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Current knowledge of COVID-19: Advances, challenges and future perspectives

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ABSTRACT

The pandemic of coronavirus disease 2019 (COVID-19) has already evoked massive influence. The global pandemic has been ravaging the whole world for a year, with the number of confirmed human infection cases over 150 million and a death toll exceeding 3 million. Although the genomic sequence of the cognate pathogen SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has been quickly determined, there are still many unknown aspects, including the virus origin and evolution trend, and the effectiveness of current vaccines and drugs against the mutating virus. This review summarizes current knowledge and advances about COVID-19, including virus origin, transmission and infection, with the aim to improve the understanding of COVID-19 and provide a new perspective for future studies.

1. Introduction

The emergence of COVID-19 is a milestone in mankind history, irrespective of whether SARS-CoV-2 can be completely eliminated like SARS-CoV, or whether it becomes a seasonal epidemic in the human population like other human-infecting coronaviruses. To date, the scientific knowledge gained in response to this pandemic has improved our understanding of SARS-CoV-2 and the cognate disease, and will benefit the control and prevention of emerging infectious disease in the future.

However, our concerns have been deepened by the warning from WHO (World Health Organization), that the world is in a “new and dangerous phase”: small-scale re-emergence, and the accelerating deterioration of the situation in many countries, especially in South America, Africa and India. Within this context the COVID-19 pandemic continues (Fig. 1), and the virus population is rapidly diversifying in different countries [1] (Fig. 2). The most difficult choice for governing bodies is to balance pandemic control and social/economic sacrifices in response to this unprecedented situation.

To combat with the ongoing COVID-19, we reviewed and summarized current knowledge across diverse aspects, with the aim to provide a new perspective for COVID-19 studies now and going forward.

2. Origin of SARS-CoV-2

Many scientists believed that identification of the “original host animal” is vital to contain the COVID-19 pandemic, and to prevent further pandemics in the future [2]. But current research about the virus origin is still unclear.

Phylogenetic analysis, through the comparative analysis of genome sequences, has the potential to provide evidence for the original or intermediate host(s) of a pathogen, which is essential for us to understand its origin and transmission. According to the sequence homolgy between different coronaviruses, SARS-CoV-2 is most similar to a bat

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coronavirus RaTG13 (with a sequence homology of 96.2% across the whore genome), suggesting SARS-CoV-2 may originate from bats [3–5].

Many studies have shown that some other animals, such as pangolin (The pangolin coronavirus isolate shares a sequence homology of 91.02% with SARS-CoV-2), can be infected by closely-related coronaviruses [6]. The species could therefore be potentially used as model animals for evaluating vaccines and therapeutic drugs. *Avian* [7] and *Reptilia* [8] are unlikely to be the intermediate animals for transmitting SARS-CoV-2 to humans, whereas a similar coronavirus, PsNV (Pacific salmon nidovirus), causing respiratory symptom manifestations has been identified in salmon [7]. This observation is reminiscent of the small-scale outbreak of SARS-CoV-2 in a fresh food supermarket, suggesting that aquatic animals may also be possible intermediate hosts of this virus. An alternative possibility is that SARS-CoV-2 virion in contaminated water or environment may maintain infectivity at low temperatures, which offers the chance to cause human infections via contact with the contaminated water or animals.

The use of reverse genetics systems together with synthetic biology to recreate CoVs, including SARS-CoV-2, has been reported by labs in the USA and other European countries [9–13]. Humans still do not know why the virus suddenly emerged. Identifying the "Patient Zero" - would be particularly important to understand this pandemic and control future possible pandemics [14]. It is possible that the virus may gradually acquire key mutations during ongoing transmission in the human or animal populations which could lead to a highly adapted and more difficult to eradicate pathogen [15]. It has been reported that dominant D614G substitution in S protein may increase infectivity by nearly ten fold [16]. E484K reduced susceptibility to neutralization by antibodies, identified as part of lineage of South Africa. In addition to the E484K and D614G mutations in the spike protein, the Indian mutant strain can evade and weaken the human immune response to

