Pathological changes in the lungs of affected individuals include epithelial proliferation, diffuse alveolar damage and increase in macrophages. The infection may involve the gastrointestinal, liver, kidney, brain and spleen causing white pulp atrophy (similar to H5N1 infection) [1,12].

MERS-CoV was initially recognized in Saudi Arabia in 2012. Transmitted from camels to humans, the infection spread throughout the Arabian Peninsula and to twenty-six countries worldwide. The virus has an incubation period ranging between 2 to13 days and a mortality rate of 37%, making it one of the deadliest viruses in modern times [13]. The severity of the disease ranges from

**TABLE II**

HUMAN CORONAVIRUSES AND THEIR RESPECTIVE DISEASES

| Genus | Virus | Disease | Severity | Mortality | Year |
|---|---|---|---|---|---|
| Alpha | CoV-NI-63 | Respiratory tract infection | Mild | Rare | 1965 |
| Alpha | CoV-229E | Respiratory tract infection | Mild | Rare | 1967 |
| Beta | CoV-HKU-1 | Respiratory tract infection<br>Pneumonia | Mild<br>Moderate | Rare<br>Unusual | 2005 |
| Beta | CoV-OC43 | Respiratory tract infection | Mild | Rare | 2004 |
| Beta | SARS-CoV | Acute respiratory syndrome | Severe | 10 % | 2002 |
| Beta | MERS-CoV | Acute respiratory syndrome | Severe | 37 % | 2012 |
| Beta | SARS-CoV-2 | Acute respiratory infection | Severe | ~2 % | 2019 |

*Modified from Loeffelholza, M.J.; Tang, Y.W. Emerging Microbes & Infections. 17 March 2020, VOL.9 [39]

asymptomatic or mild infection to difficulty in breathing and respiratory distress, severe pneumonia, septic shock and renal impairment and even death. The illness usually starts with cough, sore throat, fever, myalgias and arthralgias. It then rapidly develops to dyspnea and pneumonia. Gastrointestinal involvement is seen in around one third of patients manifesting with vomiting and diarrhea [1,14].

## SARS-CoV-2 BEGINNINGS

Unexplained number of patients with pneumonia appeared in Wuhan, Hubei Province, China, in December 2015 [15]. Applying sequence analysis technique, the causative agent for these pneumonias turned out to be a new coronavirus (CoV) named then 2019-nCoV [16]. Later by February 11, the World Health Organization (WHO) named this novel viral entity "Coronavirus Disease-2019 (COVID-19)" [17]. Meanwhile, the International Committee on Taxonomy of Viruses named it SARS-CoV-2 [18]. Both nomenclatures avoided linking this virus to any specific geographic location, city, country or ethnic group, avoiding any unnecessary stigma or future discrimination. The source of the novel virus remains unclear. A recent phylo-epidemiological analysis hints that the virus, that circulated at Huanan Seafood Market, might have been introduced from other places [19]. The possibility that at least two different strains of SARS-CoV-2 had occurred before the official recognition of COVID-19 adds further to the confusion about its origin [20].

## SARS-CoV-2 IDENTIFICATION, CLASSIFICATION & GENOME ORGANIZATION

The first recognition of the SARS-CoV-2 virus was from an infected individual in Wuhan Province on December 30, 2019. The virus was identified from bronchoalveolar lavage (BAL) of the patient [16]. It was classified as a member of the ß-CoVs through sequencing and evolutionary tree analysis [16,21]. Both MERS-CoV and SARS-CoV are also members of ß-CoVs [22].

The SARS-CoV-2 has a genome sequence identity of 79.5% and 50% with both SARS-CoV and MERS-CoV, respectively [16,21,23]. Based on the similarities in sequence identity between the SARS-CoV-2 and the SARS-CoV (94.6%) and with that of other betacoronaviruses (less than 90%), experts suggested that SARS-CoV-2 can be placed in the lineage B of CoVs [16,24]. (Figure-1)

