

**Epidemiology, virology, and clinical features of severe acute respiratory syndrome -  
coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19)**

Running title: SARS-CoV-2 (COVID-19)

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## **Abstract**

A cluster of severe pneumonia of unknown etiology in Wuhan City, Hubei province in China emerged in December 2019. A novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was isolated from lower respiratory tract sample as the causative agent. The current outbreak of infections with SARS-CoV-2 is termed Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). COVID-19 rapidly spread into at least 114 countries and killed more than 4,000 people by March 11 2020. WHO officially declared COVID-19 a pandemic on March 11, 2020. There have been two novel coronavirus outbreaks in the past two decades. The 2002-2003 outbreak of severe acute respiratory syndrome (SARS) in 2002-2003 caused by SARS-CoV had a case fatality rate of around 10% (8,098 confirmed cases and 774 death), while Middle East respiratory syndrome (MERS) caused by MERS-CoV killed 861 people out of a total 2,502 confirmed cases between 2012 and 2019. The purpose of this review is to summarize known-to-date information about SARS-CoV-2, transmission of SARS-CoV-2, and clinical features.

**Key words:** SARS-CoV-2, COVID-19, coronavirus, SARS-CoV, MERS-CoV

## Introduction

In December 2019, a cluster of patients with pneumonia of unknown origin was identified in Wuhan, Hubei Province, China. Most patients witnessed a history of visiting Huanan Seafood Wholesale Market. On December 31, 2019, the Chinese Center for Disease Control and Prevention (China CDC) and Wuhan city health authorities reported an outbreak of pneumonia of unknown cause in Wuhan City.<sup>1,2)</sup> On January 7, 2020, the China CDC identified a novel coronavirus from the lower respiratory tract samples of the patients with pneumonia and disclosed the genomic sequence on January 11.<sup>3,4)</sup> This novel coronavirus was later named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The World Health Organization (WHO) named this infection, caused by SARS-CoV-2 identified in 2019, Coronavirus Disease 2019 (COVID-19).<sup>5)</sup> Despite the effort to stop the transmission of COVID-19, the infection spread throughout mainland China, and in January 2020, cases were reported in Thailand, Japan, and South Korea.<sup>6,7)</sup> Within less than 3 months since the discovery of the unknown pathogen, the infection spread to at least 114 countries and caused more than 4,000 deaths. On March 11, the WHO announced COVID-19 outbreak a pandemic.<sup>8)</sup> In South Korea, the first case was identified on January 20, 2020, and as of March 26, a total of 9,241 confirmed cases leading to 131 deaths (1.42% fatality rate) has been reported.<sup>9)</sup>

Two novel strains of coronavirus have jumped species from animal to human, spread by human-to-human transmission, and caused severe acute respiratory syndrome leading to high fatality rate in the past 2 decades.<sup>10)</sup> Severe acute respiratory syndrome-associated virus (SARS-CoV), previously unknown coronavirus traced to horseshoe bats in southern China, caused 8,096 confirmed cases and 774 deaths (9.6% fatality rate) in 29 countries from November 2002 to July 2003.<sup>11)</sup> In South Korea, the first suspected case was reported in April 3, 2003. As of June 15, 2003, three probable cases and 17 suspected cases were identified

without any fatality.<sup>12)</sup> Globally, no SARS-CoV infection has been reported since 2004.<sup>10)</sup> In 2012, another novel coronavirus was first identified in a patient with acute severe respiratory syndrome and multiple organ failure in Saudi Arabia.<sup>13)</sup> This pathogen, later named MERS-CoV, associated with pneumonia and acute respiratory syndrome (Middle East respiratory syndrome; MERS), leading to an outbreak in Arabian Peninsula. Between April 2012 and December 2019, a total of 2,502 confirmed cases and 861 deaths (34.4% fatality rate) were reported in 27 countries.<sup>14)</sup> In May 2015, a returned traveler from Saudi Arabia was linked to 186 confirmed MERS-CoV infections and 38 deaths (20.4% fatality rate) in South Korea.<sup>15)</sup>

This article reviews characteristics, pattern of transmission, and clinical features of COVID-19. We also briefly describe distinct features of SARS-CoV-2 in comparison to SARS-CoV and MERS-CoV (Table 1).

