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Research Progress on a SARS-CoV-2 Vaccine in China

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Abstract

Although many countries have controlled the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) through strict management, there are still many countries with record-breaking numbers of new cases. Therefore, it is very important to develop a vaccine that can cause wide cross reactivity in clinical trials. At present, more than 90 vaccines are entering clinical trials and progressing smoothly, including inactivated vaccines, adenovirus-vectored vaccines and other types of vaccines. Here, we review and summarize the efficacy and potential threats of a SARS-CoV-2 vaccine. We reviewed whole-virus vaccines, adenovirus-subunit vaccines and recombinant protein vaccines and discussed the positive and negative consequences of a SARS-CoV-2 vaccine. However, there are still heated debates on the mechanism, effectiveness, and breadth of protection. In conclusion, this study can predict the risk of new coronavirus outbreaks in the future by discussing the research and development status of new coronavirus vaccines in China and other countries. Looking to the future, it is important to mine the large amount of data generated in clinical trials of universal new coronavirus vaccines to ensure that these vaccine programs are equally useful in the face of new coronavirus mutations.

Keywords

SARS-CoV-2, Whole-Virus Vaccines, Adenovirus-Subunit Vaccines, Recombinant Protein Vaccines

1. Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory contagion that was first reported as a cluster outbreak in Wuhan and is now spreading worldwide [1]

[2]. Although some studies have described some antiviral drugs and preventive methods, the virus is still spreading at an alarming rate [3] [4]. Even in places imposing strict lockdowns, there is a possibility of COVID-19 reappearing. Therefore, vaccines for SARS-CoV-2 appear to be a better choice than drugs for controlling the pandemic. In this article, we summarize the development of SARS-CoV-2 vaccines.

SARS-CoV-2 was reported to be the pathogen that causes COVID-19 [5] [6]. SARS-CoV-2, a member of coronaviruses that cause diseases such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), is a positive-sense, single-stranded RNA virus [7]. At present, about 120 million people have infected and 4 million people have been killed by SARS-CoV-2 worldwide.

2. Structure

Coronaviruses are so named due to their distinctive "corona" or crown-like appearance, which is caused by how spike (S) glycoproteins assemble on the virion surface. The subfamily of Orthocoronavirinae in the coronavirus family can be divided into four genera: α, β, γ and δ, which usually infect mammals (α and β) and birds (γ and δ). Coronaviruses are common human pathogens. Similar to SARS coronavirus (SARS-CoV), SARS-CoV-2 is considered as originated in bats and transmitted to other animals that were sold in the Wuhan animal market [8]. SARS-CoV-2 encodes a variety of structural proteins, including the spike protein, envelope protein, membrane protein and core-shel protein. In addition, there are as many as 16 types of nonstructural proteins (NSPs). NSPs are produced by the PP1a and PP1ab polyproteins, which are viral proteases encoded by replicases [9].

3. The Replication Cycle

The replication cycle of SARS-CoV-2 is similar as that of other coronaviruses. First, the virus attach to the surface protein receptor angiotensin-converting enzyme 2 (ACE2) of the host cell [10]. Then, the virus fuses or is endocytosed into the cell. After that, the virus release genome into the cytoplasm. Then, the positive-strand RNA is translated into the negative-strand RNA polymerase precursor protein. Later, RNA-dependent RNA polymerase is produced through a protein hydrolysis process. In addition, negative-strand RNA is generated by RNA polymerase with a positive strand as the template, and it is also used to synthesize subgenomic mRNAs [11]. The translation of subgenomic mRNAs produces structural proteins of viruses, and finally, viral membrane proteins assemble in the endoplasmic reticulum (ER) and form vesicles with RNA [12]. However, some mechanisms, such as the function of NSPs in the replication cycle, need to be further studied.

4. Vaccines

At present, SARS-CoV-2 vaccines mainly include whole-virus vaccines, adeno-

virus-subunit vaccines, nucleic acid vaccines and recombinant protein vaccines. Here, we mainly discuss vaccines that have entered clinical trials in China.