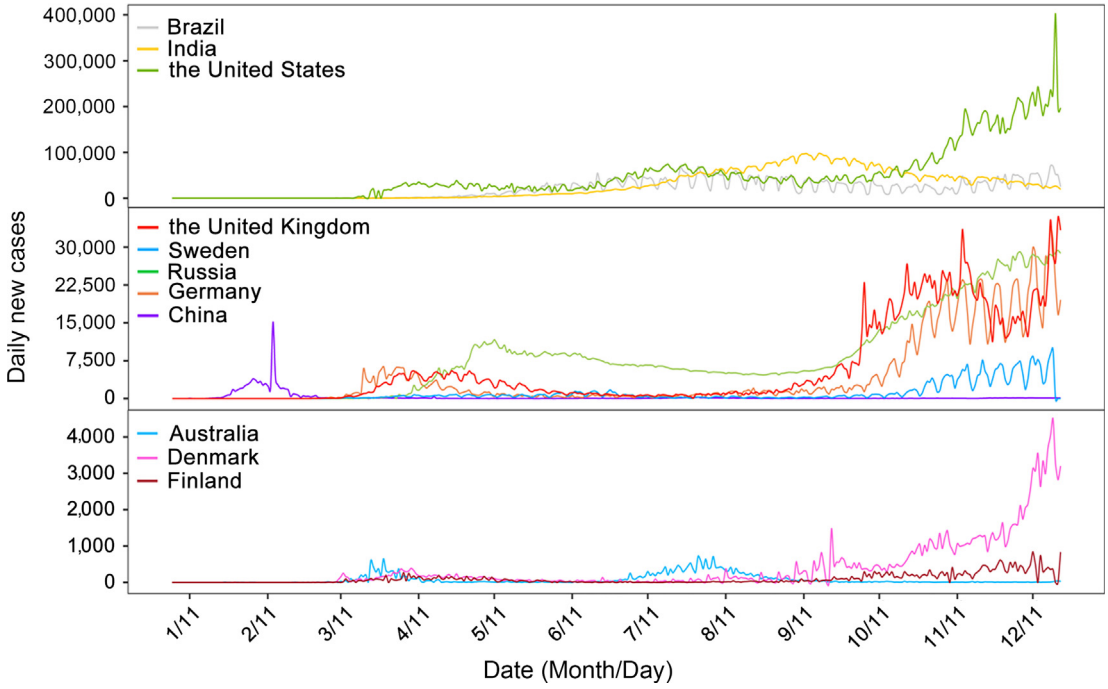

Fig. 1. The number of new confirmed infection cases in different countries. The line chart represents the daily new cases in Australia, Brazil, China, Denmark, Finland, Germany, India, Russia, Sweden, the United States, and the United Kingdom (data from WorldoMeters). These statistically significant discrepancies may be due to the various models and measures adopted by different countries.

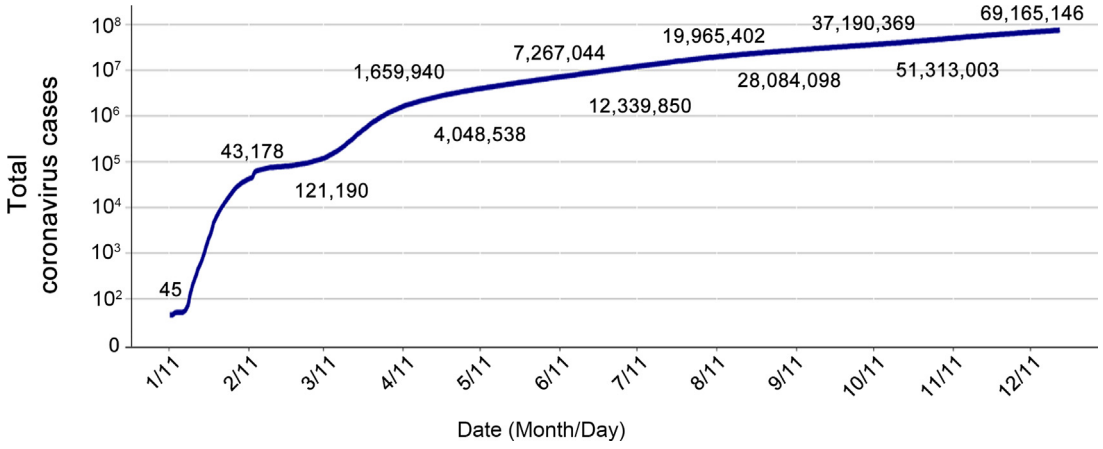

Fig. 2. Global COVID-19 infection curve from the outbreak to Dec 25. The cumulative number of cases around the world is small in the early stage, but the growth rate is fast. The number is still growing, with no signs of containment.

the virus. It also has a chromosomal rearrangement of 6 nucleotides (H146del and Y145del)[17].

