

New challenges to fighting COVID-19: Virus variants, potential vaccines, and development of antivirals

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SUMMARY Despite strict control measures implemented worldwide, the COVID-19 pandemic continues to rage. Several drugs, including lopinavir/ritonavir, hydroxychloroquine, dexamethasone, and remdesivir, have been evaluated for the treatment of COVID-19 during the past year. While most of the drugs failed to display efficacy in treating COVID-19, scientists have encouraged herd immunity to control the pandemic. Immunity generated after natural infection with SARS-CoV-2 is precarious, as indicated by real-world evidence in the form of epidemiological data from Manaus, Brazil. Vaccines using different platforms are therefore the most promising approach to help us return to normality. Although several vaccines have been authorized for emergency use, there are still many concerns regarding their accessibility, the vaccination rate, and most importantly, their efficacy in preventing infection with emerging virus variants. Continued virus surveillance and rapid redesign of new vaccines to counter new variants are crucial to fighting COVID-19. Rapid production and extensive vaccination are also essential to preventing the emergence of new variants. Nevertheless, antivirals including monoclonal antibodies and oral medicines need to be developed in light of uncertainties with regard to vaccination. In the battle between humans and SARS-CoV-2, the speed with which we fight the virus, and especially its emerging variants, is the key to winning.

Keywords COVID-19, SARS-CoV-2, vaccine, variants

The COVID-19 pandemic has infected more than 100 million people and caused 2 million deaths as the end of February 2021. Since its outbreak, China implemented various interventions, including a complete lockdown of the population, mandated wearing of masks outside the home, and handwashing during the first wave of the disease. Public participation in and adherence to control measures helped the Chinese Government to quickly control the epidemic. Although cases have been imported and contaminated imports have caused recent COVID-19 outbreaks in several cities, these outbreaks were stamped out thanks to China's disease control system, which involves quarantine upon entry, rapid case diagnosis, active case surveillance, strict follow-up, and quarantine of close contacts. Unlike China, many countries implemented an incomplete lockdown. More importantly, people failed to fully adhere to control measures. The number of the infected fluctuated depending on the strength of the control measures but never declined to zero.

These measures have been at the expense of the economy. More importantly, these strict control measures alone are not effective enough to stop the COVID-19 pandemic. Even in China, where the strictest

control measures were implemented, sporadic cases of COVID-19 have still been reported. The world is, therefore, looking forward to effective medicines and vaccines to prevent or treat COVID-19. During the past year, several drugs to treat COVID-19 were investigated, most of which were repurposed. While most of the drugs including lopinavir/ritonavir and hydroxychloroquine failed to display efficacy in clinical trials, dexamethasone has been found to decrease mortality among some patients with COVID-19, and especially those with severe or critical disease (1,2). However, the role of remdesivir in treating COVID-19 is still controversial. Although several clinical trials indicated that remdesivir was superior to a placebo in reducing the time to recovery in adults who were hospitalized with COVID-19, the WHO has recommended against its use in inpatients, regardless of disease severity, as there is currently no evidence that it improves survival (3,4).

Herd immunity, achieved either by natural infection or by vaccination, is therefore being pursued to prevent the spread of disease and to control the pandemic. However, mounting evidence suggests that natural infection is not able to achieve herd immunity as expected. Dozens of reinfections with SARS-CoV-2

have been reported, indicating that immunological memory generated by natural infection may not strong or last long enough to protect people from reinfection. More importantly, epidemiological data from the city of Manaus, Brazil, have indicated the precarious state of natural herd immunity in the real world. The rate of infection with SARS-CoV-2 was estimated to increase from 66% in June to 76% in October in Manaus based on seroprevalence data (5). The high seroprevalence indicates that natural herd immunity has been achieved, given a basic reproduction number of 3 (6). However, the number of hospitalizations for COVID-19 in Manaus increased sharply in January 2021. Several possible explanations have been put forward, including overestimated seroprevalence before the second wave and a rapid decline in immunological memory post-infection, but the most pressing concern is new variants of the virus (7). In a preliminary study, the new virus variant P.1 was identified in 42% (13/31) of samples from patients reported in Manaus in December 2020, though it was absent in 26 samples collected between March and November 2020 (8). Indeed, the new variant has been linked to increased infectivity in mouse models (9). Reinfection with the P.1 lineage in Manaus was also reported in January 2021 (10). This evidence suggests that the high transmission of P.1 may require a higher seroprevalence to achieve herd immunity and that P.1 may evade immunological memory generated post-infection (11). Therefore, herd immunity from an infection should not be an option either from an ethical or scientific point of view (12).

