Genomic variation, origin tracing, and vaccine development of SARS-CoV-2: A systematic review

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Graphical abstract

Public summary
- Clinical manifestations and epidemiology of COVID-19
- The efficacy of the developed vaccine against SARS-CoV-2
- Phylogenetic tree of evolutionary relationships in current SARS-CoV-2 strains
- Structural analysis and origin tracking of SARS-CoV-2
- Mechanism involved in infection and immunological pathogenesis of SARS-CoV-2
COVID-19 has spread globally to over 200 countries with more than 40 million confirmed cases and one million deaths as of November 1, 2020. The SARS-CoV-2 virus, leading to COVID-19, shows extremely high rates of infectivity and replication, and can result in pneumonia, acute respiratory distress, or even mortality. SARS-CoV-2 has been found to continue to rapidly evolve, with several genomic variants emerging in different regions throughout the world. In addition, despite intensive study of the spike protein, its origin, and molecular mechanisms in mediating host invasion are still only partially resolved. Finally, the repertoire of drugs for COVID-19 treatment is still limited, with several candidates still under clinical trial and no effective therapeutic yet reported. Although vaccines based on either DNA/mRNA or protein have been deployed, their efficacy against emerging variants requires ongoing study, with multivalent vaccines supplanting the first-generations vaccines due to their low efficacy against new strains. Here, we provide a systematic review of studies on the epidemiology, immunological pathogenesis, molecular mechanisms, and structural biology, as well as approaches for drug or vaccine development for SARS-CoV-2.

Key words: COVID-19; SARS-CoV-2; origin tracing; infection mechanism; SARS-CoV-2 vaccine

INTRODUCTION

Since early 2020, a novel highly infectious disease, coronavirus disease 2019 (COVID-19), emerged as a worldwide epidemic.1,2 COVID-19 was declared to be a “pandemic” by WHO on March 11, 2020, and more than 40 million cases were confirmed and one million deaths recorded across more than 200 countries by November 1, 2020.3,4 COVID-19 is a pulmonary disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the Coronaviridae family.5 Coronaviruses contain a single-stranded RNA genome ranging from 25 to 32 kilobases and are generally categorized into four major genera: alpha-, beta-, gamma-, and delta-coronavirus.6 SARS-CoV caused an outbreak in 2002, resulting in more than 8,000 infections and 774 deaths across 37 countries.7,8 Another coronavirus discovered in Saudi Arabia, MERS (Middle East respiratory syndrome), is reportedly responsible for 2,494 confirmed cases and 858 deaths since September 2012.9,10 Several coronaviruses that cause mild to moderate symptoms in humans have not gained worldwide attention, whereas the HKU2 coronavirus, a newly reported mammalian coronavirus, was found to be responsible for fetal acute diarrhea syndrome in pigs in 2017.11

Coronaviruses have also been identified in several other mammalian hosts, such as birds, bats, civets, and mice, among other species.12,13 Similarly, SARS-CoV-2 has raised major concerns globally, with clinical features ranging from mild or moderate upper respiratory symptoms to severe cases involving respiratory, gastrointestinal, hepatic, renal, and neurological system failure.14–17 In the worst case scenarios, SARS-CoV-2 infects the lower respiratory tract, and can quickly develop into acute respiratory distress syndrome (ARDS), which requires mechanical oxygen support. The basic reproductive rate (R0) is an epidemiological metric to estimate the extent of epidemic transmission without control measures, as well as to evaluate the efficiency of reducing the transmission of disease by human intervention. Initial evaluation of trends of COVID-19 transmission showed that R0 is close to 2.5, which appeared similar to the spread of SARS-CoV in 2003, which had an R0 of 2.90 (range 2.3–3.7). However, the basic reproduction number of SARS-CoV-2 dropped markedly to lower than 1 after implementing strict physical distancing and preventive hygiene measures.18–20 Globally, the R0 of SARS-CoV-2 ranges between 2.5 and 7.1 when in the absence of human intervention (Figure 1A).

