

Coronavirus disease 2019 vaccines: landscape of global studies and potential risks

Hu-Da-Chuan Jiang¹, Yan-Yang Tao¹, Si-Yue Jia², Jing-Xin Li², Feng-Cai Zhu^{1,2,3}

¹School of Public Health, Southeast University, Nanjing, Jiangsu 210009, China;

²NHC Key Laboratory of Enteric Pathogenic Microbiology, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, Jiangsu 210009, China;

³Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 210009, China.

Abstract

With the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, the importance of vaccines in epidemic prevention and public health has become even more obvious than ever. However, the emergence of multiple severe acute respiratory syndrome coronavirus 2 variants worldwide has raised concerns about the effectiveness of current COVID-19 vaccines. Here, we review the characteristics of COVID-19 vaccine candidates in five platforms and the latest clinical trial results of them. In addition, we further discuss future directions for the research and development of the next generation of COVID-19 vaccines. We also summarize the serious adverse events reported recently after the large-scale vaccination with the current COVID-19 vaccines, including the thromboembolism caused by the AstraZeneca and Johnson & Johnson vaccines.

Keywords: Severe acute respiratory syndrome coronavirus 2; COVID-19; Vaccine; Immunogenicity; Safety; Clinical trial

Introduction

Following severe acute respiratory syndrome coronavirus (SARS-CoV), which caused an outbreak in 2002, and Middle East respiratory syndrome coronavirus, which caused an outbreak in 2012, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third highly pathogenic coronavirus that has emerged in humans over the past 20 years.^[1] Since the whole genome sequence of SARS-CoV-2 was released by Chinese scientists on January 11, 2020, there has been an upsurge in the research and development of vaccines against coronavirus disease 2019 (COVID-19) worldwide. The World Health Organization (WHO) reported that there are currently >270 COVID-19 vaccines/vaccine candidates, including protein subunit vaccines, viral vector vaccines, inactivated vaccines, DNA or RNA vaccines, virus-like particles vaccines, and live-attenuated vaccines; of which, approximately 90 have been approved for the use in clinical trials.^[2] Till date, 14 COVID-19 vaccines have been approved for marketing or emergency use authorization.^[3] In China, five COVID-19 vaccines have been conditionally approved for marketing or emergency authorization for use by the government, including vaccines based on inactivated SARS-CoV-2 (produced by National Vaccine & Serum Institute (Beijing Institute of Biological Products

[CNVSI Beijing] and Wuhan Institute of Biological Products [CNVSI Wuhan]), and SINOVAC Biotech, Co., Ltd., China), recombinant SARS-CoV-2 using an Ad5 adenoviral vector (produced by CanSino Biologics, Inc., Tianjin, China), and recombinant SARS-CoV-2 using Chinese hamster ovary (CHO) cells (produced by Anhui Zhifei Longcom Biopharmaceutical, Anhui, China).^[4-8] With the approval of a variety of COVID-19 vaccines for marketing or emergency use, concern has shifted to the safety of their use in large-scale vaccination.^[9]

Here, we aimed to review the research progress regarding the main currently available COVID-19 vaccines [Table 1] and to analyze the safety events that have occurred after large-scale vaccination to provide a scientific basis for the subsequent development and use of COVID-19 vaccines.

Nucleic acid vaccines

The main component of COVID-19 nucleic acid vaccines is a nucleic acid (RNA or DNA) expressing the target antigen

Correspondence to: Feng-Cai Zhu, School of Public Health, Southeast University, Nanjing, Jiangsu 210009, China; NHC Key Laboratory of Enteric Pathogenic Microbiology, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, Jiangsu 210009, China; Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 210009, China
E-Mail: jszfc@vip.sina.com
Jing-Xin Li, NHC Key Laboratory of Enteric Pathogenic Microbiology, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, Jiangsu 210009, China
E-Mail: jingxin42102209@126.com

Copyright © 2021 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2021;134(17)

Received: 06-05-2021 Edited by: Jing Ni

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000001688

Table 1: An overview of the different platforms and their current status of the main currently available COVID-19 vaccines.

