

Trends, Epidemiology and Pathogenesis of Sars Cov1 and Sars Cov2

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Abstract

Within two decades, there have emerged three highly pathogenic and deadly human coronaviruses, namely SARS CoV, MERS-CoV and SARS-CoV-2. On 30 January 2020, the WHO declared the COVID-19 outbreak as the sixth public health emergency of international concern, following H1N1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in the Democratic Republic of Congo (2019). COVID 19 was caused by a newly identified coronavirus, initially termed 2019 Novel Coronavirus and subsequently severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreaks of these hCoVs are related to interactions between humans and animals, especially, both SARS CoV and SARS-CoV-2 emerge from wet markets in China. Considering early SARS patients were associated with wild animal markets in Guangdong, SARS-CoV was considered to emerge from wild animals (included palm civets) which were sold in these markets. SARS-CoV-2 is closely related to two bat-derived severe acute respiratory syndrome-like coronaviruses, RaTG13 and RmYN02. Similarities among SARS-CoV, MERS-CoV and SARS-CoV-2 have been investigated in the light of available data. SARS-CoV, MERS-CoV and SARS-CoV-2 evolved in bats and have positive-sense RNA genomes of 27.9 kb, 30.1 kb and 29.9 kb, respectively. Molecular and serological tools used for diagnosis of SARS and MERS patients resemble COVID-19 diagnostic tools.

Keywords: Coronavirus, Covid 19, Sars Cov1, Sars Cov2

List of Abbreviations

3CLpro-1 3CLpro inhibitor
ACE2 Angiotensin Converting Enzyme II
CDC Center for Disease Control
CoV SARS Coronavirus
DPP4 Dipeptidyl peptidase 4
HCoV Human Coronaviruses
ICTV International Committee on Taxonomy of Viruses IFN interferon
MERS Cov Middle East Respiratory Syndrome Coronavirus
NBSC National Bureau of Standards China
NLRP3 inflammasomes and trigger pyroptotic cell death,
ORF Open Reading frames
PHEIC public health emergency of international concern
R0 Reproduction number
RaTG13 bat coronavirus detected in Rhinolophus affinis
RBD Receptor- Binding Domain

SARS Severe Acute Respiratory Syndrome

SARS-CoV-1 Severe Acute respiratory syndrome coronavirus

1. SARS-CoV-2 severe acute respiratory syndrome coronavirus

2 TMPRSS2 endosomal cysteine proteases

WHO World Health Organization

1. Introduction

Coronaviruses (CoVs), systemically classified as Coronaviridae, are enveloped viruses that can infect poultry, domestic animals, and humans. The Coronaviridae, which belongs to the order Nidovirales, was first isolated from chickens in 1937 and from humans in 1965 (Drexler et al., 2010). Coronaviruses (CoVs) are members of the family Coronaviridae, the enveloped viruses that possess extraordinarily large single-stranded RNA genomes ranging from 26 to 32 kilobases in length (Su et al., 2016). Coronaviruses (CoVs) consist of four genera: Alpha coronavirus, Beta coronavirus (β), Gamma coronavirus (γ) and Delta coronavirus (δ). Among these, alpha and β only infect mammals, whereas γ and δ mainly infect

birds. Beta coronaviruses are further divided into four lineages: A, B, C and D. Previously, there have been six human coronaviruses: 229E, HKU1, OC43, NL63, middle east respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV). Among these lineages, 229E, HKU1, OC43 and NL63 are low pathogenic CoVs, whereas SARS-CoV and MERS-CoV are highly pathogenic CoVs (Cui et al., 2019). CoVs are the cause of a variety of diseases in humans and animals. They are capable of adapting to new environments through mutation and recombination, and are programmed to alter host range and tissue tropism (Alsaadi and Jones, 2019).

Although hCoV-HKU1, hCoV-OC43, hCoV-NL63 and hCoV-229E mainly cause asymptomatic or mild respiratory and gastrointestinal infections, they have been circulating in humans since they were recognized, and accounting for approximately 5–30% of common colds (Zhu et al., 2020b). Severe illness can be caused by the remaining three viruses, namely SARS-CoV, which resulted in the outbreak of SARS in 2002 and 2003 (Zhong et al., 2003); the coronaviruses that are responsible for the Middle East respiratory syndrome (MERS-CoV), which emerged in 2012 and remains in the circulation in camels (Zaki et al., 2012); and SARS-CoV-2, the virus emerged in December 2019 in Wuhan of China and a great effort is being undertaken to contain its spreading (Zhu et al., 2020a).

SARS (severe acute respiratory syndrome) was a new disease in the fall of 2002, which first occurred in Guangdong Province, China and spread to 29 countries with 8422 cases and 916 fatalities (WHO, 2003). A newly discovered coronavirus (SARS-CoV) has been identified as the cause of SARS (Ksiazek et al., 2003). SARS-CoV-like viruses have been detected in Himalayan palm civets and a raccoon-dog in a market in southern China, suggesting that the origin of SARS CoV may have been from these or other wild animals (Guan et al., 2003). The first train of transmission of SARS occurred in Foshan City, Guangdong Province, China (Hon et al., 2003). During the period from November 16, 2002, until February 9, 2003, there were 305 cases reported in Guangdong Province. SARS was spread to Hong Kong on February 22, 2003, by a patient from Guangdong Province who, before his hospitalization, stayed in the Metropole Hotel in Hong Kong for 1 d. Ten secondary cases occurred in hotel guests, and these infected persons led directly to tertiary cases in two Hong Kong hospitals and outbreaks in Singapore, Toronto, and Hanoi (CDC, 2003). No more infected human cases have been reported since May 2004 (Amirian et al., 2016).

After the emergence of SARS, MERS was the second coronavirus resulting in a major global public health crisis. It first emerged in 2012 in Saudi Arabia when a 60-year-old man presented with severe pneumonia (Mackay and Arden, 2015). An outbreak of the virus did not occur until 2 years later, in 2014, with a total number of identified cases of 662 and a 32.97% case-fatality rate (Al-Omari et al., 2019). From 2014 to 2016, 1364 cases were observed in Saudi Arabia. 27 countries were affected by MERS during the outbreaks spanning Europe, Asia, the Middle East and North America.