The genome of SARS-CoV-2 is 29.9 kb in size, similar to other betacoronavirus [25]. Like all coronaviruses it has a nucleocapsid made of genomic RNA and N protein. The N protein is hidden within phospholipid layers and concealed by two different classes of spike proteins. The first is the S protein, a glycoprotein trimmer unanimously present in CoVs. The second is the hemagglutinin-esterase (HE) which forms a discrete inner border of short peplomers only found in certain group II CoVs (OC43, bovine CoV). Both the M protein and the E protein are situated amid the S proteins in the viral envelope. The gene order of SARS-CoV-2 is as follows: (5') replicase ORF1ab – S – E – M – N (3'). SARS-CoV-2,

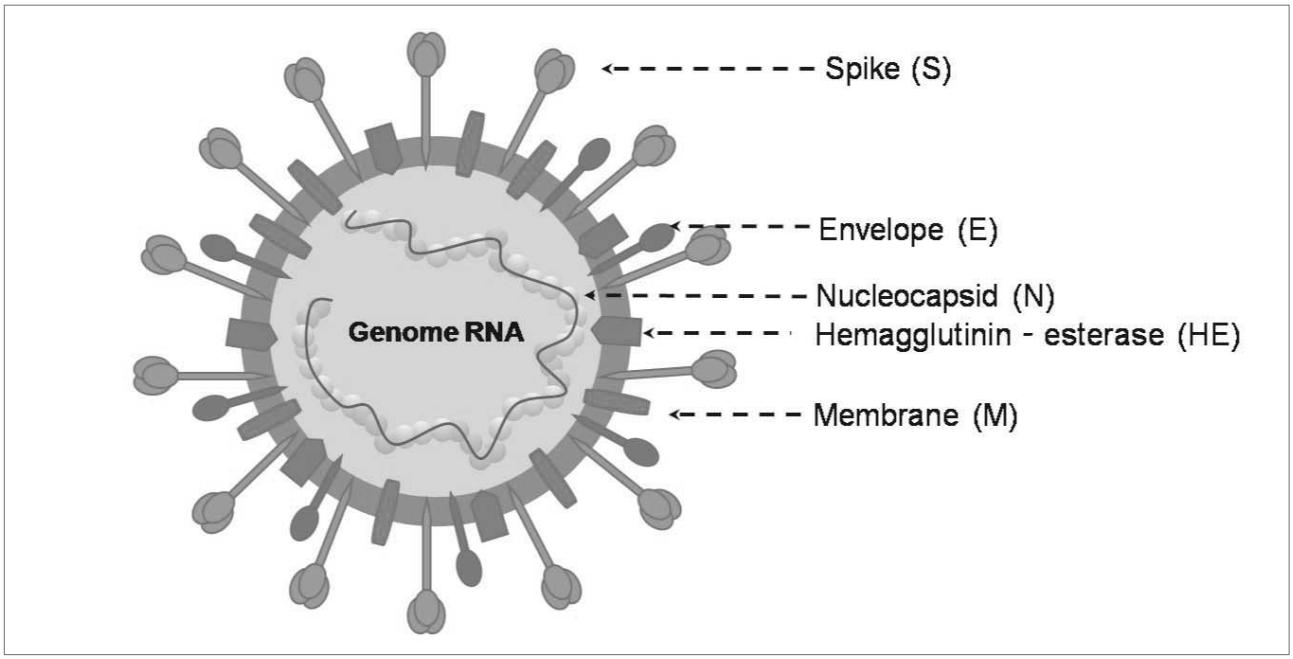


**Figure 1.** SARS-CoV-2 virion
*From Jin Y, Yang H, Ji W et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020; 12 (4): 372. [40].

encodes for an ORF8 gene situated between the M and N ORF genes, a characteristic similar to SARS-CoV [24]. (Figure-2)

## SARS-COV-2 PHYSICAL & CHEMICAL PROPERTIES

The viral particle appears as round or oval and has a dameter of 60-100 nm. It can be deactivated by heating for 30 min at 56 °C or by ultraviolet light. It is susceptible to most disinfectants including 75% ethanol, diethyl ether, peracetic acid, chlorine, and chloroform [26]. Viral stability depends on the nature of surfaces, where it is believed to be more stable on stainless steel and plastic than on cardboard and copper where viable viruses were detected up to 3 days. SARS-CoV has a shorter half-life than SARS-CoV-2 on cardboard. However, both viruses had long viability on plastic and stainless steel [27].