Vaccine platform	Developer/manufacturer	Name of vaccine	Immunization schedule	Vaccine efficacy	Number of COVID-19 cases
Nucleic acid vaccine	Pfizer, Inc. and BioNTech SE	BNT162b2	Days 0, 21	95.0%	170 (eight in vaccine group)
	Moderna, Inc	mRNA-1273	Days 0, 28	94.0%	196 (11 in vaccine group)
	Inovio Pharmaceuticals	INO-4800	Days 0, 28	–	–
Viral vector vaccine	Institute of Biological Engineering, Academy of Military Medical Sciences, and CanSino Biologics Inc.	Ad5-nCoV	Day 0	68.8%	101
	Johnson & Johnson	Ad26.COVS.2.S	Day 0	66.0%	464 (116 in vaccine group)
	AstraZeneca/University of Oxford	AZD1222	Days 0, 28	62.1% (two standard doses); 90.0% (low + standard doses)	131 (30 in vaccine group)
	Gamaleya Research Institute/Health Ministry of the Russian Federation	Sputnik V	Days 0, 21	91.4%	78 (16 in vaccine group)
Inactivated vaccine	SINOVAC Biotech Co., Ltd., China	CoronaVac	Days 0, 14 or 28	91.3% (in Turkey); 50.4% (in Brazil)	29 (three in vaccine group)
	Sinopharm, Beijing Institute of Biological Products	BBIBP-CoV	Days 0, 21	78.1%	116 (21 in vaccine group)
	Sinopharm, Wuhan Institute of Biological Products	WIBP-CoV	Days 0, 21	72.5%	121 (26 in vaccine group)
Subunit protein vaccine	Bharat Biotech, Ltd.	COVAXIN	Days 0, 28	81.0%	130
	Novavax	NVX-CoV2373	Days 0, 21	89.3%	62 (six in vaccine group)
	Clover Biopharmaceuticals	SCB-2019	Days 0, 21	–	–
	Anhui Zhifei Longcom Biopharmaceutical	ZF2001	Days 0, 28, 56	–	–

Ad26.COVS.2.S: Ad26 adenovirus-vectored vaccine; COVID-19: Coronavirus disease 2019.

component of SARS-CoV-2 in a vector, such that the effective antigen (eg, S protein) of the virus is manufactured *in vivo* instead of being manufactured *in vitro* before its injection into the body. Two major advantages of nucleic acid vaccines are that they are easy and fast to prepare and they can induce high levels of specific antibodies. However, mRNA can cause acute adverse reactions, and these types of vaccines require colder temperatures for preservation, usually below -70°C . Before the research and development of COVID-19 vaccines, no nucleic acid vaccines had been approved for marketing in China or elsewhere.

Three main available nucleic acid COVID-19 vaccines are as follows: BNT162b2 developed by Pfizer, Inc. (New York, USA), and BioNTech SE (Mainz, Germany), the mRNA-1273 vaccine developed by Moderna, Inc. (Cambridge, USA), and the INO-4800 DNA vaccine developed by Inovio Pharmaceuticals (Plymouth Meeting, USA). The

interim data from phase 3 clinical trials have been announced for both the mRNA vaccines, and the efficacy of them were $>90\%$. Their immunization schedules both require two injections, administered at intervals of 21 days (BNT162b2) or 28 days (mRNA-1273). Regarding BNT162b2, the results of a phase 3 clinical study conducted in over 40,000 people in 152 regions worldwide showed that the most common local adverse reaction in vaccinated subjects was pain at the injection site, and the most common systemic adverse reactions were headache and fatigue. Most of the adverse reactions were mild to moderate in severity, and the vaccine was 95.0% effective for preventing COVID-19 in people aged >16 years old.^[10] Similar to BNT162b2, the mRNA-1273 vaccine was also found in a phase 3 clinical trial, conducted in approximately 30,000 people in 99 regions of the United States, to cause pain at the injection site as the most common adverse reaction to vaccination and have an

efficacy of 94.0% against COVID-19.^[11] Additionally, BNT162b1 and BNT162b2, jointly developed in China and licensed by BioNTech and Fosun Pharma (Shanghai, China), were also found to have good safety and produce high specific antibody levels. BNT162b2 was approved for emergency use authorization in Hong Kong of China and Macau of China at the beginning of this year.

Viral vector vaccines

COVID-19 viral vector vaccines use a genetic technology to deliver genes expressing antigen proteins (eg, SARS-CoV-2 S protein) to adenoviruses, and the resulting viruses produce SARS-CoV-2 antigen proteins in infected cells. The production of viral vector vaccines has well-established processes that are relatively inexpensive. This vaccine type sometimes causes acute adverse reactions, and a vaccine recipient's existing antibodies against adenovirus can interfere with the vaccine function.