Cases that were identified outside of the Middle East, including the outbreak in South Korea in which 186 individuals were infected as a result of a super spreader, were transplanted individuals that had previously been infected in the Middle East (Kim et al., 2017a). Since 2012, 2494 laboratory confirmed cases of MERS have been reported, and 858 associated deaths have occurred (34.4% case-fatality ratio) (WHO, 2020).

In late December 2019, several health facilities in Wuhan, in Hubei province in China, reported clusters of patients with pneumonia of unknown cause (Zhu et al., 2020a). The causative pathogen was identified as a novel coronavirus that was named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Shang et al., 2020; Zhou et al., 2020). The disease rapidly spread internationally, raising global public health concerns, and was subsequently termed coronavirus disease 19 (COVID-19) (Xu et al., 2020). The most common clinical manifestations of patients with COVID-19 are fever, cough, shortness of breath, and fatigue. Some patients have also shown radiographic ground-glass lung changes and eventually died of acute respiratory distress syndrome (ARDS) (Wang et al., 2020a). The World Health Organization (WHO) declared COVID-19 as a global pandemic on March 11, 2020 (WHO, 2020). SARS-CoV-2 is mainly transmitted human-to-human through close contact, respiratory droplets, fomites, and contaminated surfaces (Cheng et al., 2020). The WHO adapted a 1-m social distancing policy, based primarily on the assumption that the virus is transmitted through largely isolated droplets within this range (WHO, 2020). However, the possibility of airborne transmission through airborne particles with diameters smaller than 5 µm has been suggested (Morawska and Cao, 2020).

Following the WHO announcement of COVID-19 that was caused by SARS-CoV-2, the Global Emergency Committee identified the need for early detection, quarantine, and prompt treatment as a global concern (Sohrabi et al., 2020) because people with the virus do not have clinical symptoms such as fever, cough, etc., in the early stages. For this reason, there is not enough information on how to disinfect and disinfect surfaces and hands, human-to-human transmission through air, food, and water, and the presence of the virus in human wastewater and waste. There are several factors involved in transmitting the virus. These conditions can be included in environment and human behavior. The distribution of human population, migration, social interactions, climate change (deforestation, habitat invasion), agricultural growth, and direct contact with domestic and wild animals fall into this category (Dehghani and Kassiri, 2020). Although HCoVs have been identified for decades, their clinical importance and epidemic possibility was not recognized until the outbreak of SARS and MERS (Zaki et al., 2012).

The general objective of this review was to indicate the similarities among SARS-CoV-2, MERS-CoV and SARS-CoV is essential to limit the spread and to treat the patients with COVID-19. This review also illustrated the involvements of farm and wild animal in

the current SARS COV 2 pandemic.

2. Litratue Review

2.1. Biological Characteristics of Corona Virus

Coronaviridae is a family of viruses containing a large number of virus variants that well known to infect various animals universal-ly; however, they have been scarcely recognized to infect humans (Pennisi et al., 2020). Transmission electron microscopy images show that CoVs are spherical-shape viruses with spike proteins projecting from the virion surface, leaving themselves resemble solar crowns, therefore being termed “coronaviruses” (Ashour et al., 2019). According to previous studies, SARS-CoV-2 has been confirmed to share 79.5% sequence identity with SARS-CoV and 94.6% sequence identity with SARS-CoV in ORF1a/b; the sequencing results were used for CoV species classification and revealed that both of these viruses are lineage B beta coronaviruses (Zhou et al., 2020; Lu et al., 2020 a). However, SARS-CoV-2 shares only 40% sequence identity with MERS-CoV, which is a lineage C betacoronavirus (Chan et al., 2020). Civets are the intermediate hosts of SARS-CoV, whereas dromedary camels are the intermediate hosts of MERS-CoV (Zhou et al., 2020; Lu et al., 2020 b). However, the intermediate hosts of SARS-CoV-2 have not been determined. At present, the prevailing viewpoints suggest

Malayan pangolins and turtles (Liu et al., 2020a). Viruses of the family Coronaviridae as well as in many animal viruses enclose 26 -32 kb enveloped positive senses ssRNA (Su et al., 2016). Within the coronavirus particle a nucleoprotein (N) wraps the RNA genome to form a coiled tubular structure together. The RNA includes at least six open reading frames (ORFs). The first ORF (ORF1a/b) comprises approximately 2/3 of the genome and encodes replicase proteins, and the remaining ORFs mainly encode four structural proteins. The viral envelop (E) surround this helical nucleocapsid. Two or 3 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 is found in several of the beta coronaviruses. (Brian and Baric, 2005) .The major distinctions between SARS-CoV-2 and SARS-CoV are in open reading frame-3b (orf3b), spike and open reading frame-8 (orf8), especially in spike S1 and orf8 (Hu et al., 2020). Orf8 is an accessory protein. The SARS-CoV orf8b can activate NLRP3 inflammasomes and trigger pyroptotic cell death, whereas the new orf8 of SARS-CoV-2 does not contain a known functional domain or motif (Shi et al., 2019). The receptor of SARS-CoV-2 is angiotensin-converting enzyme II (ACE2), which is also the receptor of SARS-CoV (Wrapp et al., 2020).

| | SARS Cov2 | SARS Cov | MERS Cov |
|-----------------------------------|--|---|---|
| Homology | | 79.5% | 40% |
| Possible reservoir | Bat (Zhou et al., 2020; Lu et al., 2020) | Bat (Zhou et al., 2020; Lu et al., 2020) | Bat (Zhou et al., 2020; Lu et al., 2020) |
| Possible intermediate host | Malayan Pangolins and turtles (Zhou et al., 2020; Lu et al., 2020) | Palm civet (Zhou et al., 2020; Lu et al., 2020) | Camel (Zhou et al., 2020; Lu et al., 2020) |
| The lineage of Beta coronaviruses | B (Zhou et al., 2020; Lu et al., 2020) | B (Zhou et al., 2020; Lu et al., 2020) | C (Zhou et al., 2020; Lu et al., 2020) |
| Predominant cellular receptor | ACE2 (Hu et al., 2020) | ACE2 (Belouzard et al., 2009) | Dipeptidyl peptidase 4 (DPP4, also known as CD26) (Wang et al., 2013) |
| Symptom | Severe acute respiratory syndrome, 4.2% mortality rate (Yang et al., 2020) | Severe acute respiratory syndrome, 11% mortality rate (Yang et al., 2020) | Severe acute respiratory syndrome, 34% mortality rate (Yang et al., 2020) |

Table 1: A comparison of biological features among sars-cov-2, sars-cov and mers-cov.

