SARS, MERS, and COVID-19: discovery of reasons causing COVID-19 evolving into a global pandemic

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Abstract: Since December 31, 2019, Coronavirus disease 2019 (COVID-19) has spread to 221 countries and territories to date. It has caused several millions of deaths with several hundred millions of confirmed cases worldwide, posing a serious threat to global public health. COVID-19 is caused by a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 virus is not the first virus belonging to the B lineage of betacoronavirus. Two recent outbreaks of human coronavirus caused by betacoronavirus are severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In 2002, SARS first occurred in China and spread quickly, resulting in hundreds of deaths; in 2012, MERS first emerged in Saudi Arabia and spread to several countries linked through the Arabian Peninsula. Therefore, it is worthwhile to find the similarities and differences among these three human coronaviruses to examine the reality that COVID-19 has become the only one among three to be labeled as "pandemic". Hence, this review will capture possible reasons behind the high spread of COVID-19 by comparing the known characteristics of SARS and MERS, including cause, transmission, and risk factors.

1. Introduction

In late December 2019, several cases of pneumonia of unknown causes occured in Wuhan City in Hubei Province in central China. A few days later, the causative agent of this unknown pneumonia was identified as a novel coronavirus by several laboratories. [1] The World Health Organization has temporarily named the causative virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the related infected disease as coronavirus disease 2019 (COVID-19). [1] Later, in March, COVID-19 developed into larger outbreaks spreading all over the world. According to the daily report of the World Health Organization, globally, there have been 240,940,937 confirmed cases and 4,903,911 deaths by 19 October 2021. COVID-19 has become a pandemic, which has posed a threat to global health.

However, COVID-19 pandemic was not the first human coronavirus of this century, belonging to the subfamily Orthocoronavirinae. So far, there have been seven known coronaviruses that sicken humans. Four of them caused only mild to moderate disease. The other three of them including COVID-19 caused severe human disease. Within the subfamily Orthocoronavirinae, there are four genera, and both alphacoronavirus (α-CoV) and Betacoronavirus (β-CoV) are worked to infect mammals. [2] Two recent outbreaks of human coronavirus caused by β-CoV were severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Starting in 2002, severe acute respiratory syndrome CoV (SARS-CoV) had lasted about one and a half years and ended by early 2004. It mostly affected East Asian countries, but spread worldwide in the end. It had infected at least 8,000 people and the mortality rate for it was approximately 10%. However, SARS did not burn itself out. Instead, simple public health measures, such as testing, isolating, quarantining, and restricting travel, brought the outbreak under control.

Later, in September 2012, Middle East respiratory syndrome (MERS) was identified in Saudi Arabia. But an outbreak of MERS happened two years later in 2014, and spread to 27 countries linked

through traveling, living, or being in proximity with the Arabian Peninsula. [3] The mortality rate for MERS was approximately 34%, but overall, exposure and infection of MERS was imperative in further transmission. Hence, since 2012, 2494 confirmed cases of MERS have been reported primarily around Saudi Arabia, and localized health measures have been carried out around those territories to eliminate the MERS.

However, although COVID-19 shares similar lineage with SARS and MERS, the development and mutation of COVID-19 has been different and instant, posing huge challenges in controlling it. So far, the mortality rate for COVID-19 has been around 2%, which would be estimated to be much lower than that of SARS and MERS, but it spread faster and farther and has become the only one among three to be labeled as "pandemic". Therefore, the purpose of this review is to find possible reasons behind the high transmission rates of COVID-19 by comparing the known characteristics of SARS and MERS, including cause, transmission, and risk factors.

2. Epidemiological Characteristics

In late December 2019, several cases of pneumonia of unknown causes occured in Wuhan City in Hubei Province in central China. A few days later, the causative agent of this unknown pneumonia was identified as a novel coronavirus by several laboratories. [1] The World Health Organization has temporarily named the causative virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the related infected disease as coronavirus disease 2019 (COVID-19). [1] Later, in March, COVID-19 developed into larger outbreaks spreading all over the world. According to the daily report of the World Health Organization, globally, there have been 240,940,937 confirmed cases and 4,903,911 deaths by 19 October 2021. COVID-19 has become a pandemic, which has posed a threat to global health.