### **Characteristics and taxonomy of the virus**

Coronaviruses are enveloped positive sense single-stranded RNA viruses sized 80-220nm in diameter. The envelop bears crown-like, 20nm-in-length spikes that resemble corona of the sun under electron microscopy, hence given its name coronavirus. The virus can cause disease both in animal and in human. It carries the largest genome among the currently known RNA viruses.<sup>16)</sup> Coronaviruses are members of the subfamily *Coronavirinae* in the family *Coronaviridae* and the order Nidovirales. This subfamily divides into four genera – Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. So far, six coronaviruses are known to cause human diseases. Four coronaviruses are endemic in humans. These are human coronaviruses (HCoV) 229E, OC43, NL63, and HKU1. Two epidemic human coronaviruses are SARS-CoV and MERS-CoV. Alphacoronavirus includes HCoV 229E and NL63, and betacoronavirus includes HCoV OC43, HKU1, SARS-CoV, and MERS-CoV. The gammacoronavirus includes avian infectious bronchitis virus and several

other coronaviruses, and deltacoronavirus includes several recently discovered avian coronavirus.

Within the coronavirus particle, a nucleoprotein (N) wraps the RNA genome to form a coiled tubular structure together. The viral envelop (E) surround this helical nucleocapsid. Two or three structural proteins are associated with viral envelop. The matrix protein (M) embedded in envelop. The spike structural protein (S) anchored in envelop is target of neutralizing antibody. The hemagglutinin esterase (HE) is found in several of the betacoronaviruses.<sup>17)</sup> The coronaviruses have five essential genes which are for four structural proteins (N, E, M, S) and for viral replication/transcription (RNA dependent RNA polymerase, RdRp). The genome organization is 5'-RdRp-S-E-M-N-3'. This gene order of coronaviruses is highly conserved.<sup>17)</sup>

Whole genome sequencing of SARS-CoV-2 reveals that it is a novel betacoronavirus distinct from SARS-CoV.<sup>18)</sup> The nucleotide sequence of SARS-CoV-2 showed 79.0% and 51.8% identity with SARS-CoV and MERS-CoV, respectively and it is closely related to bat-origin SARS-like coronavirus (bat-SL-CoVZC45) with 87.6-89% identity.<sup>19,20)</sup> The virus was initially called 2019-novel coronavirus (2019-nCoV) upon its emergence, until the Coronaviridae Study Group of International Committee on Taxonomy of Viruses named the virus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) based on the phylogenetic analysis, on February 11, 2020.<sup>21)</sup> On the same day, the WHO named the disease caused by the novel coronavirus Coronavirus Disease 2019 (COVID-19), in alignment with WHO best practices for naming of new human infectious disease.<sup>5)</sup>

Based on the virus genome sequencing data, bats are assumed to be the reservoir of SARS-CoV-2, but the intermediate hosts are yet to be known. Data indicate SARS-CoV evolved from bat coronavirus in horseshoe bats through civet cats or other intermediated animal hosts. MERS-CoV also likely evolved from bat coronavirus, with dromedary camels as intermediate

hosts.<sup>22-25)</sup>

SARS-CoV-2 gains entry to a host cell through binding its spike proteins, which determine host tropism, to host cell receptors.<sup>26)</sup> Preliminary researches had suggested that SARS-CoV-2 might share a host cell receptor with SARS-CoV, because the two strains have similar receptor-binding protein structures. Successive studies showed that SARS-CoV-2 binds to angiotensin converting enzyme 2 (ACE2) as SARS-CoV does.<sup>27,28)</sup> HCoV NL63 also binds to ACE2, but with less avidity than SARS-CoV; HCoV 229E binds to aminopeptidase N (CD-13); receptor for HCoV OC43 is still unknown; MERS-CoV binds to dipeptidyl peptidase-4 (DPP4).<sup>28)</sup>