The four main available adenovirus-vectored COVID-19 vaccines are the Chinese Ad5-vectored vaccine jointly developed by the Institute of Biological Engineering, Academy of Military Medical Sciences, and CanSino Biologics Inc., the chimpanzee adenovirus-vectored vaccine (AZD1222) jointly developed by AstraZeneca (London, UK)/University of Oxford (UK), the Russian Ad26/Ad5 adenovirus-vectored vaccine (Gamaleya Research Institute, Moscow, Russia), and the Ad26 adenovirus-vectored vaccine (Ad26.COV2.S) developed by Johnson & Johnson (New Brunswick, USA). The results of interim analyses of phase 3 clinical trials for these four vaccines have been published, and both the chimpanzee adenovirus-vectored vaccine and the Ad26/Ad5 adenovirus-vectored vaccine have a protective efficacy of >90%. The Chinese Ad5 adenovirus-vectored vaccine and the Johnson & Johnson Ad26.COV2.S can each induce a protective efficacy of >60% with a single-dose immunization strategy, which meets the WHO's requirement for useful COVID-19 vaccines of a protective efficacy of >50%. Consequently, all four of these vaccines have obtained conditional marketing or emergency use authorization. In addition, a recombinant COVID-19 vaccine (adenovirus type 5 vector) for inhalation, developed in cooperation with the Institute of Biological Engineering, Academy of Military Sciences and CanSino Biologics, Inc., has been recently approved for the clinical trial by the National Medical Products Administration (NMPA) on March 22, 2021. Compared with the humoral and cellular immunity formed by the intramuscular injection of COVID-19 vaccines, a vaccine administered by inhale injection can also form mucosal immunity, which will be the most ideal state of this triple immunity.

Preliminary efficacy studies of the AZD1222 vaccine in the United Kingdom and Brazil showed that the protective efficacy of two standard doses was 62.1%, whereas the efficacy achieved by administering an initial injection of low-dose vaccine followed by a second injection of standard-dose vaccine could reach 90.0%. Importantly, the overall safety of this vaccine, regardless of the dosing regimen, was good. However, the transverse myelitis was observed in one participant at 14 days after the booster

vaccination which was considered to be related to the vaccination by the study investigators.^[12]

A randomized, double-blind, placebo-controlled phase 3 clinical trial of the Ad26/Ad5 adenovirus-vectored vaccine in Russia (Gamaleya Research Institute) found that its protective efficacy against COVID-19 was 91.4% and that most of the reported adverse reactions were mild, with any serious treatment-emergent adverse events unrelated to vaccination.^[13]

The interim analysis of a phase 3 clinical trial of Johnson & Johnson's Ad26.COV2.S vaccine revealed that a single-dose vaccination was well tolerated in adults aged ≥18 years and that its overall efficacy was 66%. At 28 days post-vaccination, the protective efficacy of Ad26.COV2.S for preventing severe cases of COVID-19 was 85%.^[14]

The CanSino Ad5-vectored vaccine is the only COVID-19 vaccine approved for use in China that uses a single-dose immunization schedule. The data from an interim analysis of its phase 3 clinical trial show that the overall efficacy of the Ad5-nCoV vaccine for preventing COVID-19 at 28 days post-vaccination was 68.8%, but its protective efficacy for preventing serious disease was 90.1%, and that no serious adverse events related to the vaccine were observed during the study period.^[15]

Inactivated virus vaccines

Inactivated virus vaccines are made from viruses that have lost their infectivity and pathogenicity following the application of physical or chemical processes but have retained the complete viral structure and consequently have antigenicity recognizable by the immune system. Because inactivated vaccines have been used for a long time, the research and development technologies for making this type of vaccine are well-established, and these vaccines have the advantages of a mature industrial technology platform, good stability, and high safety. However, the major disadvantage of inactivated vaccines is their weak immunogenicity; they generally either fail to induce a cellular immune response or induce a very weak one. Consequently, an immunization schedule of two or even three injections is usually required, or adjuvants are added to the vaccine components to enhance the vaccine immunogenicity.