2.2. Animal Host and Spillover of Sars Cov2

Subsequently, a strain of CoV shared highly homological similarity to SARS-CoV (99.8%) was isolated from palm civets from wild animal markets, thus palm civets- derived CoVs were believed to be able to switch their hosts to human, causing the human-to-human transmission (Guan et al., 2003).Bats are important natural hosts of alpha coronaviruses and beta coronaviruses. The closest relative to SARS-CoV-2 known to date is a bat coronavirus detected in Rhinolophus affinis from Yunnan province, China, named ‘RaTG13’, whose full-length genome sequence is 96.2% identical

to that of SARS-CoV-2 (Zhou et al., 2020). This bat virus shares more than 90% sequence identity with SARS-CoV-2 in all ORFs throughout the genome, including the highly variable S and ORF8. The high genetic similarity between SARS-CoV-2 and RaTG13 supports the hypothesis that SARS-CoV-2 likely originated from bats (Paraskevis et al., 2020). Another related coronavirus has been reported more recently in a Rhinolophus malayanus bat sampled in Yunnan. This novel bat virus, denoted ‘RmYN02’, is 93.3% identical to SARS-CoV-2 across the genome. In the long lab gene, it exhibits 97.2% identity to SARS-CoV-2, which is even high-

er than for RaTG13 (Zhou et al., 2020). In addition to RaTG13 and RmYN02, phylogenetic analysis shows that bat coronaviruses ZC45 and ZXC21 previously detected in *Rhinolophus pusillus* bats from eastern China also fall into the SARS-CoV-2 lineage of the subgenus Sarbecovirus (Zhang and Holmes, 2020).

Another study demonstrated that the similarity in genome between SARS-CoV-2 and the CoV isolated from pangolin (pangolin-CoV) was high 92.4% and pangolin-CoV was their closest common ancestor. Pangolin-CoV is another closely related kin of SARS-CoV-2, and pangolins rather than bats might be the natural reservoirs for SARS-CoV-2 (Zhang et al., 2020b). Although RaTG13 and SARS-CoV-2 share the highest homology regarding the overall genomic sequence, SARS-CoV-2 exhibits the highest sequence similarity (97.4%) to pangolin-CoV in terms of receptor-binding domain (RBD), however, RBD sequence similarity between RaTG13 and SARS-CoV-2 is far less (89.2%). More notably, six key RBD residues of SARS-CoV-2 and pangolin-CoV are identical (Zhou et al., 2020).

2.3. Trends and Epidemiology of Human Coronavirus (Hcov)

SARS-1 broke out in Foshan, Guangdong Province, in November 2002 (Xu et al., 2004). SARS-2 started in Wuhan in Hubei Province no later than early December 2019 (Lu et al., 2020). In China, November and December are winter months, and are the coldest months of the year in these two locations (NBSC, 2019).

2.3.1. Trends and Epidemiology of Sara Cov1

SARS 1 remained isolated in China from November 2002 until 21 February 2003, when a physician with SARS traveled from Guangdong province to a hotel in Hong Kong, infecting 10 other guests (CDC, 2003). The movements of these 11 individuals resulted in the spread of SARS worldwide and sparked all of the major epicenters outside of China (WHO, 2003). Based on observations of data from the early outbreak in mainland China from 10–24 January 2020, the trend of an increasing incidence largely follows exponential growth, and the mean basic reproduction number (R_0) was estimated to range from 2.24 [95% confidence interval (CI) 1.96–2.55] to 3.58 (95% CI 2.89–4.39), associated with two- to eight-fold increases in the reporting rate (Zhao et al., 2020). The rate of spread of an epidemic and whether it is self-sustaining depend on the basic reproduction number (R_0). R_0 is defined as the average number of secondary cases generated by 1 primary case in a susceptible population (Donnelly et al., 2003).

From November 2002, when the first known case of SARS occurred in Foshan, China, to July 2003, when the WHO declared the SARS pandemic over, a total of 8,096 cases were reported in 27 countries, including 774 deaths for a CFR of 9.6% (De Wit et al., 2016). Among these 8,096 cases, 23.1% were health workers, the male–female ratio was 1:1.25, and the mean age was 39.9

years, ranging from 1 to 91 (Rota et al., 2003). The mean incubation period was 6.4 days (range 2–10) (Park et al., 2019). Carrying a HLACw0801 allele is a risk factor for SARS (Chen et al., 2006). Older age and male gender were predictive of poor prognosis (Chan et al., 2007).

2.3.2. Trends and Epidemiology of Sars Cov 2

Based on observations of data from the early outbreak in mainland China from 10–24 January 2020, the trend of an increasing incidence largely follows exponential growth, (Zhao et al., 2020). The estimation based on data from 31 December 2019 to 28 January 2020 suggested similar findings, with the R_0 for COVID-19 being 4.68 [95% credible interval (CrI) 2.47–2.86] and the epidemic doubling time being 6.4 days (95% CrI 5.8–7.1 days) (Wu et al., 2020a). The current estimate of the mean incubation period for COVID-19 is 6.4 days, ranging from 2.1 days to 11.1 days (2.5th to 97.5th percentile) (Backer et al, 2020).