A host of potential COVID-19 vaccines is currently being developed based on different platforms, from conventional inactivated and live attenuated vaccines to more creative message RNA (mRNA) and DNA technologies including viral vector and subunit vaccines. Most potential COVID-19 vaccines target the spike protein of SARS-CoV-2. Several vaccines have been authorized for emergency use with varied efficacy in preventing COVID-19 and in decreasing disease severity. In a real-world study, the BNT162b2 mRNA COVID-19 vaccine was effective for a wide range of COVID-19-related outcomes (13). With the high rate of protection from infection after vaccination, herd immunity could theoretically be achieved. However, the use of vaccines to control the pandemic still faces many challenges. The most serious concern is the availability of vaccines. As of March 5, 2021, only around 291 million people have been vaccinated (14). A shortage of vaccines, especially in developing countries, is one of the main reasons for the low vaccination rate worldwide. Another explanation might be the limited willingness of people to be vaccinated. According to a recent survey, around half of respondents would not take a vaccine even if it was available (14). Moreover, there are still several questions about vaccines that remain unanswered. These include the duration of the protective

effect of a vaccine and cross-protection against virus variants, and especially emerging mutations. A most recent study examined immunogenicity 119 days after initial vaccination with mRNA-1273 and noted high levels of binding and neutralizing antibodies against SARS-CoV-2 even though those levels were expected to decline over time (15). The study in question indicated that immunity generated by a vaccine, or at least mRNA-1273, has the potential to provide sustained protection against SARS-CoV-2. However, virus variants also diminish the efficacy of vaccines. Although most researchers believe that the D614G variant and the B.1.1.7 strain will not affect the efficacy of vaccines, the B.1.351 variant was found to be partially resistant to neutralizing antibodies induced by most of the common vaccines used worldwide, including the Pfizer mRNA vaccine, the Moderna mRNA vaccine, and the Novavax protein vaccine (16,17).

As the vaccination rate increases, new cases of COVID-19 are now declining. However, there is still much uncertainty, given emerging new variants, the unknown duration and efficacy of protection, and questions about efficacy against new variants. There are several strategies that could be adopted now to control the pandemic and eventually eliminate the disease. The most important approach is to continue viral surveillance and rapid design of vaccines against new variants. We cannot predict whether virus variants will emerge in the future. Therefore, viral surveillance and rapid evaluation of vaccine efficacy against new viral variants are extremely important. Indeed, under the current threat of new variants and B.1.351 in particular, all leading vaccine companies are now redesigning their vaccines to counter new variants. The development of a broad-spectrum vaccine against SARS-CoV-2 by retaining the conserved amino acids in the receptor-binding domain region also offers promise (18).

Rapid production of vaccines and extensive vaccination are also essential to winning the battle. Virus variants can only emerge when a large number of people are infected. While herd immunity is generated by vaccination, the number of the infected would decrease sharply, thus limiting the emergence of virus variants. However, mutations that evade the vaccine might appear when immunity wanes or in the event of incomplete vaccination (e.g., taking only one dose of a vaccine that requires two doses). Therefore, rapid and complete vaccination and monitoring of the immune response should be implemented.

Until vaccine-induced herd immunity is achieved, another favorable strategy would be to develop new medicines that are effective against SARS-CoV-2. The FDA has authorized the emergency use of two monoclonal antibodies for the treatment of COVID-19 as they were able to limit SARS-CoV-2 replication in the nasopharynx and therefore prevent disease progression if administered early (19). However, the efficacy of

monoclonal antibodies against viral variants, and B.1.351 in particular, has raised concern. In a recent study, binding of the REGN-COV2 cocktail to B.1.351 variants was nine times lower than that to other prevalent SARS-CoV-2 strains (20). Therefore, the combination of several different monoclonal antibodies should be tested in future clinical trials. More importantly, new monoclonal antibodies or spectrum neutralizing antibodies should be developed faster than new variants emerge.

Besides vaccines and monoclonal antibodies, the development of antivirals to treat COVID-19 should not be ruled out. Given the uncertainty of vaccines, affordable and convenient medicines (e.g. oral preparations) for the treatment of COVID-19 may not only help to limit the spread of the pandemic but more importantly alleviate the fears of the general public. In developing countries, the best strategies are to social distance, wash one's hands, and wear a mask while awaiting vaccines and affordable drugs. These countries need to control the epidemic as much as they can, though vaccines and drugs should be provided as early as possible. In this battle between humans and viruses, the slower the process, the more likely we are to lose.

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