3. Cell entry of SARS-CoV-2

This step is thus a critical determinant for the efficiency of virus entry [18] and host tropism [19]. It has been reported that SARS-CoV-1 and MERS-CoV can enter host cells via endocytosis and require the proteolysis of S protein by cathepsin in the endosome to trigger membrane fusion [20]. The SARS-CoV-2 might utilize similar mechanisms for cell entry and membrane fusion [21].

Compared with SARS-CoV-1 S protein, the unique features of SARS-CoV-2 S protein may lead to differences in the ability to bind the receptor [22], which may partly explain its higher infectivity than other human coronaviruses. Other putative receptor molecules in addition to ACE2 have also been proposed, including CD209 (cluster of differentiation 209) and CLEC4M (C-type lectin domain family 4 member M) and neuropilin-1 [23,24]. These molecules also indicate candidate targets for antiviral intervention. These facts also suggest that the infection mechanism of SARS-CoV-2 has not been fully understood. There are still many other questions remain unanswered, such as whether other receptors/factors are involved. Non-proteinaceous factors, such as fatty acids, should not be overlooked, as they may also play some important roles in the interaction between the viral S protein and host receptors [25].

Since the identification of SARS-CoV-2, this virus has undergone several significant nutations (e.g. D614G from UK [26], N501Y from South Africa [27], E484K from Brazil [28]) that boosted its ability of infection, transmission and immune evasion. However, the underlying mechanisms for these properties are not fully understood, which warrent detailed analysis at the molecular and disease level.

4. Tissue tropism and pathogenesis of SARS-CoV-2

The clinical manifestations of SARS-CoV-2 are similar to that of SARS-CoV-1. The main organ of virus infection is lung, and the patients may develop ARDS (Acute Respiratory Distress Syndrome), leading to respiratory failure and even death [29]. Of note, some clinical cases also revealed other clinical manifestations in addition to respiratory system pathology [30].

More and more clinical studies have shown that SARS-CoV-2 not only attacks the lung but also causes injury in other organs of the human body, especially in critically illed patients. SARS-CoV-2 can directly infect extra-pulmonary organs which express ACE2 and TMPRSS2 [31]. Further, SARS-CoV-2 infection may cause some unexpected complications, such as impaired sensory capacity, abnormal hepatic and renal functions, brain and heart damages, impaired gastrointestinal function [32].

Moreover, increase of XIAP associated factor 1 (XAF1)-, tumor necrosis factor (TNF)-, and FAS-induced T cell apoptosis in COVID-19 patients was observed [33]. In addition, severe COVID-19 patients showed a stronger response to interferons and virus infection compared to mild patients and healthy ones [33].

A striking clinical feature of the SARS-CoV-2 infection is the significant increase in thrombotic and micro-vascular complications, or COVID-19-associated coagulopathy (CAC) [34]. The incidence rate of thrombotic complication in COVID-19 patients in ICU is as high as 31% [35]. SARS-CoV-2 may also infect vascular endothelial cells (EC) [36], which express the receptor ACE2 [37]. A recent study suggests that endothelial cell (EC) injury plays a significant role in the pathogenesis of CAC, and the level of soluble thrombomodulin in the blood are correlated with mortality [38]. In addition, it is reported that the injury of ECs may be a key driver of COVID-19 severity and death [38].

SARS-CoV-2 can also destroy the blood–brain barrier and invade the central nervous system by attacking the vascular system [39], causing some neurological complications, such as partial loss of sight/smell/taste [40] (see Supplementary Table), headache, aortic ischemic stroke and spinal cord injury (SCI) [41]. It has also been reported that about 10% of patients have gastrointestinal symptoms, such as diarrhea, vomiting, etc [39]. This may be driven by infection of gastrointestinal epithelial cells which express high levels of ACE2. These evidences indicate that the SARS-CoV-2 can actively infect the digestive system.