Till date, only China and India have applied the technology platform of inactivated vaccines to the development of COVID-19 vaccines. In China, three COVID-19 vaccines were developed by SINOVAC Biotech, Beijing Institute of Biological Products Co., Ltd., and Wuhan Institute of Biological Products Co., Ltd., respectively, all of which use aluminum adjuvants to enhance their immune effect. They have all obtained emergency use authorization or conditional marketing in China as well as in some other countries. The inactivated vaccines produced in India have also obtained local emergency use authorization.

The results of phase 3 clinical trials show that the protective efficacy of each of the three inactivated COVID-19 vaccines in China is >50%, using two-dose immunization schedules with an interval of 14 or 21 days. The phase

3 clinical trials of the inactivated COVID-19 vaccine (CoronaVac) developed by SINOVAC were conducted in Brazil and Turkey in July 2020. The interim efficacy results show that the vaccine had a protective efficacy of 50.4% for COVID-19 in people aged ≥ 18 years. The most common adverse reactions included pain at the injection site, headache, and fatigue; and no serious adverse events related to the vaccines occurred during the study period.^[5,16] Additionally, in a serum cross-neutralization test of 12 prevalent SARS-CoV-2 strains conducted in 80 subjects before and after immunization in China and elsewhere, the neutralizing antibodies induced after vaccination could effectively neutralize different SARS-CoV-2 strains (including the D614G mutant strain), and the positive antibody conversion rate was $\geq 80.0\%$. In contrast, a phase 1/2 clinical study of CoronaVac conducted in 550 children aged 3 to 17 years who were vaccinated on the immunization schedule of days 0 and 28 found that at 28 days after the second vaccine dose, the adverse reaction rates in the low-dose, middle-dose, and placebo groups were 25.6%, 29.0%, and 23.7%, respectively, while the positive SARS-CoV-2 neutralizing antibody conversion rates in the low-dose and middle-dose groups were 96.8% and 100.0%, respectively. The induced levels of SARS-CoV-2 neutralizing antibodies were significantly higher in juveniles than in adults or the older adults, suggesting the strong immunogenicity of this vaccine in children and adolescents.^[16] Since the safety and immunogenicity of CoronaVac in children 3 to 17 years of age and adults ≥ 18 years of age are comparable, NMPA has recently approved the emergency use of CoronaVac in individuals ≥ 3 years of age. Besides, because the benefits of using SINOVAC's inactivated COVID-19 vaccine are greater than the known risks, CoronaVac was approved for emergency use under the WHO Emergency Use Listing procedure on June 2, 2021.^[17]

The phase 3 clinical trial of the COVID-19 inactivated virus vaccine developed by CNVSI Beijing, conducted in United Arab Emirates, revealed that high levels of SARS-CoV-2 neutralizing antibodies were produced after the administration of two vaccine doses, with a positive antibody conversion rate of up to 99.5%, and that the efficacy of preventing COVID-19 infection was 78.1%, with good safety.^[6] Similarly, the mid-term analysis data of the phase 3 clinical study of the COVID-19 inactivated virus vaccine produced by CNVSI Wuhan found that the positive SARS-CoV-2 neutralizing antibody conversion rate after two-dose vaccination was 99.1%, and the overall protective efficacy of the candidate vaccine was 72.5%.^[18]

In the phase 3 clinical trial of the COVID-19 inactivated virus vaccine COVAXIN independently developed by Bharat Biotech Ltd. (Andhra Pradesh, India), about 25,800 subjects were vaccinated on the immunization schedule of days 0 and 28; the results indicate that the protective efficacy of a two-dose vaccination with COVAXIN is 81.0% in people aged ≥ 18 years.^[19]

Subunit protein vaccines

Subunit protein vaccines are prepared by culturing an antigenic protein (eg, SARS-CoV-2 S protein) from a

pathogen, which can be achieved in various ways, and then purifying it. Protein vaccines have the advantages of high purity and ease of large-scale production. Because this type of vaccine contains only the target antigenic protein of the pathogen, rather than the entire pathogen, it is safer than those that contain the entire pathogen. However, adjuvants are generally required to produce a good immune effect, and the immune memory effect can be weak. Therefore, their immunizations schedules usually required two or three doses.