## SARS-COV-2 LIFECYCLE

The virus gains entry to human cells via angiotensin-converting enzyme 2 (ACE2) receptors. These type I membrane proteins are mainly associated with cardiovascular diseases and also present in lung, intestine, kidney, liver and brain tissues [21,28]. ACE2 offers a binding site for the S proteins leading to cleavage of angiotensin (Ang) I to yield Ang-(1-9) [29]. The S proteins go through significant structural reorganization to be able to fuse the virus with human host cell membrane. The S1 subunit binds with a host-cell receptor initiating fusion through destabilizing the prefusion trimer. This process results in the shedding of the S1 subunit and transition of the S2 subunit to an extremely stable postfusion adaptable conformation [30]. To be capable of engaging receptors on host-cells, S1 receptor-binding domain (RBD) undertakes hinge-like adaptive conformational movements that momentarily expose or hide receptor binding determinants [31]. Analyzing the RBD domain of the S protein in SARS-CoV-2 revealed through structural, physical and biological evidence that SARS-CoV-2 S protein probably binds to human ACE2 with 10-20 times higher affinity than SARS-CoV [32]. (Figure 3)

## SARS-COV-2 EVOLUTION & ECOLOGY

All human CoVs are possibly zoonotic in origin and their most likely hosts in nature are bats [33]. During the SARS pandemic early signs suggesting a zoonotic source were civets being pointed out as the natural reservoirs for human infection [34]. The discovery of SARS-like CoVs isolated from various bat species in China indicated that the Chinese horseshoe bats can be the natural host of the SARS-CoV [35,36]. In the case of SARS-CoV-2, the high sequence identity to certain bat CoVs such as Bat-CoV RaTG13 (96.2% nt identity to SARS-CoV-2), pinpoints towards a potential bat origin [24,35]. Since bats habitats are ordinarily found in distant places far from human habitats, any CoV virus must have another intermediary animal host in order to infect humans. The bat SARS like-CoVs cannot directly affect humans without undergoing certain mutations or recombination in another animal host [34]. It is well known that the animal host for MERS-CoV is the camel, while civet cats are the natural hosts of SARS-CoV prior to being transmitted to humans. The intermediate animal host for the SARS-CoV-2 is not fully identified. However, SARS-CoV-2 and pangolin origin CoVs share 99% sequence identity suggesting that the former may have a pangolin origin [37]. (Figure 4)

## SARS-CoV-2 GENOMIC VARIATION

Evaluating early COVID-19 patients, the ten genomic sequences obtained revealed extreme similarities reaching up to 99.8%. This implies that little or no variation has taken place [21,23]. However, since the virus uses RNA polymerase for replication, several copies are expected to be produced. This was supported by a study showing that around 120 substitution sites were uniformly spread over eight coding regions, without any obvious recombination episodes [19].

Meanwhile, Tang et al. in their report revealed that SARS-CoV-2 evolved into two major types. After evaluating and analyzing 103 genomes they concluded that as a result of selective pressure two main types L and S, that differ in their ability to spread and severity of illness, can be identified. L type can be more aggressive and spread faster than the S type [38].

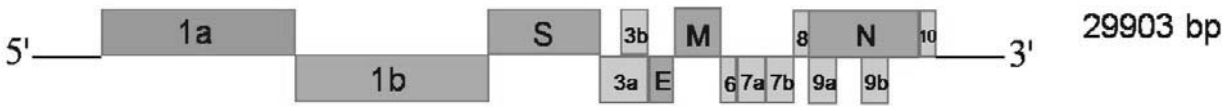


**Figure 2.** ß-coronavirus genome

*From Jin Y, Yang H, Ji W et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020; 12 (4): 372. [40].