5. Population susceptiblity

The early reports of epidemiological studies did not reveal significant differences in the susceptibility to SARS-CoV-2 of human populations with different ages or genders. The accumulating data implies that the elderly bears a higher chance of infection and could result in a higher mortality rate due to the degeneration of immunity. Therefore, these people should be given a high priority for testing and protection. Although children are much less likely than adults to experience severe complications from the infection because of healthy blood vessels, kids with Kawasaki syndrome and other artery diseases are at a high risk of developing severe symptoms by SARS-CoV-2 infection [42]. It noteworthy that the relatively higher infection rate of younger population could be attributed to the insufficient social distancing and less mask protection [1].

Generally, males reveal a higher rate of infection and mortality than females. This might be the result of several factors, including the - higher expression of ACE2 in lung cells of males, primarily type II lung cells, perhaps other tissues as well, and also sex hormones levels, immunological factors and smoking [43–45]. Interestingly, the ACE2 receptor is expressed in the reproductive organs of males, such as the testes and prostate, but not in the ovaries of females [46]. It is proposed that AR (androgen receptor) activation induces the expression of ACE2 and TMPRSS2 genes, resulting in gender differences [39]. The long-term exposure to smoke triggers the expansion of respiratory secretory cell populations, which as a result up-regulates the expression of ACE2 and may increase the susceptibility for SARS-CoV-2 infection [47].

GWAS also revealed that the susceptibility to SARS-CoV-2 infection may also be related to blood types. The epidemiological data indicated that the blood group A was associated with a higher risk of acquiring COVID-19, whereas blood group O might be more resistant to the infection [48].

6. Key factors of COVID-19 transmission

The SARS-CoV-2 is thought to be transmitted mainly by close contact with one another which is generally defined as a distance of about 6 feet or 2 m [49]. This concept leads to the proposal of “social distancing” as an effective measure for preventing infections [50].

Because the virion itself is very fragile, it would be inactivated when exposed outside the cells for a certain period. The virus is mainly transmitted through airborne respiratory droplets when an infected person coughs, sneezes or talks, thus the virus transmission can be cut off by a face mask [51]. It is also publicly accepted that face mask is one of the most critical PPEs (Private Protection Equipment).

Mother-to-child transmission of COVID-19 is controversial and there is a lack of data to confirm this route as a major concern. Although increased SARS-CoV-2 specific IgM (immunoglobulin M)

antibodies have been detected in some new-born infants [31,52], viral nucleic acid tests of amniotic fluid and cord blood were negative. Recent studies have reported the positive detection of SARS-CoV-2 in breast milk [53] and semen [54], which alerts the potential risk of virus infection by breastfeeding and sexual transmission [55].

Another issue is how long the live virus could keep alive on the surface of solid substances that people could touch with bare hands. An experiment on how long the virus could survive reveals a significant difference in wood, stainless steel, copper and cardboard which are widely used for packages [56]. Another study showed the 9-hour survival of SARS-CoV-2 on human skin may increase the risk of contact transmission, thus, it is widely accepted that hands should be washed after touching any hard surfaces [57].

It is also well known that most living cells and viruses are sensitive to the extreme environmental conditions, such as high temperature and low moisture. This leads to the misunderstanding that the virion could only be stable under the “cold and wet” conditions in winter and would be inactivated by the “dry and hot” weather in summer. It is not the case for COVID-19, as evidenced by the outbreaks in tropical countries.

The infection of workers in slaughterhouses in Germany, the USA, and other countries, as well as the detection of live virus in seafood markets, raise concerns for another transmission-enhancing factor, for example, “cold-chain”.

The advancement of technologies to sequence trace amount of DNA/RNA, has opened the door to detect viruses or viral products in various environments. Italian scientists detected the traces of SARS-CoV-2 RNA in sewage water samples collected in December 2019, which suggested that the virus had been circulating much earlier in the country, several months before the outbreak at the end of February 2020. It is also hypothesized that the SARS-CoV-2 might originate from the cryosphere that can hide many unexpected and ancient pathogens, which needs to be confirmed in the future.