4.1. Whole-Virus Vaccines

Whole-virus vaccines are not only the most traditional vaccine preparation method but also the most mature vaccine preparation method at present. In short, by injecting artificially inactivated pathogenic microorganisms into the body, the human body generates antibodies against antigens through recognition. Once it is invaded by viruses, it stimulates the immune system to produce immune substances (such as antibodies) to resist the invasion of viruses. At present, at least five types of SARS-CoV-2-inactivated vaccines have been approved for phase III clinical trials in China [13] [14] [15] [16] [17]. The companies that developed these vaccines are Sinopharm (Wuhan) inactivated (Vero Cells), Sinovac PiCoVacc (CoronaVac), BBIBP-CorV (Vero Cells), KCONVAC (Vero Cells), CanSino.

4.1.1. Sinopharm (Wuhan) Inactivated Vaccine (Vero Cells)

Sinopharm (Wuhan) inactivated vaccine (Vero Cells) was developed by the Wuhan Institute of Biological Products affiliated with Sinopharm. As the world's first inactivated SARS-CoV-2 vaccine, it has received extensive attention [18].

At the beginning of February 2020, the Institute of Biology of Medical College began to isolate and screen viruses. In March 2020, the pathogenic mechanism and immunology of SARS-CoV-2 infection were studied, and the key production process system and quality control standard system of vaccines were established [19]. It was approved for clinical trials on April 12, 2020 [18]. On May 13, 2020, the Institute of Biology of Medical College received an approval document issued by the State Drug Administration to begin clinical experiments for a phase I and phase II clinical trial. On May 15, the phase I clinical trial was officially launched. Nearly 200 healthy adults were enrolled. After 5 months, the phase I clinical trial was successfully completed. After that, phase II clinical trial was officially launched on June 20, 2020 to further evaluate the immunogenicity and safety of the vaccine and determine the immunization plan and dose [18].

As the first clinical safety and efficacy data after collecting two doses of the vaccine, the phase III clinical trial of the candidate vaccine has been taken on June 23, 2020. It may provide scientific and valuable data for epidemic prevention and emergency use. On May 26, 2021, the researchers published the phase III clinical data of the vaccine. Of these, 13,459 adults received the vaccine in the United Arab Emirates and Bahrain. Before enrollment, the PCR test results of participants were negative. However, the inactivated vaccine can produce a high titer antibody 14 days after two injections to form effective protection. The results showed that the geometric mean titer of participants at baseline was 2.3 (similar to the control group). After 14 days of two doses of vaccination, the geometric mean titer of the experimental group was 94.5 (95% confidence interval (CI), 89.7 - 99.5), and the positive conversion rate of neutralizing antibody in

the whole population was more than 99%. During the follow-up, 26 participants in the experimental group got the positive result in the SARS-CoV-2 test. The vaccine efficacy was 72.8% compared with that of aluminum adjuvant alone. Within 7 days after injection, the most common adverse reactions reported were local pain and headache [19].

At present, the global COVID-19 epidemic situation is still severe, and effective SARS-CoV-2 vaccines are needed to control respiratory contagion and limit the spread and recurrence of the disease [20]. The production process of inactivated vaccines is simple, well-established, and stable, and inactivated vaccines are easy to transport and use in cases of outbreaks or emergencies. At present, many kinds of SARS-CoV-2-inactivated vaccines have entered the clinical research stage in China, and the overall research and development (R & D) progress has been smooth [13] [14] [15] [16] [17]. However, safety and efficacy are still the focus of vaccine research. The potential safety problems of the COVID-19 inactivated vaccine should be given more attention because of the antibody-dependent enhancement observed in research on SARS-CoV and MERS-CoV vaccines [21] [22]. In addition, the efficacy and duration of primary immunization with the vaccine still need to be further examined.

4.1.2. PiCoVacc (CoronaVac)

PiCoVacc is a candidate vaccine developed by Sinovac Biotech and is based on the CN2 strain, which was selected from 11 strains of SARS-CoV-2. The vaccine was made by propagating the virus strain in Vero cells and inactivating it with β-propiolactone after harvesting cells. By using macaques to imitate SARS-CoV-2 infection, the data showed that 6 μg PiCoVacc completely defended against SARS-CoV-2 infection [10].

