

COVID-19: Look to the Future, Learn from the Past

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Abstract

There is a current pandemic of a new type of coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The number of confirmed infected cases has been rapidly increasing. This paper analyzes the characteristics of SARS-CoV-2 in comparison with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and influenza. COVID-19 is similar to the diseases caused by SARS-CoV and MERS-CoV virologically and etiologically, but closer to influenza in epidemiology and virulence. The comparison provides a new perspective for the future of the disease control, and offers some ideas in the prevention and control management strategy. The large number of infectious people from the origin, and the highly infectious and occult nature have been two major problems, making the virus difficult to eradicate. We thus need to contemplate the possibility of long-term co-existence with COVID-19.

Keywords: COVID-19; coronavirus; epidemiology; SARS-CoV-2

1. Introduction

In December 2019, a cluster of patients presenting with viral pneumonia were reported in Wuhan, China. This was identified to be Coronavirus Disease 2019 (COVID-19), caused by a new type of coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The coronavirus quickly spread across people living in or visited Wuhan, and human-to-human transmission was soon confirmed(1). Figure 1 shows the outburst of COVID-19 in early days at the beginning in China. The diagnosis of the infection over time was based on data taken from the past daily statements of National Health Commission, China (2). Since then, the virus has been spreading rapidly and caused a pandemic across the world. As of May 22nd, 2020, it has been diagnosed in >5.11 million people globally, causing >333,000 deaths. According to Wu and McGoogan(3), 81% patients with COVID-19 had mild symptoms, 14% had severe symptoms, and 5% were critically ill. We studied the characteristics of COVID-19 in comparison with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and influenza, in terms of virology, etiology, epidemiology and virulence. Prevention and control strategies are analyzed and discussed in the following text.

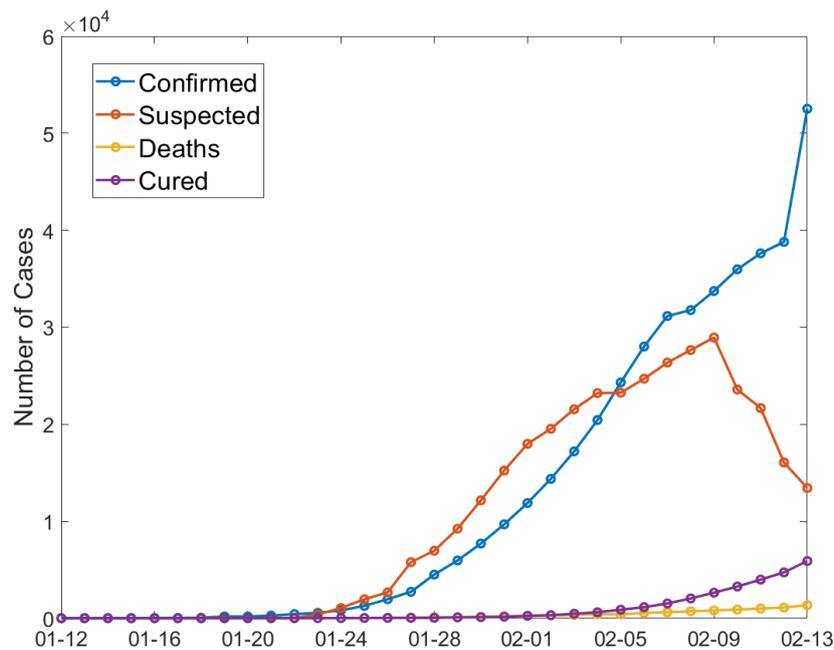


Figure 1. Number of confirmed cases, suspected cases, deaths and cure over time in early days in China.