Since December 2019, an increasing number of patients with pneumonia of unknown etiology in Wuhan, a city with 11 million people, have alarmed the local hospital. On 29 December 4 cases were linked to Huanan Seafood, wholesale market, where non-aquatic live animals, including several kinds of wild animals, were also on the sales. The local Center for Disease Control (CDC) then found additional patients linked to the same market after investigation, and reported to China CDC on 30 Dec 2019 (Jun, 2020). China CDC (WHO, 2020) informed the second day, World Health Organization (WHO) of the cases of pneumonia of unknown etiology. On 6 Jan 2020, China CDC (Li et al., 2020a) launched a level 2 emergency response. More patients with no history of exposure to Huanan Seafood Wholesale Market were identified. Several familial clusters of infection were reported, and nosocomial infection occurred in health-care facilities. All these cases provided clear evidence for human-to-human transmission of the new virus (Han et al., 2020).

2.3.3. The Key Events of Sars-Cov-2 Outbreak and the Pathogen Characteristics

As the outbreak coincided with the approach of the lunar New Year, travel between cities before the festival facilitated virus transmission in China. This novel coronavirus pneumonia soon spread to other cities in Hubei province and to other parts of China. Within 1 month, it had spread massively to all 34 provinces of China. The number of confirmed cases suddenly increased, with thousands of new cases diagnosed daily during late January (NHCPRC, 2020). On 30 January, the WHO declared the novel coronavirus outbreak a public health emergency of international concern. On 11 February, the International Committee on Taxonomy of Viruses named the novel coronavirus ‘SARS-CoV-2’, and the WHO named the disease ‘COVID-19’ (Ben et al., 2020).

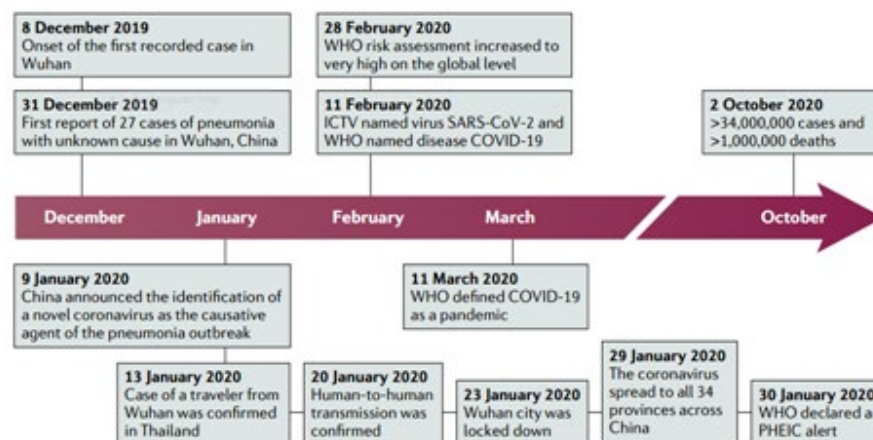


Figure 1: Timeline of the key events of the covid-19 outbreak. The first recorded cases were reported

In December 2019 in Wuhan, China. Over the course of the following 10 months, more than 30 million cases have been confirmed worldwide. COVID-19, coronavirus disease 2019; ICTV, International Committee on Taxonomy of Viruses; PHEIC, public health emergency of international concern; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization. (Ben et al., 2020).

2.3.4. Hosts Range of Covid 19

It is important to monitor infections in animals to better understand their epidemiological significance for animal health, biodiversity,

and human health. Evidence from risk assessments, epidemiological investigations, and experimental studies indicate that animals do not play a significant role in the spread of SARS-CoV-2, which is sustained by human-to-human transmission (OIE, 2021). Several animal species have tested positive for SARS-CoV-2, with infection being introduced to a population as a result of close contact with humans or animals infected with SARS-CoV-2 or in experimental infection studies performed in laboratory settings. The list of animal species for which information on natural or experimental infection is available is presented in Table 2 (WHO, 2020).

| Species | Type of infection experimental/natural infection | Susceptibility to infection none/extreme/ low/medium/high | Clinical sign | Transmission |
|---|--|---|------------------------------------|--|
| American mink/ neovision vision | Natural and experimental | High | Yes in some case | Yes (between mink and from mink to human) |
| Ferrets | Natural and experimental | High | Yes in some case | Yes between ferrets |
| Raccoon dog (nyctereutes procyonoides) | Experimental | High | No | Yes between raccoon |
| Rabbits (new Zealand white rabbits, oryctolagus naniculis) | Experimental | Medium | No | No |
| Pig (American York shire crossbreed pig sus scrofa) | Experimental | Extremely low | No | No |
| Cattle (bos Taurus) | Experimental | Extremely low | No | No |
| Poultry (chicken, ducks and turkeys) | Experimental | None | No | No |
| Cats (domstics) | Natural and experimental | High | Yes (but not observed in all case | Yes between cats |

| | | | | |
|--|--------------------------|------|------------------------------------|--------------------|
| Dog | Natural and experimental | Low | Yes (but not observed in all case | No |
| Large cats (tigers, lions, snow leopards and pumas | Natural | High | Yes in most case | Yes between animal |

Table 2: summary of findings in animals to date (who, 2020; Denis et al., 2020)

2.4. Routes of Transmission Human Coronavirus (Hcov)

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 (Englund et al., 2019). SARS-CoV has been isolated in sputum samples, nasal secretions, serum specimens, feces samples, and bronchial washings. The mechanism and route of transmission of SARSCoV and MERS-CoV remains elusive. Direct contact with intermediary host animals or consumption of milk, urine, or uncooked meat were hypothesized to be the main routes of SARS-COV and MERS –CoV transmission (Hu et al., 2020). 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 (Kimberlin et al., 2018).

2.4.1. Route of Transmission Sars Cov2

As a new coronavirus, it is not known yet about how SARS-CoV-2 spreads. Current knowledge for SARS-CoV-2 transmission is largely based on what is known from the similar coronaviruses, particularly SARS-CoV and MERS-CoV, in which human-to-human transmission occurs through droplets, contact and fomites. SARS-CoV is predominantly transmitted through indirect or direct contact with mucous membranes in the mouth, eyes, or nose (Cheng-wei et al., 2020). Notably, most of the SARS-CoV-2 human-to-human transmission early in China occurred in family clusters, and in other countries large outbreaks also happened in other settings, such as migrant worker communities, slaughter-

houses and meat packing plants, indicating the necessity of isolating infected people. Nosocomial transmission was not the main source of transmission in China because of the implementation of infection control measures in clinical settings (Wu and Mcgoogan, 2020).

