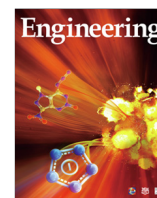




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## Views &amp; Comments

## Challenges in the Development of a Vaccine Against COVID-19

Wei Chen<sup>a</sup>, Feng-Cai Zhu<sup>b</sup><sup>a</sup> Beijing Institute of Biotechnology, Beijing 100071, China<sup>b</sup> Jiangsu Provincial Center of Disease Control and Prevention, Nanjing 210009, China

## 1. Introduction

The emergence of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a large-scale global outbreak and is a major public health crisis [1]. The serious epidemic situation has highlighted the need for effective therapeutic and preventive solutions to reduce the perils and transmission of the disease. A number of countries have accelerated the process of clinical trials to develop an effective and safe vaccine to curtail the current ongoing pandemic [2].

There are over 160 candidate vaccines against SARS-CoV-2 under development worldwide [3]; among these, around 29 candidate vaccines have been tested in clinical trials, including six viral-vector-based vaccines, six messenger RNA (mRNA) vaccines, four DNA vaccines, eight recombinant-protein-based vaccines, and five inactivated-virus vaccines. The initial findings of the first human trial for a potential vaccine against SARS-CoV-2 have been published [4]. Richard Horton, editor-in-chief of *The Lancet*, shared this progress via social media, saying that the world's first clinical trial of the COVID-19 vaccine shows that the vaccine is safe, well-tolerated, and can elicit a rapid immunity reaction. Horton stated, "These results represent an important milestone." A phase 2 trial of this adenovirus type-5 (Ad5)-vectored COVID-19 vaccine was conducted in Wuhan, China. A total of 508 eligible participants aged 18–83 years were randomly assigned to vaccine or placebo. The results showed that the Ad5-vectored COVID-19 vaccine is safe and induced significant humoral and cellular immune responses after a single immunization [5]. Another adenovirus-vectored COVID-19 vaccine—a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) whose development was led by the University of Oxford—published its phase 1/2 clinical trial results [6]. The ChAdOx1 nCoV-19 vaccine presented an acceptable safety profile and stimulated both humoral and cellular immune responses against COVID-19. Two mRNA vaccines, mRNA-1273 and BNT162b1, also induced both humoral and cellular immune responses against SARS-CoV-2 in participants [7,8]. An inactivated COVID-19 vaccine caused humoral immunogenicity after two doses, whereas the cellular immune response was not determined in this clinical study [9]. Nevertheless, despite the world's desperate need for a protective vaccine to help contain the epidemic, great challenges still remain in the development of such a vaccine.

## 2. Evaluation of vaccine safety

Aside from the tissue injuries that are caused by COVID-19, such as lung and kidney injury, the severity of the disease and the high mortality rates in COVID-19 patients are associated with underlying comorbidities, including cardiovascular disease, diabetes, hypertension, and chronic obstructive pulmonary disease [10]. Remarkably, there is a bidirectional relationship between COVID-19 and diabetes [11]. On the one hand, diabetes is associated with an increased risk of COVID-19 infection [11]. Diabetes was found to be one of the prevalent cardiovascular metabolic comorbidities with COVID-19, with a 9.7% incidence (95% confidence interval (CI), 6.9%–12.5%) of diabetes among 1527 COVID-19 patients in a Chinese meta-analysis [12]. At the same time, it was found that patients with diabetes had a two-fold increase in the risk of severe COVID-19 [12]. On the other hand, severe bacterial [13] and viral respiratory tract infections [14], including SARS-CoV-2 [11,15], can induce new-onset diabetes. Although the pathophysiological mechanisms are still not clearly understood, some researchers have proposed that SARS-CoV may damage islets and cause acute insulin-dependent diabetes mellitus [16]. Whether there is a link between the development of diabetes and immunization with some types of vaccines—especially inactivated and live attenuated vaccines, which contain the most components of the "killed" virus—remains an issue and requires further study. Therefore, in order to assess and monitor the safety of COVID-19 vaccines, high-quality clinical vaccine safety studies should be conducted, and more epidemiologic studies on vaccinations and the risk of diabetes are needed.

## 3. Evaluation of vaccine efficacy

COVID-19 vaccines are most commonly evaluated based on their capability of generating binding and neutralizing antibodies. However, a range of vaccine evaluation methods and models exist, making it difficult to compare the efficacy of different vaccines. In addition to humoral immunity, specific CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs) are associated with accelerated clearance of virus and recovery from infection. Previously reported studies on humoral and cellular immunity in recovered patients showed that both B and T cells participate in immune-mediated protection from viral infection, which indicated that an effective viral clearance needs

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collaborative humoral and cellular immune responses [17,18]. An rVSV-ZEBOV vaccine showed 100% protection against Ebola virus in the phase 3 clinical trial [19]. However, this vaccine only elicited neutralizing antibodies in a proportion of the participants after 28 days of immunization in the phase 1 clinical trial [20]. In preclinical studies, the correlation of total specific binding Immunoglobulin G (IgG) levels—rather than neutralizing antibody levels—proved to be a meaningful measure of the protective effect of the vaccine against Ebola virus exposure [21]. Interestingly, T-cell-inducing vaccines provide protection against the virus, even with very low neutralizing antibody levels [22]. T-cell immunity is needed and the evasion of antibody neutralization was found in SARS-CoV vaccination [23,24]; furthermore, SARS-CoV-specific memory T cells can be detected even 11 years after natural SARS-CoV infection [25].