Three representative protein vaccines for COVID-19 are NVX-CoV2373 (adjuvant: matrix) developed by Novavax (Gaithersburg, USA), SCB-2019 (adjuvant: CpG/alum) developed by Clover Biopharmaceuticals (Chengdu, China), and ZF2001 (adjuvant: aluminum) jointly developed by Institute of Microbiology, Chinese Academy of Sciences and Anhui Zhifei Longcom Biopharmaceutical Co., Ltd (Hefei, China). The NVX-CoV2373 and SCB-2019 vaccines have shown good safety and immunogenicity in phase 1/2 clinical studies using an immunization schedule of two doses administered with an interval of 21 days. However, there was a drastic difference between the level of SARS-CoV-2 neutralizing antibodies induced by these vaccines and those induced by vaccines created using other technology platforms.^[20,21] The phase 1 clinical study of the SCB-2019 vaccine was conducted in 148 subjects in Australia, and it found that the vaccine was well tolerated. The most common local adverse reaction was mild pain at the injection site. Compared with SCB-2019 vaccines with or without the adjuvant CpG/alum, SCB-2019 vaccines with the adjuvant AS03 had a higher incidence of local adverse reactions. Two doses of SCB-2019 (CpG/alum) vaccine or SCB-2019 (AS03) vaccine each induced a higher SARS-CoV-2 neutralizing/binding antibody titer and positive antibody conversion rate compared with the SCB-2019 vaccine without adjuvant (at 36 days after the full-course immunization, the geometric mean titer [GMT] of anti-SCB-2019 immunoglobulin [IgG] antibody induced by the vaccines with adjuvant AS03 was 1567–4452, whereas the GMT of anti-SCB-2019 IgG antibody induced by the vaccine with adjuvant CpG/alum was 174–2440).^[21]

The phase 3 clinical study of the NVX-CoV2373 vaccine conducted in the United Kingdom with over 15,000 subjects aged 18 to 84 years revealed that the vaccine had a protective efficacy of 89.3%. A post-mortem analysis found that the NVX-CoV2373 vaccine had an efficacy of 95.6% against the original COVID-19 strains, whereas its efficacy against the British variant strain was 85.6%. Additionally, the incidence of adverse reactions after the subjects were vaccinated with two doses of NVX-CoV2373 vaccine was low, and there was no significant difference in adverse reactions between the vaccine and placebo groups.^[22]

The ZF2001 vaccine has obtained emergency use authorization in China. This recombinant protein vaccine is made in CHO cells and encodes the SARS-CoV-2 S protein receptor-binding domain (RBD) antigen; the RBD encoded by the vaccine is designed to form a dimer joined by tandem repeats. Its immunization schedule is three

doses, administered at 30-day intervals. The phase 1 and phase 2 clinical trials of ZF2001 were completed in China. In the phase 2 clinical trial, at 14 days after subjects had received three 25- μ g doses of the ZF2001 vaccine, the GMT of SARS-CoV-2 neutralizing antibody was 102.5, and the positive neutralizing antibody conversion rate reached 97%, values which both exceeded those in the group that received 50- μ g doses of vaccine. The incidence of adverse reactions was similar in the vaccine and placebo groups, and most reported adverse reactions were mild to moderate in severity.^[23]

Live-attenuated vaccines

Live-attenuated vaccines are composed of variant strain pathogens with weakened or even non-toxic effects that still retain their immunogenicity. These variant strains are obtained by subjecting the pathogen to one or more of various mutation-inducing treatments and then cultivating the resulting strains. Vaccination conducted with a live virus variant strain does not cause the vaccine recipient to develop disease, but it can induce the development of an immune response. The advantages of live-attenuated vaccines are that they can induce a strong immune response, they generally do not require adjuvants, and they typically require only one or two doses to induce protection. Their biggest drawback is the associated safety concerns. The residual virulence of live viruses may induce disease for some individuals, and the phenomenon of “virulence reversion” can occur. Therefore, people who suffer from autoimmune diseases or have low immunity generally cannot be vaccinated with live-attenuated vaccines. At present, the COVID-19 vaccine candidates that have been developed using a live-attenuated vaccine as a technological platform are still in the preclinical stage or phase 1 clinical study stage.