7. Expectations for vaccine

Developing vaccines is a crucial measure for long-term protection against SARS-CoV-2 [58], as evidenced by the successful eradication of smallpox in humans and rinderpest in cattle. Great efforts have been made globally for developing vaccines against the virus. A hallmark feature of coronaviruses is the presence of a 3′→5′ exonuclease that proofreads RNA products in transcription and replication [59], which suggests a more stable genome than many other RNA viruses and indicates the possibility of successful vaccine development. This is in sharp contrast to the situation of developing universal vaccines against diverse strains of influenza virus or HIV that have a higher rate of genomic mutation and in the case of influenza, re-assortment.

Most of current vaccine strategies, have been applied to generate SARS-CoV-2 vaccines, such as attenuated or inactivated, adenovirus-vector-based [60], mRNA [61] and recombinant protein ones [62]. In addition, a team of researchers are proposing to give a booster dose of the measles, mumps and rubella (MMR) vaccine to people to test whether it can elict broad-spectrum viral immunity, which may help to prevent some of the most severe effects of COVID-19 [63].

8. Development of drugs

Considerable efforts have been made for the development of effective drugs to treat the disease. For example, common steroids could be an affordable and effective treatment for COVID-19 [64]. A clinical trial revealed that dexamethasone reduced the risk of death in critically ill patients [65]. Some other drugs, like *baricitinib,* which has been used for treating adults with moderate to severe rheumatoid arthritis (RA) [66], have also been evaluated in clinical trials. There is a rationale for therapies to stabilize the endothelium while tackling viral replication, particularly with anti-inflammatory/anti-cytokine drugs, ACE2 inhibitors [18], and statins. The American FDA (Food and Drug Administration) and agencies in several other countries have cancelled the emergency use authorization of hydroxychloroquine [67,68] and chloroquine [69] for COVID-19 treatment. Clinical evidence has revealed that these two drugs do not appear effective against SARS-CoV-2. The broadly-reactive nucleoside analog drugs remesdivir and favipiravir have shown antiviral efficacy in clinical reports but with a certain side effects. Mode of action studies of these two drugs will enable modification of them, which presents as promising first response measures to deal with emerging SARS-CoV-2 variants and threat of newly emerging viruses [70–72].

9. Perspectives

Although there has been massive scientific effort to understand COVID-19, there are many knowledge gaps yet to be filled. Although similar, SARS-CoV-2 has proven starkly different to SARS-CoV which was eliminated without the need for vaccine development (Fig. 3). The key to understand the biology and virus-host interactions of SARS-CoV-2 requires knowledge of mutation and evolution of this virus at both inter- and intra-host levels. However, despite quite a few polymorphic sites that have been identified among SARS-CoV-2 variants, intra-host variant spectra and their evolutionary dynamics remain mostly unknown. Recently, a SARS-CoV-2 mutant has appeared in London, UK, and caused global attention as the mutant virus has a stronger transmission ability [26]. This development warrents additional and more detailed viral surveillance at the genomic level. We should guarantee the annual surveillance of coronaviruses in humans and animals, and also in different environment, and then combine the coronavirus genomic sequence information as a database. With this database, we can easily trace the orignin of potential novel human-infecting coronaviruses, just like what we have done for influenza viruses.

The emergence of new variants will also challenge the efficacies of current vaccines and drugs. Moreover, functional studies are required as the phenotypes that arise through the interaction between the virus, its hosts and environmental changes cannot be simply extrapolated by the genome sequence information. Therefore, new methods should be applied to systematically study the COVID-19, and also the potential emerging infectious pathogens.

To deal with the challenge of future threats of new pathogens, we should call for a change from a reactive culture to a proactive one, including the establishment of global network of virus surveillance and development of broad-spectrum antiviral drugs and universal vaccines [73].