COVID-19 infection is spread using large droplets produced during coughing and sneezing by symptomatic cases but may also happen from asymptomatic individuals before starting of their symptoms (Rothe et al., 2020). These infected droplets can travel 1–2 meters and later put down on surfaces. Droplets normally do not extend more than 2 meters and do not hang on in the air. The virus could stay viable on surfaces for days in desirable environmental conditions but are ruined in less than a minute by regular disinfectants, such as sodium hypochlorite and hydrogen peroxide. SARS-CoV-2 is obtained by either breathing of the droplets or touching surface tainted by them and by then touching the nose, mouth and eyes. Cases may be contagious for as long as the symptoms continue and even after clinical improvement. Moreover, certain cases may behave as super-spreaders. As said by a joint WHO-China statement, the rate of secondary COVID-19 disease attack varied from 1 to 5% among tens of thousands of close contacts of verified cases in China (Kampf et al., 2020). In the USA, the symptomatic secondary attack rate was 0.45% among 445 close contacts of 10 verified cases. SARS-CoV-2 RNA has been demonstrated in sputum, blood and stool samples. However, fecal oral, as well as materno-fetal vertical transmission, have not been identified as an important element in the spread of infectivity (Öner, 2020).

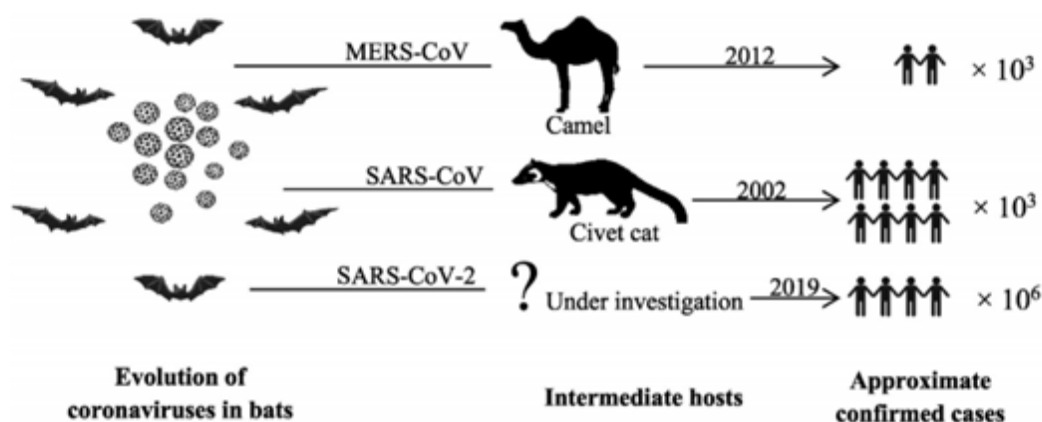


Figure 2: Human coronaviruses evolution, intermediate hosts, and transmission approximate numbers of infected cases (Abdelghany et al., 2020).

2.5. Clinical Appearance of Sars Cov1 and Sars Cov2

The medical pictures of CoVs patients ranged in symptoms from no symptoms to respiratory syndrome and death (Lupia et al., 2020). During the incubation period, hCoVs will not cause overt clinical symptoms, but the knowledge of viral incubation period has significant applications in disease surveillance, prevention and control. The median incubation period of SARS-CoV is 4 days (95% CI 3.6–4.4) (Lessler et al., 2009) and a longer one with >10 days was only observed in a small proportion of cases (Meltzer, 2004). The median incubation period of MERS-CoV was 5.2 days (95% CI 1.9–14.7) and the period could be longer in immune compromised patients or those with comorbidities as well. The longest incubation period was 20 days and observed in a female who had received hematopoietic stem cell therapy after the recurrence of diffuse large B-cell lymphoma (Kim et al., 2017). While the incubation period of SARS-CoV-2 is yet unclear, its estimate was 5.1 days (95% CI, 4.5–5.8 days) (Lauer et al., 2020).

2.5.1. Clinical Appearance of Sars Cov1

The typical incubation period of SARS ranges from 2 to 10 days but may occasionally be as long as 16 days (Lee et al., 2003).. The syndrome includes influenza-like symptoms, such as fever, myalgias, headache, and diarrhea. Fever can vary from low to high grade and can occasionally be absent at presentation, particularly in older patients. The typical respiratory phase starts 2–7 days after the syndrome and can be associated with watery diarrhea (Booth et al., 2003). The early respiratory stage includes a dry, nonproductive cough and mild dyspnea. Early-phase chest radiographs often show subtle peripheral pulmonary infiltrates that can be more readily detected as consolidations having a ground-glass appearance with high-resolution CT of the lung (Wong et al., 2003). The frequencies of symptoms at the onset of disease are summarized in following table 3.

| Characteristic or symptom | Toronto [75] (n = 144) | Hong Kong [72] (n = 138) | Hong Kong [76] (n = 75) |
|---------------------------|------------------------|--------------------------|-------------------------|
| Median age | 45 | 39 | 39 |
| Fever | 99.3 | 100 | 100 |
| Non reproductive cough | 69.4 | 57.3 | 22 |
| Myalgias | 49.3 | 60.9 | 68 |
| Headache | 35.4 | 55.8 | 15 |
| Diarrhea | 23.8 | 19.6 | 1 |
| Sore throat | 12.5 | Not report | 11 |

Table 3: Summary of clinical findings of severe acute respiratory syndrome at admission to the hospital.

