

**COMMENTARY****COVID-19 vaccines: Knowing the unknown**Huibin Lv¹ , Nicholas C. Wu² and Chris K. P. Mok¹ ¹ HKU-Pasteur Research Pole, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China² Department of Integrative Structural and Computational Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

Vaccine development against SARS-CoV-2 has drawn attention around the globe due to the exploding pandemic. Although COVID-19 is caused by a new coronavirus, SARS-CoV-2, previous research on other coronavirus vaccines, such as FIPV, SARS, and MERS, has provided valuable information for the rapid development of COVID-19 vaccine. However, important knowledge gaps remain — some are specific to SARS-CoV-2, others are fundamental to immunology and vaccinology. Here, we discuss areas that need to be addressed for COVID-19 vaccine development, and what can be learned from examples of vaccine development in the past. Since the beginning of the outbreak, the research progress on COVID-19 has been remarkable. We are therefore optimistic about the rapid development of COVID-19 vaccine.

Keywords: COVID-19 · SARS-CoV-2 · Vaccine

See accompanying review by Schijns et al.

In 2019 December, the first cluster of COVID-19 patients was identified in Wuhan, China. Since then, SARS-CoV-2, the causal virus of COVID-19, has become pandemic and infected more than 3.8 million people across 215 countries (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>, accessed on 9 May 2020). The current estimated mortality rate of the disease, based on the raw number of laboratory confirmed cases reported to WHO, is around 6.9% but varies highly among different countries, likely due to the differences in healthcare system capacities, treatment approaches, demographics, and the number of people tested. Elderly people are in the high-risk group because they are more likely to develop severe disease and have a much higher mortality rate after infection [1]. The ongoing outbreak is unlikely to end in the near future and the global influence of this virus on all aspects of public and individual life is unprecedented. Although it is possible that the virus may eventually become endemic like other human

coronaviruses, such as OC43, 229E, NL63, and HKU1, the main concern is that it will first cause millions of deaths, extrapolating from the current trend. Vaccination is considered as one of the most effective strategies against the infection of SARS-CoV-2 and may limit the spread of the disease in the human population. At the moment, a vaccine candidate using adenovirus type 5 vector is in phase II clinical trial, and four other vaccine candidates using different approaches, namely inactivated virus, lipid nanoparticle (LNP)-encapsulated mRNA, and plasmid DNA, are in phase I clinical trials (<https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus-landscape-ncov.pdf>).

Other platforms, such as live attenuated virus, protein subunit, are also being evaluated at the preclinical stage. Although there is an urgent need for these vaccines to become available, several critical features of the COVID-19 vaccine will need to be assessed, based on the experience from previous vaccine development for Feline-CoVs, MERS-CoV, SARS-CoV, and other viruses (Fig. 1).

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[Correction added on 16 July 2020, after first online publication: Peer review history statement has been added.]