Moreover, positive preliminary results were announced on June 13, 2020, for phase I and phase II clinical trials of the vaccine candidate. The results showed good immunogenicity and safety profiles (http://www.sinovac.com) [10]. A total of 743 health volunteers participated in the phase I or phase II trial. It was reported that 143 volunteers were enerolled in phase I clinical trial and 600 volunteers were enerolled in phase II clinical trial. There were no serious adverse events were reported in either phase I clinical trial or phase II clinical trial. The results of a phase II clinical trial showed that neutralizing antibodies could be strongly induced 14 days after vaccination. The seroconversion rates of neutralizing antibodies were more than 90% (in the 0- and 14th-day groups) and 97.4% (in the 0- and 28th-day groups), indicating that the candidate vaccine can induce a good immune response.

Phase III clinical trials were conducted in Turkey. Adult volunteers (aged 18 - 59 years) were recruited. Participants received intramuscular vaccine or placebo (control group) on days 0 and 14. The results showed that the vaccine group reported more frequent events than the control group, including fatigue, myalgia, chills, and nausea. During the 43-day follow-up, the vaccine group 9 volunteers infected COVID-19. Meanwhile, 32 cases were reported in the control group.

After the second vaccination, the vaccine efficacy against SARS-CoV-2 was 83.5% (95% CI, 65.4 - 92.1). A total of 89.7% of vaccine recipients were seropositive for receptor-binding domain (RBD) antibodies [23].

The report showed that the overall efficacy of the vaccine on symptomatic COVID-19 was 50.7% (95% CI, 36.0 - 62.0) after the second administration; however, the efficacy in moderate and severe cases was 100%. The results showed that the vaccine had good efficacy in severe cases (*i.e.*, hospitalization) and had good safety in people aged 18 - 59 years [23].

4.1.3. BBIBP-CorV

BBIBP-CorV is a candidate vaccine developed by the Beijing Institute of Biological Products that was examined in clinical trials. The vaccine induced high levels of neutralizing antibody titers in many kinds of model animals to provide protection against SARS-CoV-2 [24]. Two doses of BBIBP-CorV at 2 μg/dose effectively protected rhesus macaques from intratracheal infection with SARS-CoV-2, and there was no detectable enhancement of antibody-dependent infection [24] [25] [26].

Phase I clinical trials are mainly to determine the optimal vaccination dose. Among them, 600 adults participated in the experiment, including 192 in the experimental group. They were divided into 18 - 59-year-old and 60 - 80-year-old groups. Before enrollment, the PCR test results of participants were negative. To evaluate the safety doses of the vaccine, different doses of vaccine (2 μg, 4 μg, and 8 μg) or placebo (control group) were inoculated on days 0 and 28 of the trial, respectively [24].

The study showed that on the 28th day after vaccination, antibody reactions appeared in all vaccinated subjects in the 18- to 59-year-old group. The immune response and the antibody level of vaccinators aged 60 and over was slightly lower, but they also had an antibody response on the 42nd day. There was no corresponding antibody reaction in the control group. In the phase I trial, within 7 days after vaccination, the most common side effects were local pain and fever. In the phase I clinical trial, the geometric mean titer (GMT) of neutralizing antibodies in the low dose group (316) were higher than medium dose group(206) and high dose group (297) on the 14th day after three injections. Seroconversion was observed in all participants receiving the vaccine (100%) in the low dose group and high dose group. In the medium dose group, 23 of the 24 participants (95.8%) had seroconversion but not in the control group [25].

A phase II clinical trial aimed to determine the best vaccination time. A total of 448 subjects aged 18 - 59 participated in the experiment. Before the time of enrollment, the PCR test results of participants were negative. The vaccination plan of this study was as follows: participants were randomly divided into 2 groups (two weeks group and three weeks group) using 5 μg dose vaccines.

It is reported that the vaccine safety was well guaranteed and well tolerated at all test doses. The results of the phase II clinical trial were similar to those of the phase I clinical trial. Twenty-three percent of vaccinators reported adverse reac-

tion within 7 days after vaccination, and all other adverse reactions were mild or moderate. In the phase II clinical trial, with a medium dose, the GMT of the injection group (days 0 and 14) was 121 (95% CI, 95 - 154), and the GMT of the injection group (days 0 and 21) was 247 (95% CI, 176 - 345). Serum transformation was observed in participants injected on days 0 and 21. In the group injected on days 0 and 14, the serum transformation rate was 85.7% (36/42), while there was no serum transformation in the control group [25].