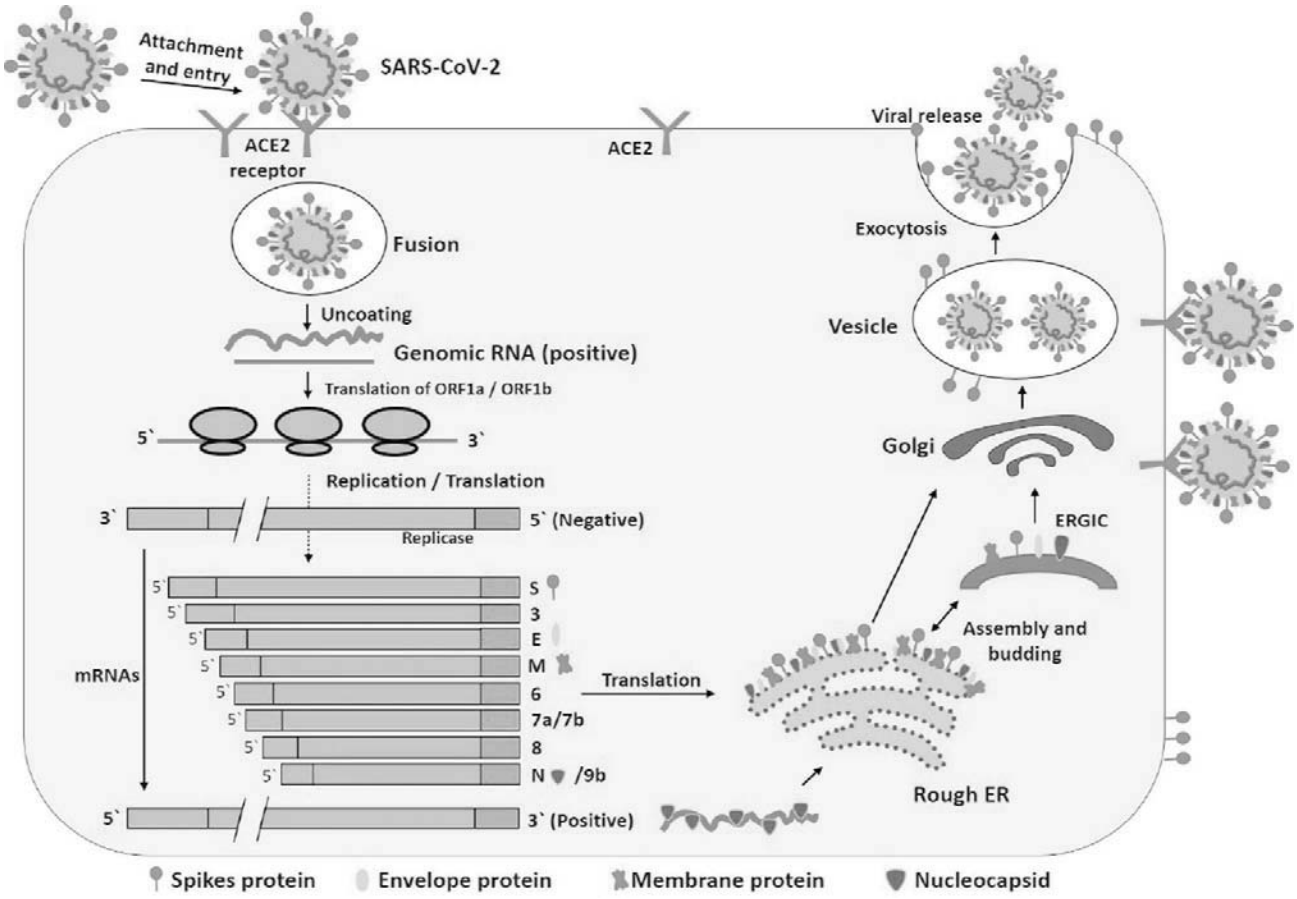


**Figure 3.** Life cycle of SARS-CoV-2
*Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020 Mar 16; 24: 91-98. [3]

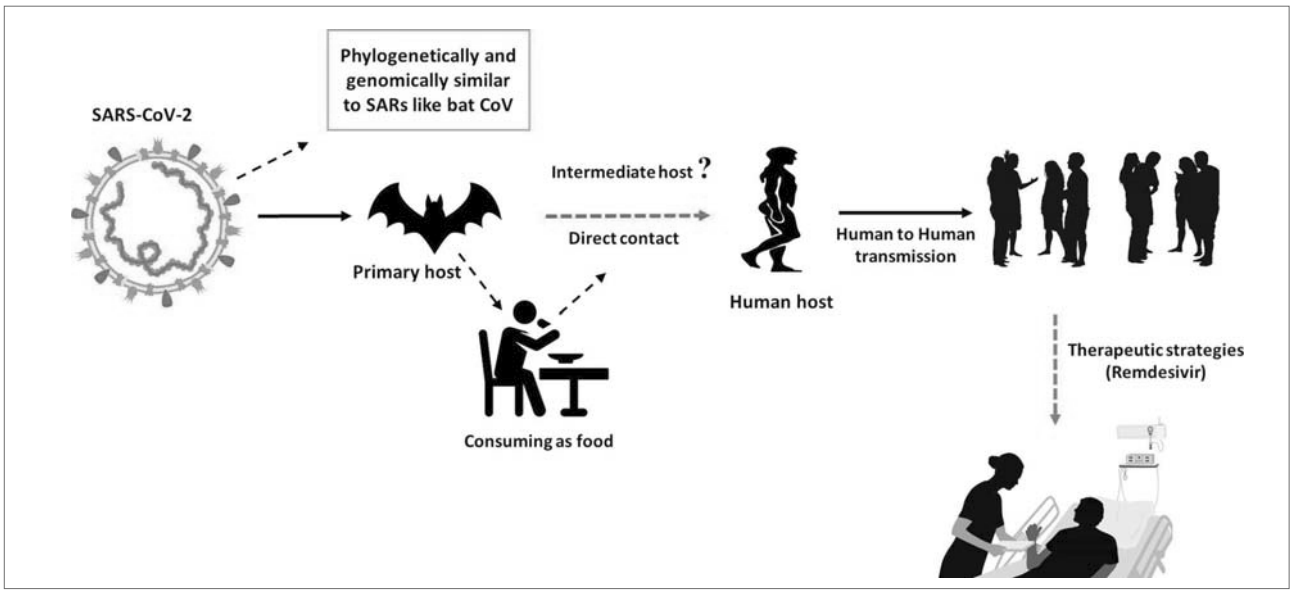


**Figure 4.** Reservoir and mode of transmission of SARS-CoV-2
*From Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020 Mar 16; 24: 91-98. [3]

## CLINICAL & PUBLIC HEALTH SIGNIFICANCE OF HCoVs

### Endemic HCoVs

In regions with temperate climates, endemic HCoVs demonstrate a winter seasonality.

Only HCoV-229E has been reported to cause sporadic disease all through the year. Endemic HCoVs are maintained in the human population and have a global distribution [39]. (Table III)

**TABLE III**

ENDEMIC AND EPIDEMIC HCoVs

| Endemic HCoVs | Epidemic HCoVs |
|---|---|
| HCoV-229E | SARS-CoV |
| HCoV-NL63 | MERS-CoV |
| HCoV-OC43 | SARS-CoV-2 |
| HCoV-HKU1 | |

### Epidemic HCoVs

The SARS-CoV and MERS-CoV epidemics were caused in part by super-spreading events, where some humans have directly affected a disproportionately big number of individuals. On the other hand, the COVID-19 (SARS-CoV-2) outbreak started in a crowded fish market that sells exotic animals as well.

The SARS-CoV epidemic ended in 2003, less than one year from the date when the first case was reported. Meanwhile the MERS-CoV epidemic continued to be reported for more than seven years following the detection of the first case in Saudi Arabia. The