2. Comparison to SARS-CoV and MERS-CoV

After Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), COVID-19 is the seventh known member of the family of coronaviruses that are pathogenic to humans. The rest of the seven members are associated with mild clinical symptoms (4). SARS-CoV emerged in China in November 2002, and resulted in more than 8000 human infections and 774 deaths in 37 countries (5, 6). MERS-CoV was first detected in Saudi Arabia in 2012 and was responsible for 2494 confirmed cases of infection and 858 fatalities, including 38 deaths following a single imported case into South Korea (7-9). SARS-CoV-2 (GenBank accession MN908947) is a beta-coronavirus (β CoV) of group 2B, and was found to have the highest similarity (89%) to a SARS-related member of the Sarbecoviruses (GenBank accession MG772933), a subgenus within the β CoV genus (10, 11).

Early patient data from Wuhan in China has shown similarities of clinical features between COVID-19 and previous β CoV infections. Similar to SARS-CoV and MERS-CoV infections, patients exhibited symptoms of viral pneumonia including fever, cough, difficulty breathing and bilateral ground-glass opacities on chest CT scans (12). However, the virulence of COVID-19 is far less than that of SARS, with Case Fatality Rates (CFR) of 0.72% according to the Centre for Evidence-Based Medicine (CEBM), Update 9th April (<https://www.cebm.net/covid-19/global-covid-19-case-fatality-rates/>), whereas the case fatality rate is around 10% for SARS (13) and 37% for MERS (14).

Similar to the 2003 SARS outbreak in Guangzhou in China, both outbreaks were initially connected to “wet markets” where wildlife animals and meat were sold (1, 15). During previous outbreaks of SARS and MERS, human to human transmission was efficient through droplets, contact and fomites, suggesting that the transmission mode of the COVID-19 can be similar (16).

In terms of transmissibility, we previously estimated the reproduction number R_0 provided by eight different research groups, and found most of the R_0 value to lie in the range between 2 and 3 (1). On 31st January 2020, Wu et al. published a comprehensive model for predicting the future spread of COVID-19 in The Lancet and estimated R_0 to be around 2.68 (17). Most recently, based on 16 published estimates, the estimate R_0 (95% CI) by CEBM is 2.65 (1.97, 3.09) (April 14, 2020,

<https://www.cebm.net/covid-19/when-will-it-be-over-an-introduction-to-viral-reproduction-numbers-r0-and-re/>). This R_0 estimation is similar to or slightly less than that of SARS (around 3) (18) and larger than MERS, which is less than one (19). To explain its transmissibility, we investigated RNA sequencing transcriptome profiling of human samples of airway and oral mucosa, and the expression pattern of the SARS-CoV-2 receptor ACE2 and the viral priming protease, TMPRSS2. We observed that ACE2 had medium levels of expression in both small airway epithelium and masticatory mucosa, and high levels of expression in nasal epithelium, and TMPRSS2 was highly expressed in small airway epithelium and nasal epithelium. These findings provided the molecular basis that the nasal mucosa is the most susceptible locus in the respiratory tract for SARS-CoV-2 infection(20). In addition, the lack of effective immune responses to eliminate the infection also contribute to the high transmissibility, e.g. IgA responses to clear respiratory tract infection may be harmful in COVID-19 as shown by our recent study(21).

While SARS-CoV-2 is similar in transmissibility compared to SARS, it is much less virulent than SARS. Why, then, has the number of confirmed cases of the disease greatly surpassed SARS and continued to increase as a pandemic? There has been a variety of potential epidemiological reasons:

(1) The occult nature of SARS-COV-2. SARS-COV-2 is not as virulent as SARS, and produces a large number of patients asymptomatic or with mild symptoms(22). According to the study on passenger on board the Diamond Princess Cruises' ship, 50.5% infected individuals were asymptomatic(23). Similarly, ~60% infected sailors on the U.S. aircraft carrier Theodore Roosevelt were asymptomatic (<https://www.reuters.com/article/us-health-coronavirus-usa-military-sympt/coronavirus-clue-most-cases-aboard-us-aircraft-carrier-are-symptom-free-idUSKCN21Y2GB>). Compared with SARS patients, asymptomatic patients with COVID-19 are likely not to go to hospitals for testing for COVID-19. In US, people with mild illness are not suggested to do testing. Even if they do the testing, false-negative has been an issue to identify the cases(24). At the same time, the incubation period of COVID-19 is longer than SARS, generally between 2-10 days (25). Furthermore, a risk of pre-symptomatic transmission was also suggested by Rothe and colleagues for the symptomatic patients(26), although this finding was met with criticisms (27). Because of these reasons, a large number of SARS-COV-2 infected people has not been identified in time and quarantined, which enabled the wide spread of transmission. SARS on the other hand, exhibits serious illness, resulting in a lower chance of mis-reporting.