In a human challenge trials (HCTs) of an oral influenza vaccine using adenovirus as a carrier, the levels of binding antibody and neutralizing antibody of the adenovirus-vectored influenza vaccine were lower than those of an inactivated vaccine, while the T-cell response and IgA level of the adenovirus-vectored influenza vaccine were remarkably higher than those of the inactivated vaccine. The protection rate of the adenovirus-vectored influenza vaccine was found to be significantly higher than that of the inactivated vaccine. This result illustrates that the protective efficacy of a vaccine is not fully correlated with its level of neutralizing antibody, and that the cellular immune and IgA responses generated by an adenovirus-vectored influenza vaccine play important roles in preventing influenza virus infection [26]. These findings suggest that a vaccine's ability to induce cellular immunity is important to consider in vaccine development.

In addition, local mucosal immunity is critical for protection against respiratory viral diseases in most cases, such as influenza and respiratory syncytial virus [27,28]. The delivery route of the vaccine is very important for the induction of local mucosal immunity. Studies on a live attenuated influenza vaccine found that intranasal delivery of vaccination was more efficient in inducing mucosal antibodies in comparison with intramuscular delivery. Since SARS-CoV-2 mostly invades the human body through the respiratory system, mucosal immunity could play a potentially important antiviral role. Our research team found that the mucosal vaccination of the Ad5-vectored COVID-19 vaccine showed better protective efficacy than intramuscular vaccination in the upper respiratory tract in mice and ferrets with SARS-CoV-2 challenge [29]. Although the effects of cellular immunity or mucosal immunity have not been quantitatively measured, and their role in establishing effective protection against COVID-19 has not been evaluated, we believe that a candidate vaccine that can elicit multiple immune responses, including mucosal immunity and cellular immunity, may provide better protection against COVID-19 than vaccines that only generate humoral immunity. This needs to be investigated in future studies.

The severity and mortality of COVID-19 disease have been found to be associated with older age [30–33]. Furthermore, it is often found that the immunization response of the elderly is not as good as that of healthy adults. In addition, underlying diseases that are common in the elderly are often considered to be contraindications to vaccination, particularly for live vaccines or viral-vectored vaccines; therefore, the use of vaccines for the elderly requires special consideration. Most vaccines that are evaluated in early-phase clinical trials are tested in healthy individuals; however, an immunization regimen that works well in a healthy population may not be suitable or good enough for the elderly or for those with underlying diseases. Using a higher dosage, or giving an additional dose, has often been considered in order to enhance the immune responses of the elderly; examples include hepatitis B vaccines and influenza vaccines [34,35]. An ideal candidate COVID-19 vaccine should be safe and should be able to induce equivalent protection for all of these populations.

#### 4. Human challenge trials and production capacity

HCTs are trials in which participants are intentionally challenged (whether or not they have been vaccinated) with an infectious disease organism, such as SARS-CoV-2. The use of controlled HCTs—instead of conventional phase 3 testing—of SARS-CoV-2 vaccine candidates could accelerate the testing and potential rollout of efficacious vaccines [36]. However, HCT volunteers risk illness (or even death) following infection with SARS-CoV-2, so reducing these risks remains an issue. The World Health Organization (WHO) has provided guidance by outlining key criteria for the ethical acceptability of COVID-19 human challenge studies [37].

Finally, although a great deal of work has been focused on the development of a COVID-19 vaccine, this is only the first step. The demand for COVID-19 vaccines will exceed the supply of pharmaceutical companies. Importantly, China is committed to the development and deployment of COVID-19 vaccines (if available) as a global public interest, as part of China's contribution to vaccine accessibility and affordability in developing countries. In addition, the WHO aims to secure two billion doses of COVID-19 vaccines by the end of 2021. Under such circumstances, we are facing an unprecedented scale of vaccine demand and urgently need to increase the capacities of manufacturing, procuring, and distributing safe and effective vaccines globally.

#### 5. Conclusion

The global COVID-19 pandemic is still ongoing, and the rapid development of vaccines against COVID-19 has become a top priority. Although there is still a long way to go in the development of COVID-19 vaccines, we believe that the collaborative efforts of the global scientific community can help to overcome these challenges and meet the increasing demand for safe, affordable, and effective COVID-19 vaccines.

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