A new generation of two-component vaccines

Most first-generation COVID-19 vaccines were designed using the SARS-CoV-2 S protein or a fragment of S protein (ie, RBD) as the target antigen. The next-generation COVID-19 vaccines should be designed as dual targets. This design concept was first proposed by the team of Feng-Cai Zhu from Jiangsu Provincial Center for Disease Control and Prevention in May 2020. This group led the conceptual design and functional verification of the COVID-19 vaccine with two-component subunits, S protein RBD and N-terminal domain (NTD).^[24] At present, the study group has signed a strategic cooperation agreement with Jiangsu Rec-Biotechnology Co., Ltd. (Taizhou, China) and the Taizhou Pharmaceutical High-tech Industrial Park Management Committee on the joint research and development of this COVID-19 subunit vaccine. A new generation of this recombinant COVID-19 vaccine has been launched in Jiangsu province, and a phase 1 clinical trial will be started in the near future. After Moderna's first-generation COVID-19 vaccine mRNA-1273 obtained emergency use authorization which employs the SARS-CoV-2 S protein as its target, the second-generation mRNA-1283 was designed to target two fragments (RBD and NTD) on the S protein, and this COVID-19 vaccine candidate has recently entered the clinical trial.^[25]

Safety after mass vaccination

Recently, the serious adverse events that occurred after vaccination with adenovirus-vectored COVID-19 vaccines have become a focus. Thromboembolic events have occurred after vaccination with AstraZeneca's chimpanzee adenovirus-vectored COVID-19 vaccine or with Johnson & Johnson's Ad26-vectored COVID-19 vaccine. In September 2020, unexplainable adverse events of transverse myelitis occurred after vaccination with AstraZeneca COVID-19 vaccine. In February 2021, two women receiving the AstraZeneca COVID-19 vaccine experienced the disturbance of blood coagulation: one of them died, and the other was hospitalized to treat a pulmonary embolism. Since March 3, 2021, use of the AstraZeneca COVID-19 vaccine has been suspended or restricted in several countries. On April 7, 2021, the European Medicines Agency (EMA) confirmed that the specific thrombotic events accompanied by thrombocytopenia are particularly rare adverse reactions to the AstraZeneca COVID-19 vaccine but stated that the benefits of immunization with this vaccine still outweigh the risks, so they still recommend the use of this vaccine. On April 9, EMA stated that it was conducting an assessment on the potential relationship between the Johnson & Johnson COVID-19 vaccine and thrombosis, and the scope of their investigation of the AstraZeneca COVID-19 vaccine was expanded. According to the relevant reports, four patients suffered from abnormal thrombosis with thrombocytopenia after vaccination with the Johnson & Johnson COVID-19 vaccine, one of whom died, and the disease in these patients was very similar to the thrombosis caused by the AstraZeneca COVID-19 vaccine. Later, the US Food and Drug Administration and Centers for Disease Control and Prevention issued a joint statement recommending that use of the Johnson & Johnson COVID-19 vaccine be suspended. On April 13, 2021, the White House announced the suspension of administering Johnson & Johnson COVID-19 vaccine injections in the United States.

The causes for the risk of suspected thrombosis after vaccination with the AstraZeneca COVID-19 vaccine still need to be further investigated. The existing data suggests that there are three possible reasons for this reaction. First, the chimpanzee adenovirus vector itself may pose a risk because this chimpanzee adenovirus does not usually infect humans. The difference in its sequence from that of human adenovirus may increase the risk of blood clotting events. The dose-toxicity relationship between the chimpanzee adenovirus vector and human adenovirus vector is different. The dose of human adenovirus-vectored COVID-19 vaccine was selected to help overcome any pre-existing vector-specific antibody, whereas the dose of the chimpanzee adenovirus-vectored COVID-19 vaccine is the same as that of the human adenovirus-vectored vaccine, which consequently increases the toxicity risk posed by the chimpanzee adenovirus vector. Second, the SARS-CoV-2 S protein may pose a risk. Post-vaccination thrombosis might be a type III allergic reaction triggered by SARS-CoV-2 S protein or the thrombosis might be caused by SARS-CoV-2 infection. Third, the risk may be related to the vaccine design. The thromboembolism caused by vaccination with the AstraZeneca or Johnson & Johnson COVID-19 vaccine may actually be vaccine-induced

immune thrombotic thrombocytopenia, which is a rare adverse event described following immunizations with other vaccines^[26]. Although the specific mechanism is not clear yet, this adverse event has been determined to be related to the immune response induced by some COVID-19 vaccines.