(2) Detection, publishing, and warning measures lagged far behind in the early stages of the outbreak, which gave time for the virus to spread. As a result, before the large-scale national prevention and control measures in China were implemented, especially before the closure of Wuhan city, a large number of patients had been accumulated in the Wuhan area. Due to technical factors such as medical resource straining and shortage of diagnostic materials, the current statistics of Hubei and Wuhan were lagging behind, thus the number of patients in Wuhan and across the country might have been greatly underestimated. The Lancet paper on January 31 estimates that as of January 25, there were more than 75 000 patients in Wuhan alone (17). After Wuhan was closed down, a few governments evacuated their citizens and performed thorough medical examination for each individual brought back. The authors searched available information on Wuhan evacuation released by governments of different countries on the public domain. Table 1 lists the citizens evacuated by each country in the last January and early February. Evacuation can be thought of as a random sampling of the population of the Wuhan area (11 million in total), and the prevalence rate is close to what the Lancet paper suggested. In other words, the infection rate in the Wuhan area may have reached one percent, or 110 000 people up to early February, 2020. Those undiagnosed patients exacerbated the spread of the transmission of COVID-19.

Table 1. Citizens evacuated from Wuhan by each country.

Country	Evacuated	Confirmed Cases	Prevalence	Converted to infected population in Wuhan	Source
Japan	566	9	1.4%	156 000	(28)
South Korea	368	1	1.4%	150 000	(29-31)
US	195	0	0	0	(32)
Germany	124	2	1.6%	177 000	(33)
Singapore	92	1	1.1%	119 000	(34-36)
Italy	56	1	1.8%	196 000	(37)
Total	1401	14	1.0%	110 000	NA

(3) Timing and Chinese culture. Both the COVID-19 outbreak in Wuhan and the SARS 2003 outbreak in Guangzhou happened in metacities in China (Guangzhou had a population of 9,942,022 in 2000). Around January each year, a huge amount of population would leave major cities and travel back to their respective hometown to celebrate Chinese New Year, and come back around February. The total number of Chinese passengers were estimated to be 2.91 billion Person-Times in 2016. This is known as the Chunyun period, or Spring Festival travel season. The COVID-19 outbreak happened in late December and early January, albeit the low number of confirmed cases due to lack of detection. Before Wuhan closed its city, 5 million people had already left Wuhan during the Chunyun period (38), which hindered any containment effort. At the same time, socio-economic globalization promoted the spread the COVID-19 across the world(39). SARS on the other hand, although detected in 2002, the real outbreak did not happen until March 2003. Chunyun period had by then ended, and the containment efforts were thus more effective.

3. Origin

Most of the first cluster of patients were connected to a wet market, the Wuhan Municipal Health Commission (WMHC) in China all had a history of exposure in the Huanan Seafood Wholesale Market, suggesting that the virus originated from wildlife animals sold in the market (40). However, a later Lancet report found 13 of the 41 first reported patients with no epidemiological link to the marketplace (12). The virus may have spread silently in Wuhan before the discovery of the cases, during its incubation period (41, 42).