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2.1 Cause

For the examination of human coronavirus, animals are usually traced back as the reservoir of coronaviruses. Then with the intermediate host, the virus continues to cause infections in humans. SARS-CoV and MERS-CoV are two recent outbreaks following this trend. However, SARS-CoV-2 contains more uncertainty in the process of seeking for a similar trend.

2.1.1 Host.

Both SARS-CoV and MERS-CoV were attributed to zoonotic transmission. Although the ancestors of SARS-CoV and MERS-CoV were probably bats, further study showed that dromedary camels were the MERS-CoV reservoir. [4] However, we still did not reach unanimity on the cause of SARS-CoV-2, hence it created more uncertainty and challenges in tracing and experimenting on SARS-CoV-2. That explained why the infected cases of SARS-CoV-2 surged overnight.

Specifically, the first cases primarily linked to Huanan Seafood Wholesale Market in Wuhan pointed to potential environmental factors. Environmental samples from this market have been reported positive for the SARS-CoV-2. [2] Moreover, besides seafoods, wild animals such as snakes, bats, and marmots were also sold at the market. But no specific animal was identified associated with the environmental samples. [5] However, some scholars suggested that bats may be the potential host of SARS-CoV-2. According to a recent study, it found that new coronavirus is 96% identical at the whole-genome level to a bat coronavirus which was detected from Yunnan Province. [6] However, based on the perception that bats are unlikely to be the host directly transmitting the virus to humans, intermediate hosts are needed to be furtherly pinpointed. [7] Above all, continuing hunting for the origins of SARS-CoV-2 will be helpful to prevent zoonotic transmission and conduct zoonotic experiments.

2.1.2 Envelope Spike (S) Protein.

The envelope spike (S) protein is of great importance for CoV for two main reasons: 1) meditating receptor binding and membrane fusion; 2) determining host tropism and transmission capacity. [1] Generally, the S1 domain of S protein was responsible for receptor binding. The cell receptor for SARS-CoV was recognized as Angiotensin converting enzyme 2 (ACE2). Similarly, SARS-CoV-2 also used ACE2 as an entry receptor in the expressing cells. Hence, SARS-CoV-2 may share the same life cycle with SARS-CoV. [8] However, some analysis indicated that S protein of SARS-CoV-2 binded ACE2 with approximately10- to 20- fold higher affinity than that of S protein of SARS-CoV. This higher affinity of S protein for the human cell receptor in SARS-CoV-2 may result in facilitated spread of SARS-CoV-2 in human populations than that of SARS-CoV. [1]

2.1.3 Variants.

Although SARS-CoV-2 has compatible genetic features with the family of CoV, it falls into a different subgenus of the Betacoronavirus (β-CoV). SARS-CoV-2 has many lineages, and all of them could cause COVID-19. Therefore, with genetic changes, such as a lineage or group of lineages, the viral genome may mutuate. The multifarious combination of lineages shown in SARS-CoV-2 has created multiple variants of it, resulting in the continued high evolution of SARS-CoV-2. First identified in India, Delta has become a variant of SARS-CoV-2, and it is nearly twice as contagious as earlier variants causing great concerns worldwide. (Table 1).

Table 1. Selected SARS-CoV-2 Variants.

WHO Label	Pango Lineage	US Class	Attributes
Alpha	B.1.1.7 and Q lineages	VBM	Spreading at much lower levels
Beta	B.1.351 and descendent lineages	VBM	Spreading at much lower levels
Gamma	P.1and descendent lineages	VBM	Spreading at much lower levels

Delta	B.1.617.2 and AY lineages	VOC	Increased transmissibility and causing more severe cases

Abbreviations: VBM, variants being monitored; VOC, variants of concern.