2.5.2. Clinical Appearance of Sars Cov 2

Study show that SARS Cov 2 patients requiring intensive care were significantly older and more likely to have underlying diseases like cardiovascular disease and hypertension were the most common underlying diseases, followed by diabetes mellitus (Wang et al., 2020d). Fever, fatigue and dry cough are the main symptoms of SARS-CoV-2 infection that represent 99%, 70% and 59% in re-

ported symptoms, respectively beside another symptoms (Huang et al., 2020) . The main Covid 19 symptom are Fever was the most common symptom (92.8 %;), followed by cough (69.8 %;), dyspnoea (34.5%), myalgia (27.7 %;), headache (7.2 %;) and diarrhoea (6.1%). Rhinorrhoea was noted in only 4.0%, a sore throat in 5.1% (Chen et al., 2020) and pharyngalgia in 17.4% (Wang et al., 2020a).

| Sign or symptom | Total number of patient | Total number of patient with sign and symptom | Percentage |
|-----------------|-------------------------|---|------------|
| Fever | 1377 | 1233 | 90% |
| Cough | 1377 | 939 | 68% |
| Dyspnea | 1376 | 301 | 22% |
| Headache | 1374 | 170 | 12% |
| Sore throat | 1336 | 182 | 14% |
| Diarrhea | 1374 | 59 | 4% |

Table 4: Common signs and symptoms of sars-cov-2 infected patients from reports (jun, 2020.

2.6. Pathogenesis of Sars Cov1 and Sars Cov 2

2.6.1 Receptor and Pathogenesis of Sars Cov1 and Sars Cov2

SARS-CoV-2 uses the same receptor as SARS-CoV, angiotensin-converting enzyme 2 (ACE2) (Zhou et al., 2020). Besides hu-

man ACE2 (hACE2), SARS-CoV-2 also recognizes ACE2 from pig, ferret, rhesus monkey, civet, cat, pangolin, rabbit and dog (Zhou et al., 2020; Chandrashekar et al., 2020). The broad receptor usage of SARS-CoV-2 implies that it may have a wide host range,

and the varied efficiency of ACE2 usage in different animals may indicate their different susceptibilities to SARS-CoV-2 infection. The S1 subunit of a coronavirus further divided into two functional domains, an N- terminal domain and a C- terminal domain. Structural and biochemical analyses identified a 211 amino acid region (amino acids 319–529) at the S1 C-terminal domain of SARS-CoV-2 as the RBD, which has a key role in virus entry and is the target of neutralizing antibodies (Shang et al., 2020). The RBM mediates contact with the ACE2 receptor (amino acids 437–507 of SARS-CoV-2 S protein), and this region in SARS-CoV-2 differs from that in SARS-CoV in the five residues critical for ACE2 binding, namely Y455L, L486F, N493Q, D494S and T501N (Wan et al., 2020). Owing to these residue changes, interaction of SARS-CoV-2 with its receptor stabilizes the two virus-binding hotspots on the surface of hACE2. Moreover, a four-residue motif in the RBM of SARS-CoV-2 (amino acids 482–485: G-V-E-G) results in a more compact conformation of its hACE2-binding ridge than in SARS-CoV and enables better contact with the N-terminal helix of hACE2 (Shang et al., 2020). Biochemical data confirmed that the structural features of the SARS-CoV-2 RBD has strengthened its hACE2 binding affinity compared with that of SARS-CoV (Letko et al., 2020).

Angiotensin converting enzyme II is the receptor of SARS-CoV-2 and SARS-CoV, and it is one of the enzymes in the renin angiotensin system (RAS). It can convert angiotensin I (AngI) to angiotensin 1–9 (Ang 1–9) and angiotensin II (Ang II) to angiotensin 1–7 (ANG 1–7) to decrease AngII, which can increase aldosterone and vasopressin secretion, cause vasoconstriction, and induce myocardial and renal fibrosis (Serfozo et al., 2020). As counter regulatory components of the ACE-Ang II-AT1 axis, ACE2 and (ANG 1–7) can control inflammation and fibrosis in cardiovascular and renal disease. Expression of the ACE2 receptor is found in many tissues, including lung, heart, kidney, liver, endothelium, intestine, oral mucosa and even testis. ACE2 is reported to improve acute lung injury, suppress hypertension and cardiac dysfunction, reduce glomerular and biliary fibrosis, stimulate brown adipose tissue and induce browning in white adipose tissue. All these factors could be targets for SARS-CoV-2 to damage human health (Minato et al., 2020; Liu et al., 2020 c).

SARS-CoV, MERS-CoV and SARS-CoV-2 employ cellular serine protease TMPRSS2 and endosomal cysteine proteases cathepsin B/L for spike protein priming, which is essential for them to enter host cells (Hoffman et al., 2020). ACE2 has a vast bio distribution, including respiratory tract, gastrointestinal tract, heart, kidney and olfactory neuro epithelium (Fodoulion et al., 2020), besides these organs, DPP4 also expresses on liver, thymus, prostate and bone marrow (Memish et al., 2020), resulting in broad cellular and tissue tropisms of SARS-CoV, MERS-CoV, and SARS-CoV-2 (Wang et al., 2020c). Thus, these hCoVs can cause a wide range of symptoms, including respiratory manifestations and those beyond respiratory system to infected cases (Wu et al., 2020b).

The pathogenesis of SARS- CoV-2 infection in humans manifests itself as mild symptoms to severe respiratory failure. On binding to epithelial cells in the respiratory tract, SARS-CoV-2 starts replicating and migrating down to the airways and enters alveolar epithelial cells in the lungs. The rapid replication of SARS-CoV-2 in the lungs may trigger a strong immune response. Cytokine storm syndrome causes acute respiratory distress syndrome and respiratory failure, which is considered the main cause of death in patients with COVID-19 (Huang et al., 2020). Patients of older age (>60 years) and with serious pre-existing diseases have a greater risk of developing acute respiratory distress syndrome and death (Wu et al., 2020a). Multiple organ failure has also been reported in some COVID-19 cases (Wu and McGoogan, 2020).

A moderate cytokine and chemokine response plays an indispensable role in the viral clearance and subsequent recovery while dys-regulated response can bring devastating outcomes to infected cases (Gralinski and Baric, 2015). A large number of immune cells, including macrophages, neutrophils, monocytes and lymphocytes, are migrated from bloodstream to infection site by the recruitment of hyperactive cytokines and chemokines, resulting in further release of high concentrations of various cytokines and chemokines and activation of immune cells, thereby underlying the basis of immune-mediated damages to hosts (Channappanavar and Perlman, 2017). The ways that SARS-CoV, MERS-CoV and SARS- CoV-2 cause histopathological injuries to infected and hCoVs have been evolutionarily acquiring the ability to encode numerous proteins that allow them to evade from the host immune system, during which the delayed release of interferon plays a crucial role, then to attract and over-activate more inflammatory and immune cell, thereby inducing cytokine storm characterized by a massive secretion and hyper-activation of cytokines and chemokines until they have achieved sufficiently high titers (Weiss, 2020).