All three aforementioned viruses (SARS-CoV, MERS-CoV and SARS-COV-2) are believed to have natural hosts in bats (43, 44). But most likely, they were able to invade the human world only after a genetic mutation in an intermediate host animal. The intermediate hosts for SARS and MERS are civets (45) and camels (46), respectively. Determining the intermediate host is crucial to our future efforts to prevent the return of coronavirus diseases. Unfortunately, scientists were only able to detect the virus in the market environment, but not in time to collect wildlife samples before the market was shut down (40). There has been various candidates proposed, but most of them have been discredited (47). On 7th February 2020, South China Agricultural University held a press release and announced that they have found a potential candidate for intermediate host and provided solid evidence for it. By analyzing more than 1,000 metagenomic samples, the research team identified pangolins as potential intermediate hosts for COVID-19. The positive rate of COVID-19 in pangolin was 70% by molecular biological tests. The virus was further isolated and identified, and the typical coronavirus particle structure was observed under electron microscope(48). Finally, through the analysis of the virus genome, it was found that the sequence similarity between the isolated virus strain and the current infected human strain was up to 99% (49). This finding is of great significance for the prevention and control of the outbreak at the source, and provide scientific basis for the adjustment of relevant health policies on wet market management and wildlife trade control. In the meantime, the scientific community should be vigilant about the possibility of return of another coronavirus in another one or two decades(50).

4. Prevention and Control

Learned from the SARS outbreak, which started as animal-to-human transmission during the first phase of the epidemic, all game meat trades should be optimally regulated to terminate this portal of transmission, to prevent the outbreak of another coronavirus pandemic. Regulation and cracking down on wildlife trafficking should be an important disease control measure (51).

For COVID-19, global experts and governments have been actively tracking the spread and virulence of the virus, and to provide advices to individuals on measures to protect health and prevent the spread of new outbreak. In response to the spreading virus, isolation strategy has been used. Many Chinese cities including Wuhan had been put on quarantine since 23rd January, 2020, and many countries have closed their boarder to people travelled internationally (1).

Since the early stage of COVID-19 pandemic, to systematically organize countries to combat COVID-19, WHO has developed a “global strategic preparedness and response plan” to support all countries to prepare for and respond to the outbreak. The goal is to stop further transmission of COVID-19 within China and to other countries, and to mitigate the impact of the outbreak in all countries. They have outlined a list of public health measures, including rapid identification, diagnosis and management of the cases, identification and follow up of the contacts, infection prevention and control in healthcare settings, implementation of health measures for travelers, awareness raising in the population, risk communication (16). With the development of pandemic, stay-at-home orders have been issued in many countries, which have contributed significantly to contain the speed of transmission of COVID-19, thus to avoid straining medical resources.

The understanding of the spread and features of the virus is still updating rapidly, but that does not prevent us from starting to think further about the problem of the future pandemic of new coronavirus and preparing plans for it, through international cooperation.

4.1 A New Perspective

Effectively and comprehensively isolating patients and their close contacts, cutting off their path to continuing transmission, and waiting for the incubation period to pass, was a very effective measure to eliminate SARS in a short period of time. This strategy may work on several premises:

1. The total number of patients was small. Therefore, the administration was able to find and quarantine the close contacts of each patient;
2. Once becomes onset, the symptoms were obvious, critical and typical. Patients were quickly identified and treated;
3. There was no transmission capability during incubation period.

COVID-19 however, does not satisfy these preconditions. Having a huge number of patients, as well as a significant proportion of asymptomatic patients, and highly infectious occult infection, has greatly increased the difficulty of prevention and control. We will not be able to identify every patient that exhibits mild symptoms for quarantine purpose, nor to put all their close contacts under isolation and observation.

On the other hand, COVID-19 shares many similar characteristics of influenza. Here are the features of the seasonal flu, which kills 646,000 people worldwide each year (52): It has low virulence, with case fatality rate of about 0.1% (53); Its reproduction number R_0 is around 1.3, which is less than SARS (54); The number of cases is much larger however, while about 10% of unvaccinated adults are infected each year; Although influenza virus usually has a short incubation period of between 1 - 4 days, transmission can occur within the incubation period (55); Flu symptoms are less distinct, with fever,

cough, sore throat and other symptoms that are difficult to distinguish from other respiratory diseases prevalent in autumn and winter. Table 2 below compares different characteristics of the three coronaviruses, as well as influenza.