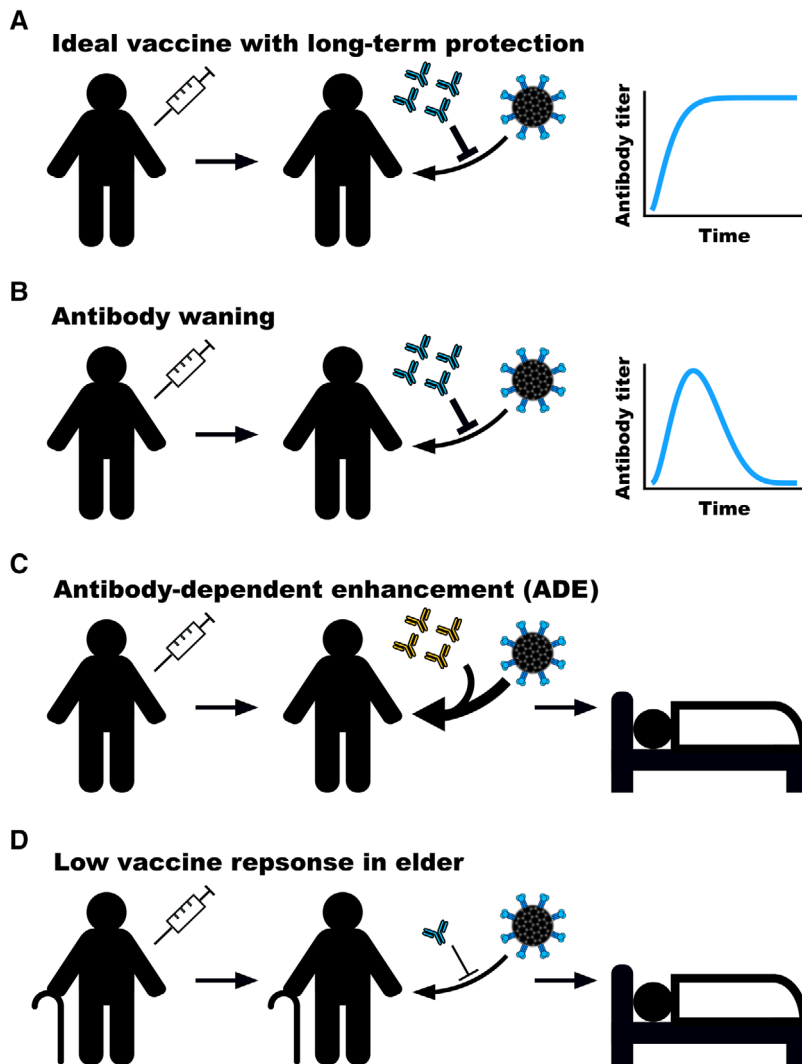


Figure 1. Potential challenges in the development of COVID-19 vaccine. (A) An ideal vaccine should provide long-term protective antibody responses. (B) Antibody waning can pose a challenge in establishing long-term protective antibody responses. (C) Antibody-dependent enhancement (ADE), if exists, can cause an adverse effect, rather than a protective effect. (D) Immune responses in different age groups are not the same. For example, vaccination may induce much lower immune responses in elders as compared to younger people.

It is highly desirable that a potential vaccine will induce a potent antibody response as well as long-term protection. Studies have shown that monoclonal antibodies isolated from the COVID-19 patients can neutralize SARS-CoV-2 [2–4]. Moreover, the use of convalescent plasma from the COVID-19 recovery patients as a treatment strategy has led to positive outcome [5, 6]. These results confirm that protective antibody response against SARS-CoV-2 can be elicited. Nevertheless, whether long-lasting protective antibody response can be elicited by vaccination remains elusive. So far, three vaccines against SARS-CoV or MERS-CoV using either inactivated virions or plasmid DNA have been tested in healthy adult cohort at phase I clinical trials [7–9]. Although the majority of the recipients were found to seroconvert and produce neutralizing antibody against MERS-CoV, antibody levels were only maintained at high level for around 30 weeks and dropped to the level of baseline 60 weeks after vaccination. Similar phenomenon was observed in patients recovered from MERS-CoV infection, where neutralizing antibodies dropped to an undetectable level as early as 6 months postinfections [10]. Studies have suggested that long-lived plasma cells play a critical role in maintaining serum anti-

body level [11]. However, the exact mechanism required to induce long-lived plasma cells, hence, long-term antibody responses, is in fact a fundamental immunological question that is central to vaccine design in general and, yet, not well understood.

Furthermore, characterizing the antigenicity of a protein of interest can be the key to successful vaccine design. Previous works on influenza virus, HIV, and RSV have demonstrated that identification of antibody epitopes on antigens can lead to effective structure-based vaccine design [12–14]. Therefore, vaccine design for SARS-CoV-2 will benefit from identifying the epitopes on the spike protein. In fact, except for the inactivated virus vaccine, all other COVID-19 vaccine candidates in clinical trials aim to elicit antibody responses using the full trimeric spike as the immunogen. A recent study has identified more than 200 monoclonal antibodies from COVID-19 patients that can bind to the receptor-binding domain (RBD) of the SARS-CoV-2 [2]. Identifying the epitopes that are targeted by these antibodies will be crucial to determine the antigenic sites on the spike of SARS-CoV-2. Although traditionally an effective vaccine should mainly aim to elicit a high titer of neutralizing antibodies, it was found that

some non-neutralizing antibodies could provide *in vivo* protection through antibody dependent cell-mediated cytotoxicity (ADCC) [15]. Thus, it will be interesting to distinguish the functions of the antibodies isolated from volunteers in clinical trials in order to understand in molecular terms vaccines' effectiveness. It is also important to note that T-cell immunity was found to be elicited by SARS-CoV or MERS-CoV DNA vaccines (both express trimeric spike protein) [7, 9]. These results imply that using SARS-CoV-2 spike protein as immunogen may also elicit cellular immune response, in addition to humoral immune response.