To date, no effective methods have been found that can prevent the spread of the epidemic, apart from emphasizing the need for extended social distancing, molecular/antibody testing for infections, and contact tracing to identify and isolate infected patients.21 In addition, antibody testing can be applied to identify individuals with previous SARS-CoV-2 infection, and those former patients with sufficient convalescent plasma may opt to donate blood to benefit the therapy of current patients. At the community level, antibody surveillance programs can be implemented to locally monitor public serological data to better inform public health policy, while increased molecular testing can be used to evaluate the efficacy of vaccination efforts.22,23 Given these current strategies for epidemic control, development of affordable and accurate non-invasive nucleic acid and antibody tests is therefore urgently needed by community health services.

In this study, we conducted a systematic review focusing on genomic variation, origin tracking, epidemiological characteristics, transmission mode, and differences between virus strains, as well as pathological mechanisms, potential treatments, and recent advances in vaccine development.
Clinical manifestations and epidemiology

COVID-19 was declared to be a "pandemic" by WHO on March 11, 2020, and more than 40 million cases were confirmed and one million deaths recorded across more than 200 countries by November 1, 2020. Similar to other coronaviruses, SARS-CoV-2 primarily spreads through respiratory droplets; although, this coronavirus was also potentially capable of transmission through the fecal-oral route. Recent reports have focused attention on shifts in the distribution of cases to an increasingly lower median age of occurrence, although the underlying reasons may be due to social practices rather than biological changes in infectivity (i.e., ignoring potential virus transmission conditions, relaxed social distancing, and less wearing of masks).24,25 Multiple cluster cases have been reported as schools re-opened, especially in university dormitories, or at large-scale social events. Moreover, although the fecal-oral transmission route has not been verified, another study detected active virus in stools from SARS-CoV-2-positive patients, suggesting that the virus was able to invade through the gastrointestinal tract.26,27

Based on data from the Center for Disease Control and Prevention, the median age of library-confirmed cases (mostly through positive results of RT-PCR) is 51, 51% of whom are male.28 Several studies have shown that the elderly and men have a relatively high susceptibility to SARS-CoV-2 infection, which aligned with previous studies that also reported similar patterns of slightly higher MERS-CoV and SARS-CoV infections among males than females.29 Case fatality ratio (CFR) is an important factor for evaluating the severity of COVID-19.30 Figure 1A presents comparative features between the CFRs of SARS-CoV-2 and SARS-CoV by the end of January 2020. These data show that the current international fatality ratio of SARS-CoV-2 is 0.7%, considerably lower than the previously reported CFR of 3.8%.

Global reports indicate that the clinical symptoms of SARS-CoV-2 patients are variable and relatively non-specific, with approximately 50% of infected patients appearing asymptomatic, exhibiting no obvious symptoms. Moreover, the early diagnostic window is short and may result in misdiagnosis since it cannot be easily differentiated from a common cold based purely on symptoms. In addition to respiratory symptoms, some patients report digestive symptoms, such as loss of appetite, stomach discomfort or nausea, and vomiting.6 The viral load reaches its peak in the respiratory tract and it remains unclear if virus persistence in the gut is a driver of aggressive damage during COVID-19 progression.31 Since the viral load increases relatively linearly, even after the active phase, viral RNA are still detectable after a patient has died.32 A persistent infectious environment can potentially lead to dendritic cell damage or incomplete maturation and thereby impair T cell activation, even with a sufficient viral load to activate immune response. This process consequently results in a chronic infective status, and several studies have reported poor outcomes of SARS-CoV-2 infection due to chronic inflammation in patients.33,34