Table 2. Comparison of four diseases.

	COVID-19	SARS-CoV	MERS-CoV	Influenza
R_0	2.68	3	<1	1.3
Virulence	Low	High	High	Low
Case Fatality Rate	2%	10%	37%	0.1%
Natural Hosts	Bat	Bat	Bat	Animals, humans
Intermediate Hosts	Pangolins	Civets	Camels	NA
Origin of Outbreak	Wuhan, China	Guangzhou, China	Saudi Arabia	NA
Incubation Period	2-10 days	2-7 days	4-8 days	1-4 days

Although COVID-19 is more similar to SARS in virology and etiology, its epidemiological impacts are less like SARS but more like a “mega flu”. This means we could take historical experiences from the fight against influenza.

Closing schools during flu outbreaks has been shown to be an effective measure (56, 57). However, when to shut down and how long to shut down are still indicators that need to be carefully considered (58). Two studies from Australia and Japan showed that monitoring body temperature at airports was not effective in reducing the spread of the disease during the 2009 H1N1 swine flu pandemic (59, 60). A similar question to consider is how much effort we need to put into monitoring passengers’ temperatures in this outbreak, given that the incubation period for COVID-19 is much longer than for influenza and the large proportion of asymptomatic patients.

4.2 Vaccines

Vaccines are the first choice against a pandemic of this magnitude. According to U.S Centers for Disease Control and Prevention (CDC), the effectiveness of the flu vaccine varies from year to year, but overall it reduces the risk by 40 to 50 percent (61). Vaccines need to go through many phases of development. The lead time to produce a vaccine lot ranges from several months (e.g. influenza vaccine) to three years (62). Thanks to the rapid publication of the COVID-19 genetic sequence, a number of biopharmaceutical firms and academic research facilities around the world have launched programs and are racing to find an effective vaccine. Many are aiming to break the vaccine development record time (63).

4.3 Hierarchical Management

“Hierarchical management” of influenza takes into account the fact that when influenza is endemic, outbreaks in different parts of the world vary from region to region, and the severity of illness varies from patient to patient. Cities with clusters of cases may take more drastic measures, from canceling public gatherings to closing schools and workplaces, while areas with fewer cases can adapt to local conditions. Patients with serious illness are given intensive treatment in hospitals, while most patients with mild symptoms can seek treatment in small clinics or even wait for the disease to self-heal.

This strategy can certainly be translated to fight against COVID-19. During a full-scale pandemic, especially in underdeveloped regions as seen in the city of Wuhan, there will not be enough medical resources to attend every patient (64). Medical needs should be given out to those with more severe symptoms or with high risk of fatal complications. The treatment of the large number of patients with

mild symptoms can be home-based. What Wuhan was doing was to create makeshift hospitals using empty facilities such as sports stadium and exhibition halls (65), although how to avoid cross secondary infection has been a challenge. Patients with less severe symptoms in Wuhan were gathered and assigned a bed and facemasks in the makeshift hospital, and less medical resource was needed for each patient in this way.

What China has done was very different from the strategy taken by other countries. Looking back the management in China, the distribution of the disease were centered in Wuhan city, Hubei province (see Figure 2 to help understanding the strategy taken by China) and its surrounding cities, while cases in other cities were mainly imported. It has taken a long time and very harsh prevention and control measures until the outbreak in Wuhan was effectively controlled. In other areas however, the situation has been largely controlled by next week, due to the isolation strategy in China after 23rd January 2020. Within 14 days after the closure of Wuhan in Hubei Province, potential patients in other cities would have already developed clinical symptoms, with high probability of being quarantined and treated. At that point, it may be more important to consider putting the society back into normal operation and function as soon as possible, to avoid further damage to people's life as well as the economy. We might consider to exercise specific disease control and management in different regions across the world, instead of a "one-size-fits-all" approach.



Figure 2. Bubble map visualization of the disease distribution around China, with data taken from (66), obtained on 13th February 2020. Created using Power BI Desktop.