SARS-CoV-2 was first isolated from a bronchoalveolar lavage sample<sup>19)</sup>, and RNA of the virus was also detected in nasopharyngeal and throat swabs as well as blood, stool, urine, and saliva.<sup>29,30)</sup>

### **Transmission of the virus**

When COVID-19 first emerged in Wuhan, China, no infection of healthcare personnel had been reported, and human-to-human transmission of the virus was considered unlikely until patients unrelated to the seafood market began to appear. As community transmission cases and outbreaks outside China were reported, human-to-human transmission became apparent.<sup>20,31)</sup>

Mode of transmission for HCoV 229E, OC43, NL63 and HKU1 are not clearly known, but as with other respiratory viruses, human coronavirus transmission occurs via droplets, indirect or direct contacts.<sup>16)</sup> Possibility of aerosol transmission remains to be investigated. MERS-CoV spreads mostly through droplet and direct contact, but transmission through indirect contact, aerosol, fecal-to-oral route are also possible.<sup>10,16)</sup> SARS-CoV primarily spreads via droplet and direct contact. Medical procedures that induce production of aerosol,

such as nebulizer treatment or intubation, are reported to increase the risk of transmission. Fecal-to-oral route may be possible, but little evidence supports it.<sup>10)</sup> SARS-CoV-2 seems to share the mode of transmission with SARS-CoV and MERS-CoV, as it spreads mainly through respiratory secretion or droplet. Recent studies showed that SARS-CoV-2 can remain viable on various surfaces such as stainless steel, plastic, glass, and cardboard at least several hours.<sup>32,33)</sup> This indicate that transmission of SARS-CoV-2 through contaminated surfaces might be possible. Aerosol is currently not considered as primary mode of transmission since no airborne transmission has been reported yet, although it seems possible in hospital settings where aerosol-producing procedures occur. SARS-CoV-2 RNA has been detected in stool, whole blood and urine of COVID-19 patients, but whether transmission via such medium is possible is still unknown.<sup>29,30)</sup>

SARS-CoV-2 is more rapidly spreading across the globe than SARS-CoV did. Within 3 months since the initial report of outbreak in Wuhan, 80,555 confirmed cases in China and 17,821 confirmed cases in 90 countries outside of China had occurred by March 5, 2020. On March 11, COVID-19 had spread to at least 114 countries around the globe and had killed more than 4,000 lives. On the same day, the WHO declared COVID-19 a pandemic.<sup>8)</sup> It is notable that SARS-CoV infection was not declared a pandemic despite of 8,096 confirmed cases leading to 774 deaths during the 8-months period since the first report of SARS case on November 16, 2002. Meanwhile, in April 2009, when H1N1pdm09 virus spread rapidly around the globe and caused more than 30,000 cases in 74 countries, the WHO announced H1N1pdm09 influenza virus infection a pandemic.<sup>34)</sup>

The transmissibility of SARS-CoV-2 is not precisely known. A meta-analysis of 12 studies published between January 1 and February 7, 2020 suggests that basic reproduction number (R0) of SARS-CoV-2 ranged from 1.4 to 6.49 (mean 3.23; median 2.79).<sup>35)</sup> Accumulation of more epidemiologic data may modify this value, but R0 is expected to be around between 2

and 3.