Some COVID-19 cases may progress quickly from a dry cough to ARDS or even to multi-organ failure, which then requires extracorporeal membrane oxygenation support. Laboratory examinations show several abnormalities associated with COVID-19: slightly increased blood cell counts, lymphopenia, increased C-reactive protein in most patients, as well as erythrocyte sedimentation.35,36 Recent studies have shown increased lactose dehydrogenase in severely affected COVID-19 patients.33,34 Most infected patients with mild symptoms typically have a good prognosis with an approximately 14-day hospital stay. However, elderly patients or patients with an underlying disease frequently have worse prognoses and require an oxygen supply. Some severe cases even need intensive care unit treatment and the fatality rate may reach

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**Figure 1.** A summary of the epidemiology, molecular docking, genetic evolution, and genome structure of SARS-CoV-2 (A) Comparison of the characteristics between SARS-CoV-2 and SARS-CoV; (B) genome structure and protein modeling of SARS-CoV-2; and (C) complex structure of human ACE2 binding with RBD of SARS-CoV-2.
17% among those patients. One retrospective study revealed that a decrease in eosinophil counts was significantly associated with poor prognosis in patients. To avoid the spread of COVID-19, clinical professionals and policymakers generally pay attention to pathogenesis and the overall infection process to establish effective measures for control of the disease. Previous studies have identified common patterns in chest CT imaging results, even before nucleic acid testing showed positive results. The results from Santamarina et al. illustrated that over 95% of COVID-19 patients present bilateral lung opacities during CT scan, while lobular and sub-segmental areas of consolidation were unique features compared with that of the common cold or other types of pneumonias. Romero et al. and Kamani et al. examined chest CTs of infected patients in different cohorts and found multiple regions of ground-glass opacities presenting with consolidation. Multiple regions of ground-glass opacities indicating patients with respiratory failure. Moreover, evaluation by thoracic radiology has been considered an informative factor for discriminating between patients with or without COVID-19 infection. From a public health perspective, the rapid isolation of infected patients is crucial to minimize disease spread. Moreover, other CT features, including lymphadenopathy, pleural effusions, pulmonary nodules, or even white lung, can indicate patients with respiratory failure. The genomic variation of SARS-CoV-2 and origin tracking of COVID-19