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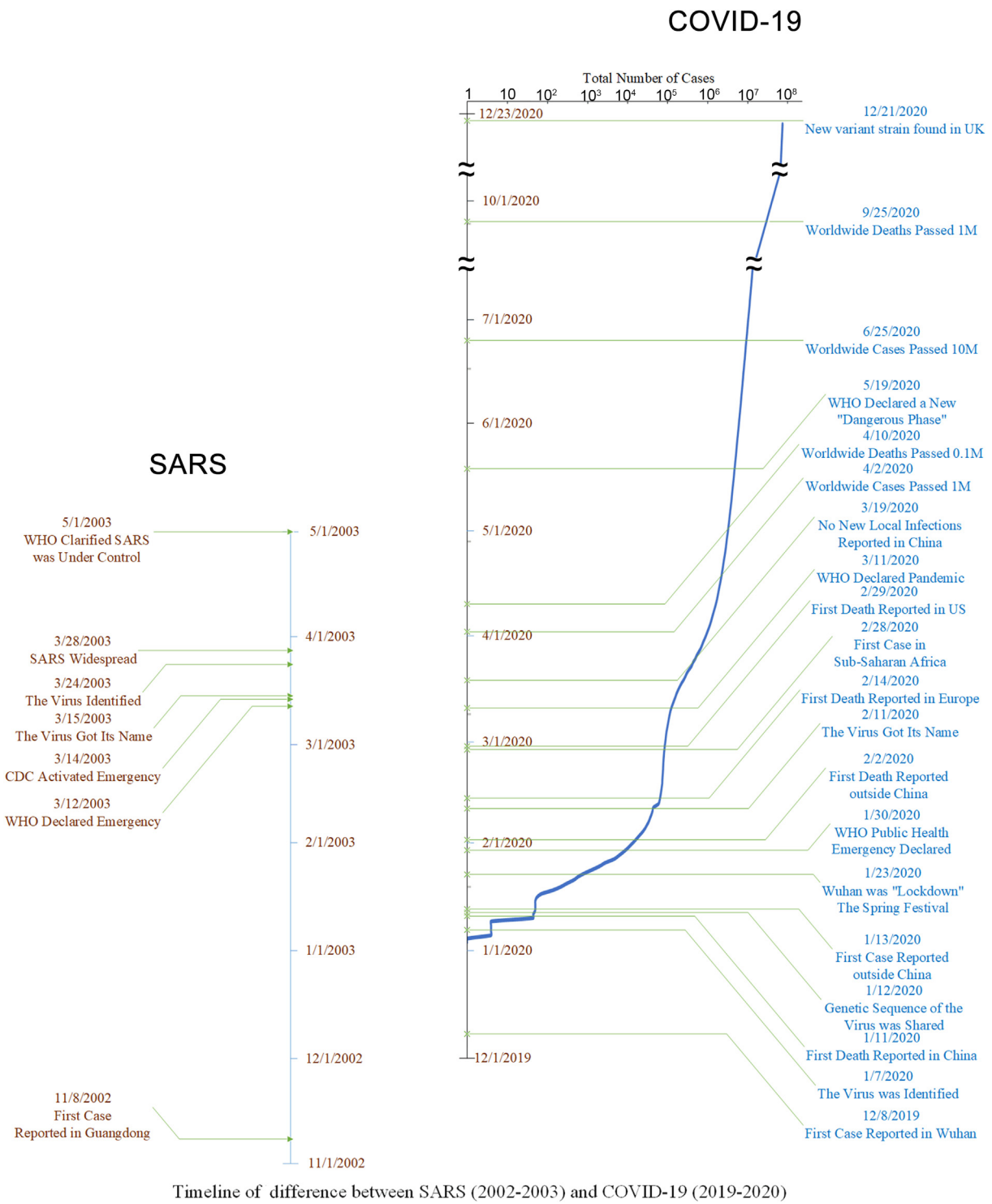

Fig. 3. Timeline of difference between SARS and COVID-19 with global infection curve from outbreak to December 25, 2020. The event characteristics of COVID-19 are significantly different from SARS. COVID-19 lasts longer and is more difficult to control.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Author contributions

Yuhan Wu: Conceptualization, Writing - Review & Editing. **Zhuobing Peng:** Visualization, Investigation. **Yongxue Yan:** Visualization, Investigation. **Jintao Hu:** Visualization, Investigation, Writing - Review & Editing. **Yalong Wang:** Visualization, Investigation. **Xiaoyu Wang:** Writing - Review & Editing. **Ruchao Peng:** Writing - Review & Editing. **Daniel Watterson:** Writing - Review & Editing. **Yi Shi:** Supervision, Writing - Review & Editing.

Supplementary data

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