SARS-CoV transmission occurs several days after the onset of symptoms, in alignment with the period of peak respiratory viral load.<sup>10)</sup> SARS-CoV was effectively contained by isolating the patient soon after the onset of illness, since secondary attack rate was greatly reduced by isolating the index case within 5 days. On the other hand, the point of transmission for SARS-CoV-2 remains unknown. In general, respiratory viruses have the highest transmissibility when the patient has symptoms, therefore we assume the same for COVID-19. According to a study that followed respiratory viral load of eighteen COVID-19 patients in China, viral load peaks shortly after the onset of illness and declines thereafter.<sup>36)</sup> The viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza virus. The study results suggested that transmission of COVID-19 may occur during first few days after the onset of symptoms. Moreover, the number of virus RNA copies from one asymptomatic case was comparable to that of the rest of symptomatic cases. Moreover, a case of transmission from an asymptomatic family member was recently reported.<sup>37)</sup> Therefore, we can assume that transmission of COVID-19 may occur with the illness onset and even with mild or no symptoms. However, further research is needed on viral transmission from an asymptomatic patient because there is a possibility that the patient may not have been aware of his or her symptoms or may not have been recognized by caregivers due to old age or underlying illness of the patient. The pattern of transmission observed in COVID-19 is distinctive from that of SARS-CoV; such pattern indicates that the spread may not be effectively controlled by isolating the patient after the illness onset. Transmissibility of the virus during incubation period is yet to be established.

Little is known about vertical transmission of COVID-19. In a study of 12 SARS-CoV infected pregnant women during outbreak in 2002-2003, 3 women (25% case fatality rate) died and 4 had spontaneous miscarriage.<sup>38)</sup> Five mothers delivered; 4 by caesarean section

and 1 by spontaneous vaginal delivery. Gestational ages ranged 26-37 weeks. All five newborns did not show evidence of SARS-CoV infection, but 2 newborns out of 5 had intrauterine growth retardation. Another study analyzed several reports about pregnancy and perinatal outcome of MERS-CoV infected pregnant women<sup>39)</sup>; of the total 9, 5 mothers received intensive care, and 3 out of 5 them died (33.3% case fatality rate). Two women had spontaneous miscarriage, and 5 mothers delivered at gestational age between 32 to term; none of the newborns had signs of MERS-CoV infection. Chen et al. analyzed 9 pregnant women who had been diagnosed with COVID-19 in their third trimester and had caesarean section.<sup>40)</sup> Clinical features of mothers and their newborns were recorded, along with SARS-CoV-2 detection in amniotic fluid, cord blood, breastmilk, and nasopharyngeal swab of the newborn. None of the 9 mothers developed severe pneumonia, died or had miscarriage. All the amniotic fluid, cord blood, breastmilk, and nasopharyngeal swab of the newborn tested negative for SARS-CoV-2. This study suggested that there is currently no evidence of vertical transmission of SARS-CoV-2 in women who developed pneumonia during 3rd trimester of pregnancy. However, the number of pregnant women of the study is very small and only the infection in the late of pregnancy is included, so it cannot be concluded at the moment on the impact of the infection especially in the early or mid-term pregnancy on pregnant women and fetuses.

### **Clinical features of COVID-19**

The median incubation period was 5.1 days<sup>41)</sup>, ranged from 2-14 days.<sup>31)</sup> An analysis of household transmissions revealed that fever and respiratory symptoms appeared 3-7 days after exposure to the virus. Fever, dry cough, and fatigue were more commonly reported, whereas nasal congestion, rhinorrhea, sore throat, and myalgia were relatively rare.<sup>42)</sup> Occasionally, non-respiratory symptoms such as palpitation, diarrhea, or headache preceded

respiratory symptoms. Some patients were initially afebrile. Clinical spectrum of COVID-19 ranged from asymptomatic to fatal pneumonia. The rate of asymptomatic infection is yet to be defined, since most initially asymptomatic infections eventually turned symptomatic.

Based on the data from the Chinese National Reporting System, as of February 20, 2020, the median age of the confirmed cases was 51 years (2days-100years), of which 77.8% were 30-69 years.<sup>43)</sup> A total of 51.1% were male. Of the reported confirmed cases, 80% were without pneumonia, or had mild to moderate pneumonia; approximately 15% had severe pneumonia; approximately 6% were under intensive care due to respiratory failure, shock, or multiple organ failure. Fatality rate of COVID-19 in China is 3.8%; the fatality rate in Wuhan City is 5.8%, in comparison to that of 0.7% in the rest of mainland China. Risk factors of severe pneumonia or death include ages 60 or older, and medical comorbidity such as hypertension, diabetes mellitus, cardiovascular disease, chronic pulmonary disease or malignancy. Laboratory tests of the confirmed COVID-19 cases showed leukopenia, lymphopenia, mild elevated C-reactive protein. But the patients with severe pneumonia had elevations in leukocytes, neutrophils, and creatinine kinase. Computer tomography (CT) revealed ground glass appearance, interstitial infiltration, or multiple patchy consolidations in both lung fields.<sup>44)</sup>