SARS-CoV-2 is a beta-coronavirus that belongs to the same family as the highly pathogenic SARS-CoV and MERS-CoV, and contains the largest genome of all known RNA viruses. Both SARS-CoV and MERS-CoV were first documented in bats or dromedary camels and then later transmitted to humans. However, possible intermediate hosts of the newly identified SARS-CoV-2 virus remain unknown. Coronaviruses can infect humans primarily due to the unique structure of their spike protein and variable numbers of open reading frames (ORFs). Sequence analysis has shown that the SARS-CoV-2 genome could be divided into several ORFs, including ORF1a, ORF1b, ORF3a, ORF6, ORF7a, ORF7b, and ORF8, as well as the spike structural protein (S) viral envelope (E), membrane protein (M), and nucleoprotein (N) protein coding regions (Figure 1B). ORF1a/ORF1b cover approximately 67% of the SARS-CoV-2 genome. The RNA genome is wrapped by the N protein, which thus forms a coiled tubular structure. This helical nucleocapsid is surrounded by the viral E protein, which is associated with other structural proteins, such as the M and S proteins. Previous studies have reported that surface glycoproteins on the SARS-CoV spike protein play an important role in binding to the host receptor via their receptor-binding domains (RBDs). The SARS-CoV infection process is reportedly mediated by a receptor for an angiotensin-converting enzyme (ACE2), whereas MERS-CoV primarily utilizes a dipeptidylpeptidase 4 receptor. Alignment of the whole genomes of these 3 coronaviruses indicated a high degree of conservation in ORF1a and ORF1b, with only 5 nucleotides out of a total of 29,800 differing among them. SARS-CoV-2 is relatively similar to SARS-CoV, with some notable changes in amino acid sequence that current studies are aiming at characterizing for their influence on the functionality or pathogenesis of SARS-CoV-2. The phylogenetic history of the SARS-CoV-2 was reconstructed using a maximum likelihood approach by Nextstrain. The phylogenetic tree showed 12 different classes of genomic variations, including types 19A, 19B, 20A, 20B, 20C, 20D, 20E, 20F, 20G, 20H/501Y.V2, 20I/501Y.V1, and 20J/501Y.V3 (Figure 2). The major shared and other mutations within the spike protein of different strains are shown in Table 1. The clustered cases were shown to be relatively related to the geographical location and formed a mosaic pattern of phylogenetic placement in those countries. Types 19A and 20C are primarily found in the United States and Europe, whereas type 20B is mainly present in Asia, while type 20H is now the major type in Africa. Among these, type A has been proposed as the ancestral variant of these three types of SARS-CoV-2. Although the intermediate host in SARS-CoV-2 transmission to humans still remains unclear, several studies have suggested a warm-blooded vertebrate likely served as an intermediate host. The coronavirus genome displays an inherently high recombination frequency, as well as high mutation rates, which together facilitate their transmission among different species. Korber et al. found that a mutated variant has arisen as the most prevalent strain in the worldwide epidemic. This SARS-CoV-2 variant has a single amino acid conversion at residue D614G, resulting from a single, non-synonymous A-to-G nucleotide switch from that of the first reported SARS-CoV-2 reference genome. The proportion of newly infected patients infected by this SARS-CoV-2 variant has rapidly increased. The cryoelectron microscopy (cryo-EM) structure of the spike protein illustrated that...
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SARS-CoV strains in bats from other caves. Recent studies conducted by investigators possible intermediate hosts between the reservoir (bat) and direct species jumping due to infrequent encounters, many studies have concluded that SARS-CoV-2 is more likely to be the reservoir of SARS-CoV and MERS, respectively, whereas its identity with the SARS-like bat CoV, with spike and accessory proteins showing lower similarity to SARS-CoV-2 than that of SARS-CoV, which can at least partially explain why SARS-CoV-2 is highly contagious and exhibits increased infectivity.11 A recent study showed that SARS-CoV-2 manipulates host splicing machinery during infection to affect viral replication. Moreover, other studies have suggested that the notch signaling pathway is involved in SARS-CoV-2 infection via the host protease, furin, which can interfere with viral entry into host cells.7,77 The nucleocapsid (N) protein is located within virions and reportedly participates in packaging the RNA genome. The membrane (M) and envelope (E) structural proteins are essential for viral assembly and pathogenesis. M protein interactions lead to downregulation of mitochondrial fusion-mediated interferon-gamma responses by host cells.77 By contrast, the E protein can interact with protein bromodomains BRD2 and BRD4 to regulate gene transcription.

Other work has shown that S protein binding affinity with ACE2 is 20-fold greater than that of SARS-CoV, and that high levels of ACE2 receptor have been associated with elevated risk for infection as well as poor prognosis during disease development.74 Unfortunately, SARS-CoV-2 infection can result in hypoxic conditions which may ultimately lead to the onset of ARDS and/or toxic encephalopathy in its later stage.75,76 Conti et al. revealed that SARS-CoV-2 could consistently induce an aggressive inflammatory response resulting in damage to airways, while severely affected patients died primarily due to the effects of ARDS.77,78 In general, patients with ARDS present symptoms, such as difficulty breathing and low blood oxygen levels, causing them to succumb to secondary bacterial and fungal infections. Among these symptoms, ARDS is the major cause in 70% of COVID-19-related patient deaths.79,80 Cell infiltration mediates pulmonary damage through excessive secretion of proteases and reactive oxygen species, and subsequently those inflammatory cells can directly damage lung structure, hinder macrophage infiltration, and induce diffuse alveolar damage and pulmonary edema.