4.4 A long winter

Governments around the world are doing their best in combatting COVID-19, and it is still probable that we could eradicate the virus comes summer, as with the fight against SARS. Considering the unstable RNA genome of SARS-CoV-2 (and tendency to lose infectivity) under high environment temperature, after the temperature warms up in summer, it might be harder for the virus to survive in the summer heat. However, we still need to be prepared for a long term epidemic. The development of COVID-19 is closer to a "mega flu" that is more difficult to eradicate. That brings a possibility that this virus, like the flu, will persist in the human world for a long time to come, until the success of effective vaccine, or herd immunity achieved until large proportion of human population has been infected(67). Currently, humans are still at a loss for influenza viruses that are less transmissible than COVID-19,

and given the early accumulation of cases in the Wuhan area, it may be necessary to start embracing the possibility of long-term co-existence with COVID-19.

It is worth to emphase that that possibility may not be as scary as it sounds. The case fatality rate for COVID-19 has fallen from an initial 15% to about 2% in China. Furthermore, while the large number of undiagnosed cases is taken into account (68), it fell another order of magnitude to 0.72%, which is getting much closer to the seasonal flu. While having a new pandemic flu-like pneumonia that occasionally flare-up is not a future anyone wants to be in, it should not be a cause of public panic or social collapse.

Many of the current methods of prevention and control in China have been similar to wartime measures, such as rapid construction of new hospitals, extensive restrictions on the movement of people, delaying the start of school, high levels of martial law in communities, banning outsiders, and quarantining the residents of a building if a patient is found. These measures were unsustainable, and would put an unbearable strain on civil liberties and socioeconomic activity in the long term. It will be necessary to start setting a timetable for the withdrawal of such war measures before implementing these measures in another country, depending on the situation of each city. Meanwhile, the Chinese government should start focusing on developments towards more universal, milder measures for the control of new burst of COVID-19, such as public education, social distancing, rapid response mechanisms, tiered management, and regular disinfection of public appliances, etc.

The media around the world is doing an excellent job in covering all aspects of COVID-19, and raising public awareness, however, this exerts enormous pressure on governments to make over-drastring policies (69). Instead of proper alarm, the media portrait of a “deadly/killer virus” may cause panic and can harm efforts to implement a cost-effective and safe infection control strategy(70). It may be time for the media and education to start adjusting their tone to reduce unnecessary panic. Instead, the emphasis should move towards the popularization of public health, such as wearing masks when sick, washing hands frequently, coughing and sneezing etiquette, etc.

After SARS was contained through extraordinary efforts, much of the research and drug development related to SARS stopped because of lack of funding and market prospects. A simple bibliometric analysis from PubMed databases, using “SARS” as a search term, reveals around 800 articles in 2003, which dropped to 27 in 2019. Given that the new coronavirus invades the human body in a similar way to SARS, if many of the previous studies had persisted, we might have been better prepared scientifically and medically for the new coronavirus. Perhaps we should learn from this lesson and rethink whether our entire scientific system is paying enough attention to re-emerging coronavirus diseases.

5. Conclusion

Through consolidating foreign citizen evacuation data, the early prevalence rate of COVID-19 in Wuhan population is found to be around one percent, or 110 000 infected people, which suggests that a large number of infected people have been neglected because of asymptomatic or mildly ill. It also explains the outburst of COVID-19 across the world after it has been contained in China. A large number of infected people in the origin city, plus the highly infectious and occult nature of COVID-19, made COVID-19 difficult to eradicate. The virulence and transmissibility of the new virus are somehow close to that of the influenza, and it would not be entirely unacceptable to tolerate some persistence. We need to contemplate the possibility of long-term co-existence with COVID-19, rather than allowing overly-drastring measures to affect our normal lives and the normal social-economic activities of a country. These conclusions are based on our current knowledge of the new coronavirus and COVID-19, which may change, as may the virus and the disease itself. We need to be very cautious in the face of an enemy we have never seen before.

Conflict of Interest Statement

The authors declare no conflict of interest.

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