natural reservoirs that maintain SARS-CoV and MERS-CoV are zoonotic. It is believed that SARS-CoV-2 has an animal reservoir but its distribution among various mammalian species is unknown. The role of pets and farm animals in the epidemiologic cycle of SARS-CoV-2 is not fully clear. Their ACE2 receptors share similarity with ACE2 human receptors [39]. On April 22 of this year, the Center for Disease Control and Surveillance declared that the National Veterinary Services Laboratories reported SARS-CoV-2 infection in two domestic cats. However, there is no clear evidence confirming cat to human transmission. (Table-III)

## CONCLUSION

SARS-CoV-2 is the viral agent of the current COVID-19 pandemic. It is the 7th identified HCoV associated with respiratory infectious diseases and the 3rd HCoV associated with epidemics following SARS-CoV and MERS-CoV. Believed to have originated from BatCoV due to 96.2% genomic resemblance, intermediate host of SARS-CoV-2 is not clearly identified yet. It replicates efficiently in human cells gaining entry through ACE2 receptors virtually found in all organ systems. Its linear genome structure shares more similarities with SARS-CoV than MERS-CoV. Individuals with asymptomatic infection can spread the viral illness. It has affected more individuals than SARS-CoV or MERS-CoV but seems to be associated with less case fatality rate.

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