Table 1. Amino acid mutations emerged in spike proteins of six SARS-CoV-2 strains

| Clade | 20A | 20B | 20C | 20H | 20I | 20J |
|-------|-----|-----|-----|-----|-----|-----|
| Shared mutations | S: D614G | S: D614G | S: D614G | S: D614G | S: D614G | S: D614G |
| | S: E484K | S: E484K | S: E484K | S: E484K | S: E484K | S: E484K |
| | S: N501Y | S: N501Y | S: L18F | S: L18F | S: K417N | S: K417N |
| | S: A701V | S: A701V | S: A701V | S: A701V | S: A701V | S: A701V |
| Other mutations | S: V1176F | S: V1176F | S: V1176F | S: V1176F | S: V1176F | S: V1176F |
| | S: H69- | S: L5F | S: D80A | S: A570D | S: T20N | S: T20N |
| | S: V70- | S: T9I | S: D215J | S: P681H | S: P26S | S: P26S |
| | S: Y144- | S: D253G | S: L241- | S: T716I | S: D138Y | S: D138Y |
| | S: Q52R | S: L242- | S: S982A | S: R190S | S: R190S | S: R190S |
| | S: A67V | S: A243- | S: D1118H | S: H655Y | S: H655Y | S: H655Y |
| | S: Q677H | S: T1027I | S: T1027I | S: T1027I | S: T1027I | S: T1027I |

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Structural analysis of the virus, potential drug therapy, and vaccine development

Molecular docking analysis, followed by chemical stability studies, with subsequent target point determination, is the standard bioinformatics workflow that contributes to innovation in drug design, overcoming drawbacks of the traditional, more time-consuming, less predictable, drug development process. Among these processes, molecular docking can provide advantages in drug design, comparison, and evaluation of their efficacy. The COVID-19 pandemic is largely characterized by a lack of effective therapeutics, and with only a few candidates under clinical trial. Using the crystal structure of SARS-CoV-2 protease in conjunction with traditional herbal medicines in docking analyses yielded some promising terpenoid natural products that could inhibit the viral protease activity.75,81 Another docking study that screened clinically approved medicines with the structure of SARS-CoV-2 Mpro suggested that lopinavir, ritonavir, and nefifivir, and other drugs that were shown to be successful as antiviral treatments for HIV, can act as potential candidates for drug therapy of COVID-19.82,83 Protein-binding assays showed that ACE2 serves as the cellular binding receptor, of which a 17 amino acid of N-terminal signal sequence and 22 hydrophobic transmembrane sequence near the C terminus were found to be essential for the interaction. Moreover, ACE2 also contains a cytoplasmic domain with potential glycosylation sites that could mediate the initial host cell binding interaction.84 To date, seven types of animal- and human-infecting coronaviruses have been reported, four of which only infect the respiratory tract and produce mild symptoms. However, three coronavirus strains have been shown to infect and replicate in the lower respiratory tract of humans, causing pneumonia, ARD, and death.85 Compared with SARS-CoV, SARS-CoV-2 can progress to critical or ARD within a relatively short period, i.e., consistently less than 10 days after symptom onset. In addition,
SARS-CoV-2 exhibits similar characteristics in its host cell infection process as that of SARS-CoV in that they can both rely on the spike surface protein, a multifunctional molecule comprised of S1 and S2 subunits. The S1 subunit mediates host cell receptor binding, while the S2 subunit subsequently mediates viral fusion with the host cell. The structural conformation of the spike protein differs between the prefusion and post-fusion states, with membrane fusion serving as a key process in transitioning between the pre- and post-fusion conformations.