2.7. Diagnosis of Sars Cov1 and Sars Cov2

Molecular tests such as polymerase chain reaction using viral RNA extracted from clinical samples have become the standard and primary diagnostic test of SARS, MERS and COVID-19 due to its high sensitivity, specificity and simplicity (Zhang et al., 2020a). In accordance with China National Health Commission, COVID-19 disease is identified because of the epidemiological history and clinical manifestations, along with verified SARS-CoV-2 infection via one of the subsequent methods: real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay, high-throughput genome sequencing, and serological evaluation of anti-viral immunoglobulin M (IgM) and G (IgG) antibodies (Shen et al, 2020). The sensitivity of serology tests such as antibody detection was generally lower than that of molecular tests and antibody detection was predominantly used in retrospective diagnosis for SARS and MERS (Yin and Wunderink, 2018) SARS-CoV-2 RNA is identified by RT-PCR. Samples from throat swabs (nasopharyngeal in children), sputum, lower airway secretions, stool and blood could be checked for SARS-CoV-2 ribonucleic acids. Studies have demonstrated higher viral loads in the nasal cavity as compared

to the throat with no distinction in viral burden between symptomatic and asymptomatic individuals (Zou et al., 2020). Reverse transcription polymerase chain reaction–based SARS-CoV-2 RNA detection from respiratory samples (eg, nasopharynx) is the standard for diagnosis. However, the sensitivity of testing varies with timing of testing relative to exposure. One modeling study estimated sensitivity at 33% 4 days after exposure, 62% on the day of symptom onset, and 80% 3 days after symptom onset (Wang et al., 2020c).

The imaging performance of viral pneumonia is almost overlapping; however, some specific differences exist as well. Although the chest X-ray/CT performance of pneumonia caused by SARS-CoV, MERS-CoV, and SARS-CoV-2 are similar, chest CT is preferred due to its high resolution, sensitivity and efficacy (Li et al 2020 b). Imaging the characteristic chest computed tomographic imaging abnormalities for COVID-19 are diffuse, peripheral ground glass opacities. Ground-glass opacities have ill-defined margins, air bronchograms; smooth or irregular interlobular or septal thickening, and thickening of the adjacent pleura (Shi et al, 2020).

2.8 Treatment Option of Sars Cov1 and Sars Cov2

During the SARS-CoV epidemic, there were no treatments available to reduce SARS-related diseases and deaths. The earliest treated patients received intravenous injection (IV) ribavirin, which was based on its broad-spectrum antiviral activity, because there was insufficient time to perform efficacy studies (Poutanen et al., 2003). After confirming that SARS-CoV was the causative agent, many studies on treatments for SARS were started. The most commonly used treatments for SARS include ribavirin, LPV/r, corticosteroids, interferon (IFN) and convalescent plasma or immunoglobulins. Unfortunately, the above-mentioned treatments are associated with adverse effects, including avascular necrosis and osteoporosis (Stockman et al., 2006). At present, no approved antiviral therapy is available for SARS or MERS, nor for COVID-19 (Lu, 2020).

2.8.1. Supportive Therapy

The common strategies involve bed rest and palliative therapy, supplying enough calorie and water consumption, sustaining water-electrolyte balance and homeostasis, scrutinizing vital signs and oxygen saturation, maintaining airway unobstructed and supplementing oxygen when needed (Shen et al., 2020).

2.8.2 Symptomatic Therapy

The mild disease should be managed at home by advising about dangerous signs. The standard approach is continuing hydration, nutrition and managing fever and cough. If a patient has a high temperature exceeding 38.5°C with noticeable distress, bodily cooling (such as lukewarm water bath, antipyretic patches) or antipyretic medicine therapy would be given. Frequent medications involve acetaminophen orally, 10–15 mg/kg, 4–6 times/day (ibuprofen is recommended to avoid). Routine use of antibiotics and

antivirals, such as oseltamivir, should be kept away from verified patients (Shen et al., 2020).

2.8.3. Antiviral Therapy

There has not been, currently, yet widely accepted therapeutic option for COVID-19 disease. Antiviral drugs, such as ribavirin, lopinavir-ritonavir, have been tried depend on the anecdotal knowledge with HIV, SARS and MERS infection therapies (Dong et al., 2020). Remdesivir: Remdesivir is a new nucleotide analogue that has effects against SARS-CoV-2 in vitro and linked coronaviruses (including SARS and MERS-CoV) both in vitro and in animal studies (Wang et al., 2020b). So far, there has been no effective treatment of COVID-19. Several potential drug candidates, including lopinavir/ritonavir (Kaletra®), nucleoside analogues, neuraminidase inhibitors, remdesivir, umifenovir (Arbidol®), DNA synthesis inhibitors (such as tenofovir disoproxil and lamivudine), chloroquine and Chinese traditional medicines (such as ShuFeng JieDu or Lianhua Qingwen capsules), have been proposed (Wang et al., 2020b). In addition, an angiotensin-converting enzyme 2 (ACE2)-based peptide, 3CLpro inhibitor (3CLpro-1) and a novel vinylsulfone protease inhibitor, theoretically, appear to show potential for antiviral activity against SARS-CoV-2 (Liu et al., 2020 b). Chloroquine has been well described with in vitro effects on inhibition of uncoating and/or alteration of post translational modifications of newly synthesised proteins, especially inhibition of glycosylation in many viruses, including human immunodeficiency virus (HIV) (Rolain et al., 2007). Preliminary in vivo clinical studies suggest that chloroquine alone or in combination with antiretroviral agents might play an interesting role in treating HIV infection. A recent study by Wang et al. revealed that remdesivir and chloroquine were highly effective in the control of 2019-nCoV in vitro (Wang et al., 2020b).