Recently, researchers published phase III clinical trial data on the vaccine. A total of 13465 adults received vaccines in the United Arab Emirates and Bahrain. The PCR test result was negative when the participants were enrolled in the group. The results showed that the vaccine could produce a high titer antibody. Moreover, the geometric average titer of the participants at baseline was 2.3 (similar to the control group). The geometric average titer of the experimental group was 156.0 (95% CI, 149.6 - 162.7) 14 days after the completion of two doses of vaccination. The positive seroconversion rate of neutralizing antibodies in the whole population was more than 99%. During the follow-up, symptomatic COVID-19 was found in 21 participants in the experimental group. The efficacy of the vaccine was 78.1% compared with that of aluminum adjuvant alone. Within 7 days after injection, the most common adverse reaction was local pain and headache [13].

The advantage of the BBIBP-CorV vaccine is that it can induce a better antibody response in elderly individuals aged 60 and above. Protecting the elderly is one of the important goals of the BBIBP-CorV vaccine. Due to the decline of immune system function in the elderly, the effect of the vaccine is usually affected. Once the elderly are infected with COVID-19, they face a greater risk of severe disease.

4.1.4. KCONVAC

KCONVAC is a candidate vaccine developed by Shenzhen Kangtai Biological Products and Beijing Minhai Biotechnology [26]. The virus (19ncov-cdc-tan-strain03) was cultured in Vero cells, inactivated by β-propionolactone, purified, and adsorbed on aluminum hydroxide. It was reported that there were no serious adverse reactions above grade 3 in phase I and phase II clinical trials, which showed no significant difference in the overall adverse reaction rate compared with the placebo group [26].

In phase I clinical trials, both the 5 μg vaccine (low dose group) and 10 μg vaccine (low dose group) induced a strong immune response in healthy adults. It has been reported that before vaccination, participants were negative for all types of specific antibodies. However, after vaccination, 88% - 100% of the participants in the clinical phase I experiment underwent seroconversion for different types of antibodies. In addition, phase II clinical trials showed similar results. On the 14th or 28th day after vaccine injection, 83% - 100% of participants had undergone seroconversion for different types of antibodies. There was a significant difference between the placebo group and the experimental group [26].

4.2. Adenovirus Subunit Vaccines

Adenovirus subunit vaccine refers to a vaccine made of recombinant adenovirus that can express antigen genes by recombining antigen genes into the adenovirus genome with adenovirus as a vector. The S protein on the surface of coronaviruses has a trimer conformation, which is responsible for binding host cell receptors and mediating viral invasion. Therefore, the S protein is the main protective immunogen of coronaviruses that can be used in adenovirus subunit vaccines. There is an RBD on the S protein that is directly responsible for docking with the host receptor. It stimulates the production of neutralizing antibodies and blocks the binding of viruses to receptors. At present, at least two types of SARS-CoV-2-inactivated vaccines have been approved for phase III clinical trials in China [27]-[34]. The companies that developed these vaccines are Ad5-nCoV, Anhui Zhifei Longcom: Ad5-nCoVZF2001.

4.2.1. Ad5-nCoV

The Chen Wei team published the data of a phase I clinical trial of an adenovirus type-5 (Ad5)-vectored spike protein of SARS-CoV-2 vaccine (Ad5-nCoV) online on May 22, 2020. Its safety, tolerability and immunogenicity were tested. Healthy subjects aged 18 - 60 were enrolled in the phase I clinical trial and assigned to the low-dose group (5×10^{10} virus particles (VPs), medium-dose group (1×10^{11} VPs) and high-dose group (1.5×10^{11} VPs). The results showed that the Ad5-nCoV vaccine safety was guaranteed and it was tolerable in healthy subjects in the three dose groups. The most common adverse reactions included fever and fatigue. In addition, RBD-specific binding antibody responses were observed on day 14 in all three dose groups. On day 28, the high-dose group had a higher GMT (1445.8), compared with the medium-dose group and low-dose group (806.0 and 615.8), respectively. Moreover, a 4-fold increase in anti-RBD antibodies was observed in 100%, 94% and 97% of subjects in the high-, medium- and low-dose groups, respectively. The neutralizing antibody was negative before inoculation but increased steadily on the 14th day after inoculation and finally reached a peak on the 28th day. The neutralizing antibody GMT 34.0 in the high-dose group was much higher than 16.2 and 14.5 in the medium- and low-dose groups, respectively. At the same time, at least a 4-fold increase in neutralizing antibody titer was observed in 75%, 50% and 50% of subjects in the high-, medium- and low-dose groups on day 28. On the 14th and 28th days after inoculation, INFγ was detected in CD4+ and CD8+ T cells in all subjects. TNFα was expressed in CD4+ T cells of the low-dose group on the 14th day after inoculation. It was significantly lower than that of high dose group and medium dose group, and CD8 + T cells in high-dose group had higher TNFα than that in medium dose group and low dose group [35].