The S1 subunits are comprised of an NTD and RBD, through binding, which forms a complex of spike protein and human ACE2 (Figure 1C) for recognition of distinct host receptors before viral attachment. These two domains are connected by disulfide bonds at the beta-c2 and -c4 sites between five strands that form the first part, while the other one stabilizes another small flexible loop. The second S1 sub-domain is distributed on the protein surface and functions in the prefusion recognition process. Formation of the prefusion complex between SARS-CoV-2 S1 and human ACE2 NTD is initially driven by van der Waals forces, while H bond/salt bridge interactions drive further interactions. The SARS-CoV-2-CTD spans 195 residues, from T333 to P527, within which residues G466 to G502 form H bonds with amino acids of hACE2.86,87 The interface was shown to contain three interaction regions, with a bridge forming between the alpha-1 helix and sites between the alpha-2 helix and loop 3–4. High-resolution imaging by cryo-EM further supported the formation of a stable prefusion complex.88,89

By contrast, the S2 subunit contains five functional domains, including a fusion peptide, heptad repeat N- and C-terminal regions (HR-N and HR-C), a transmembrane domain (TM), and a cytoplasmic domain.90 The S2 subunit facilitates the viral fusion process via interaction with TMPRSS2 protein on the host cell surface. X-ray crystallography of the S2 subunit revealed a rod-like 6-HB fusion core that forms a deep hydrophobic groove adjacent to the HR1 domain, allowing HR2 binding to connect them.91 Structural...
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The first confirmed case in North America was identified in USA.

Mutant strains were found in South Africa, Britain and other countries.

Vaccine of Moderna (mRNA-1273) was approved by FDA for emergency use.

COVID-19 vaccine based on adenovirus developed in China was approved for use.

The first confirmed case in Europe was found in France.
Pfizer and biotech’s vaccine (BNT162b2) was approved by FDA for emergency use.

Vaccine of Sinopharm was first approved in China.

First novel coronavirus pneumonia case was identified in Wuhan.

Figure 4. Timeline of COVID-19 disease and the progress of vaccine development

and biophysical evidence has together illustrated that the considerably higher infectivity of SARS-CoV-2 is due to the 20-fold higher affinity of S protein binding to human ACE2 than that of the SARS-CoV spike protein. Vaccine development has been widely regarded as the most effective approach for prevention and management of COVID-19. The past year has seen substantial progress in the research and development of new coronavirus vaccines through the joint global efforts of medical and scientific research institutions and businesses, resulting in vaccine deployment in many countries and regions. The timeline of progression of SARS-CoV-2 vaccine development is shown in Figure 4. The WHO COVID-19 vaccine progress draft shows that 173 prospective vaccines for COVID-19 are currently in the preclinical stage as of January 2021,92,93 while 64 candidate vaccines have entered clinical trials, 22 of which are in phase II/III or phase III clinical trials. The traditional strategy for development of coronavirus vaccines relies on virus inactivation, virus attenuation, and recombinant protein methods. In recent years, new technology platforms, such as viral vector vaccines and nucleic acid vaccines (mRNA vaccines and DNA vaccines), have opened up new avenues for vaccine development.94

Although nucleic acid vaccines can be produced quickly, this new type of vaccine requires relatively stringent transportation and storage conditions to ensure vaccine stability. In contrast, the preparation method for inactivated vaccines is well established and reliable, but the resultant vaccines provide relatively weak immunity. The use of recombinant protein technology is mature and considered safer than other vaccines, with low possibility of causing adverse reactions, but the immune response may also be insufficiently strong to control the virus. To date, three vaccines have been authorized in the United States, two of which are mRNA vaccines. On November 10, 2020, Pfizer and its partner BioNTech announced that their COVID-19 vaccine candidate BNT162b2 exhibited greater than 90% effectiveness among study participants.95 The phase III clinical trial of BNT162b2 included a cohort of 43,538 participants, approximately 42% of which were recruited internationally, while 30% were US participants. Another American pharmaceutical company, Moderna, also successfully deployed an mRNA vaccine against SARS-CoV-2. Clinical safety trials showed that vaccinated people maintained high levels of antibodies for as long as 119 days.96