2.2 Transmission

Determining the mode of transmission is one of the key points in epidemiological study. Usually, in any reported outbreak, preliminary collection of information such as date and time, person and place, number of cases, and identification of "risk populations" are important metrics in deciding the mode of transmission. [9] However, in the preliminary stage, seeking for the mode of transmission of COVID-19 was challenging. Besides the uncertain cause of COVID-19, far-ranging risk populations and widespread places exploded with COVID-19 in a very short time. There was evidence showing that the transmission mode of SARS-CoV-2 was human-to-human, which was corresponding to the mode of SARS and MERS. [10] However, unlike SARS and MERS, COVID-19 has turned out to be a global pandemic after a very short period. For instance, based on the findings of some scholars, travellers from Shenzhen to Wuhan, who did not contact Wuhan markets or animals, became infected. One family member who did not even travel to Wuhan also became infected after several days of contact with the family members.

Generally, there are five modes of transmission: contact (direct and/or indirect), droplet, airborne, vector, and common vehicle. For MERS, direct contact with Saudi Arabia became imperative in getting infection and passing the virus to others. Both SARS and MERS shared relatively homogenous modes of transmission. Human-to-human transmission of those two occurred mainly through nosocomial transmission: 43.5–100% of MERS cases in individual outbreaks were linked to hospitals, and similar observations were shown in some of the SARS cases. [4] However, by contrast, based on current findings, the modes of transmission of COVID-19 were relatively more multifarious. Indirect contact of COVID-19 infection without direct contact of Wuhan markets or hospitals has greatly increased the spread of COVID-19 among populations.

Moreover, although asymptomatic patients with SARS were uncommon, possible asymptomatic carriers of COVID-19 have also posed a huge challenge for COVID-19 prevention and control. In most of the cases, the asymptomatic persons were diagnosed by screening only after their family members showed symptoms. As a result, similar to MERS-CoV, the contribution of asymptomatic cases with SARS-CoV-2 was not well characterized and was short of examinations. [11] Hence, it is reasonable to believe that many other asymptomatic persons were left as untested, and they would be a source of COVID-19 infection back into their communities. [12]

The following sections will furtherly explore the factors resulting in the global outbreak of COVID-19 pandemic regarding transmission in: 1) transmission route, 2) incubation period, 3) basic reproductive number.

2.2.1 Transmission Route.

Both SARS-CoV and MERS-CoV were attributed to zoonotic transmission. Although the ancestors of SARS-CoV and MERS-CoV were probably bats, further study showed that dromedary camels were the MERS-CoV reservoir. [4] However, we still did not reach unanimity on the cause of SARS-CoV-2, hence it created more uncertainty and challenges in tracing and experimenting on SARS-CoV-2. That explained why the infected cases of SARS-CoV-2 surged overnight.

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intermediate hosts are needed to be furtherly pinpointed. [7] Above all, continuing hunting for the origins of SARS-CoV-2 will be helpful to prevent zoonotic transmission and conduct zoonotic experiments.

2.2.2 Incubation Period.

The mean incubation period of COVID-19 is estimated to be 5.1 days (range, 2 - 14 days). [13] Based on Lauer et al.'s findings, symptom onset will occur within 11.5 days for 97.5% infected persons. [13] By contrast, for MERS patients, the median time from symptom onset to hospitalization was approximately 4 days. [14] This showed the onset of illness of MERS was much quicker than that of SARS-CoV-2. Based on this comparison, it was suggested that substantial numbers of COVID-19 cases would result from presymptomatic transmission. [15] This posed another hurdle to give immediate control and treatment to infected individuals of COVID-19.

There are many possible reasons accounting for the delayed onset of symptoms with COVID-19. Firstly, the battle between SARS-CoV-2 virus and people's immune systems can take as long as two weeks. After strenuous resistance of the immune system, if it gets inflamed at last, that will be the time when people begin to show symptoms. Secondly, different levels of exposure and routes of exposure could lead to different outcomes. This possibility is closely connected to the multifarious characteristics of transmission with COVID-19. Thirdly, genetic factors could also play a role in shaping the time when people begin to feel sick.