There is a concern that some antibodies elicited by the SARS-CoV-2 vaccine may cause an adverse effect such as antibody-dependent enhancement (ADE) or enhanced respiratory disease (ERD) [16]. Studies on feline coronaviruses have repeatedly shown that antibodies elicited by vaccination and infection can cause ADE. For example, when challenged with a lethal dose of Feline Infectious Peritonitis virus (FIPV), kittens previously immunized with the vaccinia virus that expressed the spike protein from feline enteric coronavirus (FECV) died earlier than control animals [17]. In addition, Corapi et al. previously showed that some neutralizing antibodies against FIPV could induce ADE in *in vitro* assay [18]. Subsequent study further demonstrated that passive immunization of antitype I FIPV antibodies in cats could induce ADE following subcutaneous inoculation with the same serotype of virus [19]. One study also showed that human macrophages could be infected by SARS-CoV as a result of IgG-mediated ADE, although they did not support productive replication of the virus [20]. In addition, antispikes IgG was associated with acute lung injury in macaque after challenged with SARS-CoV [21]. Interestingly, our recent study showed that the plasma of COVID-19 patients can cross-react to the RBD and S2 domain of SARS-CoV but no strong cross-neutralizing effect was observed [22]. Whether these cross-reactive antibodies provide antibody dependent cell-mediated cytotoxicity (ADCC) or result in ADE in COVID-19 patients will need further investigation. Nevertheless, a recent study demonstrated that potent neutralizing responses were elicited by SARS-CoV-2 RBD vaccination in rats without inducing ADE, suggesting such a potential complication may not be a concern, at least for RBD-based SARS-CoV-2 vaccine development [23].

To enhance the magnitude and quality of the adaptive response, adjuvants are included in some vaccination formulations [24]. Different adjuvants drive different immunological signatures and, hence, are optimal for protection against different pathogens [25]. For example, adjuvants can modulate the ratio of T helper 1 (Th1) and T helper 2 (Th2) responses, increase the generation of memory cells, and alter the breadth and affinity of the response [24]. Determining which adjuvants can enhance protective vaccine response to SARS-CoV-2 will be important. Because immune responses in different age groups are not the same, optimal vaccination strategy may be varied for different age groups [26]. For example, the MF59-adjuvanted influenza vaccine, Fluad, is only licensed and approved for adults aged 65 years and older, to elicit a higher protective immune response in the elderly (<https://www.cdc.gov/flu/prevent/adjuvant.htm>).

As it is clear that the mortality rate in the elderly is the highest among the COVID-19 patients, a specific vaccination strategy for this group will need to be considered during vaccine development.

To accelerate vaccine development, animal infection models for SARS-CoV-2 are needed. Although macaques show COVID-19-like disease upon SARS-CoV-2 infection, the nonhuman primate model is usually not readily accessible to most laboratories [27]. Ferrets and golden Syrian hamster are presented as alternatives, as all show mild disease signs and virus shedding after challenge with SARS-CoV-2 [28, 29], and are usually more widely available than nonhuman primates. Nonetheless, mouse is the most commonly used animal model during vaccine development in general. Although WT mouse is not susceptible to the infection of SARS-CoV-2, transgenic mice that express the human angiotensin-converting enzyme 2 (hACE2) receptor, which was previously established for SARS-CoV study [30], showed significant pathogenicity upon the infections of SARS-CoV-2 [31]. Expressing hACE2 through adenoviral transduction may provide another possible approach to generate a mouse model for SARS-CoV-2 infection. The feasibility of this approach is suggested by a previous study that used adenoviral transduction to generate a mouse model for MERS-CoV infection [32]. The advantage of this approach is that it can be applied to multiple genetic backgrounds including outbred mice. These animal models are thus suitable to evaluate vaccine candidates in preclinical settings.