Other countries have focused on development of different types of vaccines. The Sinopharm Group announced approval of clinical trials for its vaccine based on inactivated virus. Both Sinopharm Group overseas phase III clinical studies were conducted in cohorts of more than 60,000 global volunteers and included greater than 6 months of observation data, which showed that antibodies are maintained at high levels, resulting in a 79.34% protection rate.97,98 On November 23, 2020, AstraZeneca announced that its AZD1222 vaccine, produced in collaboration with Oxford University, could provide an average effectiveness of 70% against SARS-CoV-2.99 On January 29, 2021, Johnson & Johnson announced that its single-dose new coronavirus vaccine (JNJ-78436735) in the phase III clinical study had reached all primary clinical endpoints and planned to submit an emergency use authorization application to the FDA. At 28 days following a single-dose vaccination, this vaccine had an overall effective rate of 66% in the prevention of moderate and severe COVID-19. Overall, enough vaccines for most populations would be necessary to decrease infection cases and stop the outbreak of COVID-19.100

Unfortunately, vaccine efficacy can be limited by the emergence of novel strains in human populations. In particular, the B1.1.7 lineage from the United Kingdom, the South African 20H (B.1.351) lineage, and the Brazilian 20J (P.1) lineage (Figure 2) have spread globally due to their higher infectivity. Whether the existing vaccines remain effective against the newer virus variants has become a problem of great concern to both scientists and the general public, and several studies have (and continue to) explored the threat to vaccine protection posed by these variants. For example, the Pfizer BNT162b2 vaccine exhibited 95% efficacy against the original SARS-CoV-2 strain.101 However, recent in vitro studies investigating the efficacy of serum of BNT162b2-vaccinated volunteers showed roughly equivalent neutralization of recombinant viruses expressing the P.1- and B.1.1.7 spikes, and a two-thirds reduction in efficiency for neutralization of those bearing the B.1.351 spike.102 Similar results were obtained in an in vitro study of the Moderna mRNA-1273 vaccine in which researchers constructed a pseudovirus expressing complete spike proteins of the B.1.1.7 or B.1.351 variants. Immune serum was obtained from eight subjects from a phase I clinical trial and the degree of viral neutralization by these sera was determined. While the immune sera showed no significant neutralization of the B.1.1.7 variant, the neutralized B.1.351 mutant titer was reduced by 6.4-fold, but remained at a high level (1/290). The Novavax NVX-CoV2733 vaccine is a recombinant protein vaccine produced using proprietary recombinant nanoparticles. Interim results of a phase II trial carried out in the UK with more than 15,000 volunteers aged between 18 and 84 years, including 27% over 65 years old, revealed an 85.6% efficacy of the vaccine against the B.1.1.7 variant, compared with 95.6% against the original strain. However, a phase II trial of NVX-CoV2733 in South Africa with more than 4,400 participants showed an overall efficacy of 49.4% (95% confidence interval [CI]: 6.1–72.8). The significant drop in the efficacy compared with the UK trial was due to the B.1.351 variant, carrying an E484K conversion, which is now predominant in South Africa. Sequencing of virus isolated from 27 South African SARS-CoV-2 cases indicated that 93% involved the B.1.351 variant.103 It warrants mention that this study included 240 volunteers who were HIV-positive, and when this group was excluded from the analysis the protective efficacy was 60% (95% CI: 19.9–80.1).104 Recently, a study was conducted to investigate neutralizing activity against the B.1.1.7 and B.1.351 variants by the inactivated virus vaccines BBIBP-CorV (Sinopharm) and CoronaVac (Sinovac) by comparing the serum neutralization titer of 50 patients with two doses of either BBIBP-CorV or CoronaVac vaccine with that of sera from 34 convalescents collected at 5 months after COVID-19 infection with COVID-19. The results suggested...
that the B.1.1.7 variant showed little resistance to neutralization by either the convalescent or vaccinated sera, whereas B.1.351 showed 2-fold higher resistance to convalescent serum and 2.5- to 3.3-fold higher resistance to vaccinated serum than the original strains. The current progress in main vaccine development is summarized in Table S1.