In general, the investigation of the incubation period is important in controlling infectious diseases. Therefore, it is necessary to closely examine the full distribution of the incubation period. Suggested by some scholars, the right tail was for making the quarantine policy, the central regions were for likely times and sources of infection, and the full distribution was for pandemic planning. [15]

To accurately measure the incubation time is not easy. There are different types of uncertainty existing in the measuring process, such as incomplete observational studies, implicit source of time of infection, and imprecise record of time of exposure. [15] In these situations, coarse data arises. There are two methods normally used to estimate the incubation period distribution. Some scholars found that the doubly interval-censored method would be preferred for estimations that involve the tails of distribution, e.g. optimal length of quarantine, while the interval-reduced method would be better in quick estimation of central tendency, e.g. median incubation period. [16] Moreover, as seen in other acute respiratory viral infections, the incubation time was likely to be assumed by some scholars to follow a log-normal distribution. [13]

2.2.3 Basic reproductive number (R_0).

The basic reproduction number is a fundamental threshold related to the transmissibility of the virus. [2] The R_0 can be defined as the average number of infected contacts per infected individual. It is widely accepted that if $R_0 > 1$, the virus will continue its propagation among susceptible hosts if there is no external interference. The numbers of infected cases will increase exponentially and cause an epidemic or even pandemic. [2] Based on the current study, the estimated mean R0 for COVID-19 was around 2 - 3. The number would be even higher with one sick person infecting 4.7 - 6.6 others. [17] The estimated basic reproduction number of SARS-CoV-2 was believed to be higher than that of SARS-CoV and MERS-CoV. Noticeably, the R_0 for MERS-CoV was estimated to be less than 0.7 and closer to 0.5 [14], which was significantly lower than the marker of epidemic potential ($R_0 > 1$). Therefore, the possible extent of transmission of COVID-19 represented by its high basic reproductive number predicted its unprecedented adverse effect all over the world.

2.3 Risk factors

For MERS, approximately two-thirds of infected cases occurred in males, whereas males and females had similar fatality rates. [14] Unlike MERS, all populations generally have the risk of infecting SARS-CoV-2. Hence, COVID-19 spread more widely among populations, resulting in higher confirmed cases than those of SARS and MERS.

However, disease severity learning from SARS- and MERS-CoV suggested underlying host conditions, including age, biological sex, and overall health. [14] The highest proportions of severe illness occurred in elderly adults (> 60 years old) and those with underlying health problems, such as diabetes, hypertension, cardiovascular disease, and kidney function issues. [5] Infected patients with low immune functions such as pregnant women and newborns were also likely to develop severe pneumonia. [2] But fewer cases were diagnosed among children less than 15 years, and most of the infected paediatric patients showed mild symptoms without pneumonia. [7] Hence, vigilant management should focus more on those potentially vulnerable groups.

3. Conclusion

This review compares three major characteristics of SARS-CoV, MERS-CoV, and SARS-CoV-2, and summarizes possible reasons behind greater spread of SARS-CoV-2. SARS-CoV and SARS-CoV-2 are similar in some degrees: they share almost 80% of genetic sequences and use the same host cell receptor [18], but their adverse effects and extent are different as shown in this review. Several reasons discussed in this review are: 1) unknown cause of SARS-CoV-2, making it hard to trace its origin and conduct zoonotic experiments; 2) ongoing genetic changes and genome mutations; 3) easy person to person transmission by means of multifarious modes of transmission; 4) broader extent of transmission and longer virus persistence; 5) general risks of infection among all populations. For future study, besides the discovery of coronavirus, whose genome is the largest genome of known RNA viruses, it will be of great importance to examine other RNA viruses in respect to their development and disappearance. Lessons from SARS-CoV-2 suggest that research needs to collect more information and make more comparisons among viruses to complete our understanding of the appearance and prevention of global pandemic.

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