A group of researchers in Wuhan City analyzed 138 hospitalized patients based on the severity of pneumonia.<sup>45)</sup> Among the 138 patients with pneumonia, 36 required intensive care. The median age of the intensive care group was 66 years, while that of the other group was 51 years. The intensive care group were more likely to have underlying conditions including hypertension and diabetes mellitus. The median time from onset of symptoms to dyspnea was 5 days and to acute respiratory syndrome was 8 days. At the point of publication, six patients had died with overall mortality of 4.3%. In fatal cases, elevations in total leukocyte count, neutrophil ratio, and decrease in lymphocyte were observed 7 days after the onset of

symptoms.

Meanwhile, SARS-CoV infection most commonly presents with fever. The infection begins with systemic complaints including myalgia, chills, or fatigue, followed by dry cough and dyspnea after a few days to a week. Symptoms of upper respiratory tract infection such as rhinorrhea or sore throat are rare. Watery diarrhea may be accompanied in 10-25% patients in later course of the disease. Intensive care was required in 20-30% of patients, with 10% fatality rate. In ages older than 60years, fatality rate was 50%. Death mostly occurred in the third week from the onset of symptoms. In MERS-CoV infections, the disease course is especially severe in patients with preexisting conditions such as renal failure. Cough and dyspnea appear a few days after the onset of symptoms; plain chest radiographs reveal infiltrations in unilateral or bilateral lung fields; the symptoms aggravate rapidly, and ventilator care ensue. Fatality rate was 35%. Vomiting, diarrhea, or abdominal pain was accompanied in approximately 25% of cases.<sup>10)</sup>

## **Conclusion**

Within three months since the discovery of a novel coronavirus in patients with pneumonia of unknown origin in Wuhan City, China, COVID-19 has spread rapidly throughout the world and is beating SARS-CoV and MERS-CoV in the number of confirmed cases and deaths. Modern medical knowledge and technology enabled us to promptly identify the previously unknown pathogen, share the genomic information of the virus, develop diagnostic tools, detect the disease, isolate patients and provide appropriate medical care. However, several unanswered questions remain to be addressed: the reservoir and intermediate hosts of SARS-CoV-2, the peak periods of transmission, the duration of transmission, and pathogenesis of severe pneumonia. The world needs to not only strive to slow the spread but also invest in development of treatment and vaccines for COVID-19.

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**Table 1.** Differences in characteristics of COVID-19, SARS, and MERS

Characteristics	COVID-19	SARS	MERS
First identified location	Wuhan, China	Guangdong, China	Jeddah, Saudi Arabia
Period	2019–present	2002–2003	2012–ongoing
Host of virus			
Natural host	Bats	Bats	Bats
Intermediate host	Unknown	Civet cat or other animal hosts	Dromedary camels
Mode of transmission			
	Respiratory droplet	Respiratory droplet	Respiratory droplet
	Contact	Contact	Contact
$R_0$	2–3	2–5 <sup>46)</sup>	<1 <sup>46)</sup>
Incubation period	5.1 days <sup>a)</sup>	4.6 days <sup>47)b)</sup>	5.2 days <sup>47) a)</sup>
	(95% CI, 2.2–11.5 days)	(95% CI, 3.8–5.8 days)	(95% CI, 1.9–14.7 days)
Case fatality rate	3.8% <sup>43)</sup>	9.6%	34.4%

<sup>a)</sup>Median incubation period

<sup>b)</sup>Mean incubation period

Abbreviations: COVID-19, coronavirus disease-2019; SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome;  $R_0$ , basic reproduction number; CI, confidence interval.