There is also a pressing need to define correlates of protection, which have the additional benefit of serving as a benchmark for vaccine evaluation without the need for challenge studies, an approach that has been used for many different pathogens [33]. A typical example is influenza vaccine, where a hemagglutination inhibition (HAI) titer of $\geq 1:40$ is a surrogate of protection [34]. However, the exact serological parameters that provide best correlation with protection against SARS-CoV-2 infection will need to be investigated. On a related note, evaluating the neutralizing antibody titer against SARS-CoV-2 live virus requires operation in Biosafety Level 3 (BSL3) Biocontainment Facility. Therefore, pseudovirus assays that can be performed in a Biosafety level 2 (BSL2) setting are also valuable for vaccine development [35, 36].

Zoonotic coronaviruses are likely to be a continuous threat [37]. While the immediate goal is to develop a specific vaccine for SARS-CoV-2, development of a universal vaccine that can cross-protect all zoonotic coronaviruses is a long-term goal. Recent outbreaks have all been caused by betacoronavirus (SARS-CoV, MERS-CoV, and SARS-CoV-2), while the four circulating seasonal coronavirus strains belong to alphacoronavirus (HCoV-NL63 and HCoV-229E) and betacoronavirus (HCoV-OC43 and HCoV-HKU1) genera. Among those betacoronavirus strains, HCoV-OC43 and HCoV-HKU1 belong to lineage A, SARS-CoV-2 and SARS-CoV to lineage B, whereas MERS-CoV groups with lineage C. Although generation of a pan-coronaviruses vaccine seems unlikely, owing to the high genetic diversity among different genera, it might be possible to develop a pan-betacoronavirus vaccine to prevent the potential risk from new subtypes identified in bats, pangolins, or other species [37]. Indeed, cross-reactivity between different

betacoronaviruses has been found in human samples. For example, a conserved CD4 T-cell epitope can mediate cross-reactive protection between SARS-CoV and MERS-CoV [38]. In addition, our recent study has revealed a conserved antibody epitope shared by SARS-CoV-2 and SARS-CoV [39]. These results indicate a potential roadmap for the development of universal vaccine against coronaviruses. Although it is not possible to predict, at this moment, the strain of the next coronavirus that will jump species, continuing exploration of the B-cell repertoire to identify cross-reactive epitopes will be important for the development of a coronavirus vaccine with high breadth of coverage.

Taken together, while therapeutic approaches for COVID-19 are urgently needed (reviewed in [40]) given the increasing number of active cases, the ultimate goal of establishing sterilizing immunity in uninfected individuals will require an SARS-CoV-2 vaccine. We are confident that the rapid and collaborative efforts among researchers around the globe will offer an effective countermeasure to COVID-19 in the near future.

Acknowledgments: We thank Profs. Roberto Bruzzone and Stanley Perlman for helpful discussions. This work was supported by National Institutes of Health (NIH) K99 AI139445 (N.C.W.), Calmette and Yersin scholarship from the Pasteur International Network Association (H.L.), Guangzhou Medical University High-level University Innovation Team Training Program (Guangzhou Medical University released [2017] No. 159) (C.K.P.M.), National Natural Science Foundation of China (NSFC)/Research Grants Council (RGC) Joint Research Scheme (N.HKU737/18) (C.K.P.M.).

Conflict of interest: The authors declare no financial or commercial conflict of interest.

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Abbreviations: ADE: antibody-dependent enhancement · FECV: feline enteric coronavirus · FIPV: feline infectious peritonitis virus · hACE2: human angiotensin-converting enzyme 2 · RBD: receptor-binding domain

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See accompanying article:
<https://doi.org/10.1002/eji.202048693>

The peer review history for this article is available at
<https://publons.com/publon/10.1002/eji.202048663>

Received: 15/4/2020
Revised: 10/5/2020
Accepted: 13/5/2020
Accepted article online: 21/5/2020