A phase II clinical trial was used to guarantee the immunogenicity and safety of vaccines and aims to determine the dose of vaccines for efficacy studies. A total of 508 participants, healthy adults aged 18 years or older, had no previous SARS-CoV-2 infection and were randomly assigned to receive a high dose (1 ×

10^{11} VPs) and low dose (5×10^{10} VPs) or placebo. The primary endpoints of immunogenicity were GMT and neutralizing antibody response to RBD-specific ELISA antibody on day 28 [36].

The results showed that 24 (9%) participants in the high-dose group and 1 (1%) participant in the low-dose group reported serious adverse reactions. It suggests that high doses of vaccine are associated with an increased risk of serious adverse reactions. In the high-dose and low-dose groups, the highest peak of RBD-specific antibodies were 656.5 (95% CI 575.2 - 749.2) and 571.0 (467.6 - 697.3) on day 28, respectively, and the serum conversion rates were nearly the same (96%). Both doses of vaccine could induce a significant neutralizing antibody response to SARS-CoV-2. Among the subjects treated with one dose of vaccine, the GMTs of the high-dose group and low-dose group were 19.5 (16.8 - 22.7) and 18.3 (14.4 - 23.3), respectively. In the high-dose group, 90% of participants observed specific IFNγ enzyme-linked immunospot assay responses. In the low-dose group, 88% of participants observed specific IFNγ enzyme-linked immunospot assay responses.

Recently, the Chengwei research group designed a vaccine in aerosol inhalation dosage form and evaluated the safety and immunity of the vaccine through a clinical phase 1 experiment. In this study, 130 participants, healthy adults aged 18 or over, who had no previous SARS-CoV-2 infection, were randomly assigned to receive five experimental groups or placebo. The experimental group was designed as follows: HD group (two doses of aerosolized Ad5 ncov with 2×10^{10} VPs); LD group (two doses of aerosolized Ad5-nCoV with 1×10^{10} VPs); MIX group (an intramuscular vaccination and aerosolized booster vaccination); 1D group (one dose of aerosolized Ad5-nCoV with 5×10^{10} VPs); 2D group (two doses of aerosolized Ad5-nCoV with 5×10^{10} VPs). The results showed that the most common adverse events included fever, fatigue and headache. No serious adverse events were found. Twenty-eight days after the last vaccination, the GMT of SARS-CoV-2 neutralizing antibody was 107 (95% CI, 47 - 245) in the HD group, 105 (47 - 232) in the LD group, 396 (207 - 758) in the MIX group, 95 (61 - 147) in the 1D group and 180 (113 - 288) in the 2D group. The GMT of RBD binding IgG were 261 EU/ml (95% CI, 121 - 563) in HD group, 289 EU/ml (138 - 606) in LD group, 2013 EU/ml (1180 - 3435) in MIX group, 915 EU/ml (588 - 1423) in 1D group and 1190 EU/ml (776 - 1824) in 2D group. In addition, the MIX group induced strong IgG and neutralizing antibody responses compared with the other groups [37].

This study is the first published clinical study on mucosal immunity of a new crown vaccine in the world. Its advantage is that compared with the commonly used intramuscular injection dosage form, the atomized inhalation dosage form does not need injection, can eliminate local adverse reactions, and has better safety and convenience. In addition, aerosol inhalation can stimulate the mucosal immune response and provide additional protection in respiratory mucosal tissue. B cells and T cells distributed in the respiratory mucosa encounter pathogens earlier than systemic memory cells, which can inhibit virus replication

and reduce virus transmission faster. It also provides valuable experience for the follow-up of noninjectable new crown vaccines and other vaccines under development with adenovirus vectors.