Immunomodulatory agents. SARS-CoV-2 triggers a strong immune response, which may cause cytokine storm syndrome (Huang et al., 2020). Thus, immunomodulatory agents that inhibit the excessive inflammatory response may be a potential adjunctive therapy for COVID-19. Dexamethasone is a corticosteroid often used in a wide range of conditions to relieve inflammation through its anti-inflammatory and immunosuppressant effects. Recently, the recovery trial found dexamethasone reduced mortality by about one third in hospitalized patients with COVID-19 who received invasive mechanical ventilation and by one fifth in patients receiving oxygen. By contrast, no benefit was found in patients without respiratory support (Huang et al., 2020).

2.9. Prevention and Control of Sars Cov1 and Sars Cov2

CoVs are common zoonotic pathogens. Studies have shown that SARS-CoV, MERS-CoV, SARS-CoV-2, HCoV-NL63, and HCoV-229E may originate from bats (Zhu et al., 2020a) while HCoV-OC43 and HCoV-HKU1 may have originated from rodents and bats (Forni et al., 2016). The high population density and widespread distribution of bats provide opportunities for pathogen infection and rapid transmission. When there is frequent contact

between bats and humans, companion animals, and livestock, the possibility of cross-species transmission increases. Carnivorous bats may acquire other pathogens from insects or birds and may transmit viruses to predators that prey on bats (Rodhain, 2015).

The emergence of many zoonotic human diseases, which intimately associated with contact between animal species and with humans, as well as with human diet, has climbed during these decades. For example, SARS, Marburg hemorrhagic fever, and Ebola hemorrhagic fever are associated with human consumption of wildlife. And Public Health England (PHE) also indicated that 60% to 80% of emerging infections are derived from an animal source. And “Bush meat” harvested from remote forested areas remains a risk for animal-derived emerging infections (PHE, 2020). One study suggested that pangolins may be an intermediate host for SARS-CoV-2 (Cyranoski, 2020). Consumption of pangolins, illegal but frequent, is present throughout the world that might be an infection pathway of COVID-19. In addition, excessive emphasis on food freshness has resulted in the prevalence of cold foods, raw foods and other consumption methods. However, most bacteria and viruses (eg Ebola virus, SARS-CoV) have strong infectivity under room temperature and refrigeration conditions, causing possible food poisoning or foodborne infections in humans and providing conditions for viral and bacterial outbreaks in human societies. Therefore, China has revised the Wild Animal Conservation Law and adjusted the list of “animal sources of epidemics” to ban the consumption of wildlife. Evidently, CoVs can infect humans, and positive test results for serum antibodies have been attained in civet cats, wild boars, pheasants, cats, rabbits, frogs, camels, and birds. Therefore, it is a high risk of infection from uncooked animal-source foods such as milk and meat (Gan et al., 2021).

Although there are limited intermediate hosts for CoV transmission from bats to humans, certain bats can migrate for long distances, thereby increasing the possibility of contact with livestock and increasing the distribution range of CoVs (Wang et al., 2018). Existing studies have shown that compared with other livestock, pigs tend to promote cross-species transmission of viruses and are more susceptible to bat CoVs. SeACoVs isolated from pig guts are different from known porcine CoVs and are phylogenetically close to the bat CoV HKU2 (Pan et al., 2017). In addition, studies have shown that pigs are susceptible to SARS-CoV (Chen et al., 2005) and MERS-CoV (Vergara et al., 2017). The sequence similarity between porcine and human CD26 receptors is 94.5%, which is sufficient for cross-species transmission to occur. In addition, CoVs have been shown to have the potential for recombination in animals (Sabir et al., 2016).

COVID-19 is a potentially preventable disease. The relationship between the intensity of public health action and the control of transmission is clear from the epidemiology of infection around the world (Chu et al., 2020). However, because most countries have implemented multiple infection control measures, it is difficult to determine the relative benefit of each (Flaxman et al.,

2020). This question is increasingly important because continued interventions will be required until effective vaccines or treatments become available. In general, these interventions can be divided into those consisting of personal actions (eg, physical distancing, personal hygiene, and use of protective equipment), case and contact identification (eg, test trace-track-isolate, reactive school or workplace closure), regulatory actions (eg, governmental limits on sizes of gatherings or business capacity; stay-at-home orders; proactive school, work place, and public transport closure or restriction; cordon sanitaire or internal border closures), and international border measures (eg, border closure or enforced quarantine). A key priority is to identify the combination of measures that minimizes societal and economic disruption while adequately controlling infection. Optimal measures may vary between countries based on resource limitations, geography (eg, island nations and international border measures), population, and political factors (eg, health literacy, trust in government, cultural and linguistic diversity) (Joost et al., 2020).

3. Conclusion and Recommendations

SARS-CoV-2, SARS-CoV and MERS-CoV have considerable degree of similarities that could be basic data in predicting SARS-CoV-2 behavior. Although SARS-CoV-2 has a higher transmission rate than SARS-CoV and MERS-CoV, its mortality rate is obviously lower. Several reports investigated vaccination, epidemiology, symptoms, mode of action, control and origin of SARS-CoV-2, however confirmed data are relatively limited and require further investigations for not only SARS-CoV-2, but also SARS-CoV and MERS-CoV. No specific treatment or vaccination was developed against CoVs. Therefore, SARS-CoV-2 infection control measures are essential for the prevention of its spread in healthcare facilities, as well as in the community. COVID-19 pandemic increased studies manipulating SARS-CoV-2 in comparison with SARS-CoV and MERS-CoV.

Based on the above conclusion, the following recommendations are forwarded for controlling of ongoing pandemic of SARS-CoV-2.

- Performing well-designed large-scale case-control studies to confirm exact transmission of COVID-19 for proper intervention of control.
- Awareness was created to all stakeholder of community to implements proper method of controlling
- monitoring signs of viral genome mutations will play a major role in future research
- additional research on developments of animal vaccines is necessary because compacting spread in animal is crucial.

Competing of Interest

The authors report no conflicts of interest in this work.

Author Contribution

All authors took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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