Table S1. Comparison details of the vaccines are provided in Table S1. Comparison details of the vaccines are provided in Table S1.

To better control the epidemic and reduce immune escape caused by virus mutations, Moderna developed the mRNA-1273.351 vaccine targeting the B.1.351 S protein. Moderna then developed a multivalent vaccine, mRNA-1273.211, which combined mRNA-1273 targeting the original strain and mRNA-1273.351 targeting B.1.351, to thus provide a broader range of protection. In vivo studies in a murine model indicated that vaccination with mRNA-1273.351 could increase the neutralizing antibody against the B.1.351 lineage, and that this vaccine thus far showed the highest efficacy for broad, cross-variant neutralization.

**DISCUSSION**

COVID-19 has spread globally to over 200 countries with more than 40 million confirmed cases and one million deaths as of November 1, 2020. The total cases of COVID-19 are expected to be higher than reported due to the difficulty in identifying false-negative mild and asymptomatic cases. Moreover, accurate and reliable clinical diagnosis requires experienced professionals, while the use of symptom-suppressive medications before examination can also confound diagnosis. In most countries, an increasing trend in confirmed cases during the early stages of the outbreak is followed by an exponential growth trajectory before the epidemic peaks. Therefore, it is difficult to compare the rates of infection and fatality between countries due to differences in the stages of outbreak, highly variable scopes of population testing, differences in the burden on their respective health care systems, as well as the general health status of the population, and differences in average population demographics. Moreover, the elderly and people with underlying chronic disease were more susceptible to infection by SARS-CoV-2 at the beginning of the epidemic. The most common symptoms of early infection include mild fever, dry cough, and fatigue, while nasal congestion, diarrhea, and sore throat are rarely reported. However, some people close to COVID-19 patients, or in family cluster cases, initially showed no fever or respiratory symptoms but exhibited non-respiratory or cardiac-associated symptoms.
such as palpitation, arrhythmia, and cardiac shock accompanied by respiratory symptoms, dyspnea, or, occasionally, in the worst cases, ARD.\textsuperscript{107,108} Although asymptomatic infection can be difficult to define in the early stages of infection, many patients eventually develop pneumonia; therefore, the clinical presentations range from asymptomatic to fatal multiple organ failures.

Binding of SARS-CoV-2 to the host ACE2 receptor activates fusion with the host cell and subsequent viral replication, leading to pyroptosis in the host cell and release of the virus. This process causes damage-associated molecular patterns, which are recognized by neighboring epithelial cells, alveolar epithelial cells, and vascular endothelial cells, consequently triggering a pro-inflammatory response. The inflammatory signal cascade entails cytokine release, which in turn recruits monocytes, macrophages, and T cells to those infection sites. Furthermore, these cytokine bursts can generate a pro-inflammatory feedback loop, resulting in a cytokine storm, eventually damaging pulmonary structure and function.\textsuperscript{109} In addition, ACE2 regulates the renin-angiotensin system, which could be downregulated as viral load increases, thereby influencing fluid and electrolyte levels, and enhancing inflammatory response, vascular permeability, and infiltration of lymphocytes into the airway. Pulmonary recruitment of circulating immune cells and lymphocyte infiltration ultimately results in peripheral lymphopenia.

In summary, COVID-19 represents an urgent, worldwide health crisis. Systematic and rigorous review of genomic variations in SARS-CoV-2 and origin tracing of COVID-19 will benefit the prevention, diagnosis, and therapeutic strategies for patients suffering from COVID-19.

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AUTHOR CONTRIBUTIONS

L.W. and J.Y. conceived and coordinated the research. T.L., T.H., C.G., and A.W. searched literature and wrote the manuscript. X.S., T.H., G.T., Q.L., J.S. and X.M. reviewed the manuscript.

DECLARATION OF INTERESTS

T.L., A.W., X.S., Q.L., T.H., G.T., and J.Y. are currently employed by Geneis Beijing Co., Ltd. All other authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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