4.2.2. Recombinant Protein Vaccines

Recombinant protein vaccines involve the expression and purification of pathogen antigen protein in engineered cells by genetic engineering and then the preparation of the vaccine [38] [39] [40]. The S protein on the surface of coronaviruses has a trimer conformation, which is responsible for binding receptors of the host cell and mediating viral invasion. Therefore, the S protein is the main protective immunogen of coronaviruses. There is an RBD on the S protein that is directly responsible for docking with the host receptor. It stimulates the production of neutralizing antibodies and blocks the binding of viruses to receptors. In this study, to overcome the limitations of the small molecular weight and limited immunogenicity of the RBD, a research team constructed a series of repeated RBD single-chain dimers (RBD SC dimers). The expressed form of the tandem repeat SC dimer is uniform and does not contain foreign sequences, so vaccine efficacy can be maintained or even improved. Phase 1 and phase II trials were conducted to evaluate the zf2001 vaccine safety and immunogenicity. The dose and efficacy studies were also needed.

In a phase I clinical trial, 50 participants (18 - 59 years old) received a vaccine in China. Participants were divided into 3 groups: 3 dose of high-dose group (50 μg vaccine), 3 dose of low dose group (20 μg vaccine) and 3 dose of placebo. The results showed that in most cases, the adverse events reported were mild or moderate (grade 1 or 2). Ten percent of grade 3 or more adverse events were reported in only the high-dose vaccine. To evaluate the T cell response, IFNγ, IL-2, IL-4 and IL-5 were analyzed to determine Th1 and Th2 cell responses. The results showed that both 25 μg and 50 μg vaccines could induce Th1 (IFNγ and IL-2) and Th2 (IL-4 and IL-5) cytokine production.

In the phase II clinical trial, 900 participants (18 - 59 years old) received a vaccine in China. Participants were divided into 6 groups: 3 dose groups (high-dose group, low dose group and placebo group) and 2 dose groups (high-dose group, low dose group and placebo group). Similar to phase I clinical trials, in most cases of phase II clinical trials, adverse events reported were mild or moderate (grade 1 or 2). Eighteen participants reported grade 3 or more serious adverse events. To neutralize the antibody titer against SARS-CoV-2, the serum conversion rate and GMT were analyzed. For participants in the two-dose plan, the seroconversion rates of the low-dose group and high-dose group were 76% and 72%, 14 days after the second vaccine. For participants in the three-dose plan, 14 days after the second administration, the seroconversion rates of the low-dose group and high-dose group were 83% and 73%, respectively. Fourteen days after the third administration, the seroconversion rates of the low-dose group and high-dose group were 97% and 93%, respectively.

For participants in the 2-dose plan (14 days after the second vaccine), the

neutralization GMTs of participants in the low-dose group and high-dose group were 17.7 (95% CI, 13.6 - 23.1) and 14.1 (10.8 - 18.3), respectively. For participants in the 3-dose plan (14 days after the second vaccine), the neutralization GMTs of participants in the low-dose group and high-dose group were 19.5 (95% CI, 15.2 - 25.0) and 12.6 (10.0 - 16.0), respectively. For participants in the 3-dose plan (14 days after the third vaccine), the neutralization GMTs of participants in the low-dose group and high-dose group were 102.5 (81.8 - 128.5) and 69.1 (53.0 - 90.0), respectively [41].

5. Conclusion

There are at least six candidate vaccines, including whole-virus vaccines, adenovirus subunit vaccines and recombinant protein subunit vaccines, that have been used as preventive vaccines against COVID-19. However, in recent years, a variety of coronaviruses have caused major outbreaks, including SARS, MERS and COVID-19. Therefore, the development and storage of coronavirus vaccines and the identification of international financing mechanisms to support their development, manufacture and storage are top priorities for global security. At present, the Gao Fu research group has developed a general vaccine strategy for β-coronavirus infectious diseases, including MERS, COVID-19, and SARS. Vaccines against β-coronaviruses may play an important role in preventing the spread of other newly discovered coronaviruses in the next few years. Moreover, the popularity of COVID-19 indicates that there is an urgent need to develop optimized vaccines for pregnant women and their newborns, as these two populations are at risk of developing serious diseases. Some other countries have distributed the vaccine to high-risk groups, including pregnant women and lactating people, which may provide an opportunity for us to further understand the vaccine-induced immunity of these groups.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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