Bell palsy was once suspected to be related to vaccination with BNT162b2. In a phase 3 clinical trial of the BNT162b2 vaccine in the United States, four participants developed Bell palsy after vaccination with the BNT162b2 vaccine.^[27] However, the US FDA stated that the incidence of this adverse event is equivalent to its expected background incidence in the general population; therefore, a causal relationship between the BNT162b2 vaccine and the occurrence of Bell palsy cannot be confirmed. However, prior studies have shown that the incidence of Bell palsy is 15 to 30 cases per 100,000 person-years. According to a follow-up study on the person-years of the populations who were vaccinated with the BNT162b2 vaccine, the expected number of Bell palsy cases is only one or two, which is lower than the actual number of cases with Bell palsy.^[28] However, because the symptoms of Bell palsy are usually mild and can subside spontaneously, and the benefits of vaccination with the BNT162b2 vaccine are much higher than the associated risks, it is still recommended that people aged ≥ 16 years continue to receive the BNT162b2 vaccine. The possible risk of Bell palsy following administration of the BNT162b2 vaccine should be further monitored.

Prospects

Currently, 14 COVID-19 vaccines have been approved for marketing in some countries or regions around the world.^[3] Because of the vigorous promotion of immunization with COVID-19 vaccines, as of April 18, 2021, about 790 million COVID-19 vaccine doses have been administered to people in countries and regions worldwide.^[29] Currently, Israel has the highest COVID-19 vaccination rate. In that country, approximately 90% of people aged ≥ 60 years have received one or two doses of the BNT162b2 vaccine, which has reduced the incidence of COVID-19 by 40%.^[30] Thus, immunization with COVID-19 vaccines plays a significant role in public health. However, with the gradual increase in the number of vaccinated people, a series of unpredictable, rare, and serious adverse events have gradually emerged, including the thromboembolism caused by the AstraZeneca AZD1222 vaccine and the Johnson & Johnson COVID-19 vaccine, which are worrying. Therefore, we should monitor the serious adverse events occurring in the vaccinated populations to ensure the safety of COVID-19 vaccine recipients.

Although the protective efficacy of many COVID-19 vaccines has been confirmed and their efficacy in the prevention of COVID-19 has been proven, the constant mutation of SARS-CoV-2 strains is constantly challenging the protective efficacy of COVID-19 vaccines. Vaccines that use only the SARS-CoV-2 S protein or its RBD as the target protein may not be sufficient to provide effective protection for all people in the future. Especially in the

United Kingdom, South Africa, and Brazil, where there is an ongoing spread of SARS-CoV-2 variants of interest, there is concern about the continued efficacy of COVID-19 vaccines. Taking the BNT162b2 vaccine as an example, serological studies have shown that the SARS-CoV-2 neutralizing antibody titers of this vaccine against the British variant (B.1.1.7), the South African variant (B.1.351), and the Brazilian variant (P.1) were lower than those against the original virus strain (USA-WA1/2020); and the neutralizing ability of the induced antibodies against the South African variant was lower than that against other variants by 2.3 to 3.4 times.^[31] A similar phenomenon was also observed for the Moderna COVID-19 vaccine.^[32] Therefore, researchers worldwide still need to closely monitor the mutation and escape of SARS-CoV-2 and to develop more effective next-generation COVID-19 vaccines that can completely control the COVID-19 pandemic. The current mainstream design ideas for COVID-19 vaccine design are still based on the RBD of the SARS-CoV-2 S protein. Recent studies have shown that the heptad repeat 2 (HR2) in the S2 subunit may trigger a metastable state of the S protein and promote conformational changes, thereby achieving immune escape.^[33] Animal experiments have also confirmed that an HR2-deficient SARS-CoV-2 S protein can induce higher neutralizing antibody titers, which may be useful in the design of next-generation COVID-19 vaccines.^[34]

At present, most of the immunization programs of COVID-19 vaccine approved globally are based on clinical studies of a single COVID-19 vaccine. It is urgent to carry out studies on sequential vaccination or booster immunization conducted with different types of COVID-19 vaccines because vaccine combinations may improve the level of vaccine-induced immune response and could activate multiple immune response pathways. The first clinical trial to assess a combination of COVID-19 vaccines occurred in Russia, where two COVID-19 vaccines with different viral vectors (rAd26 and rAd5 vectors) were used in a phase 3 clinical trial. For this trial, a two-dose immunization program of basic immunization and booster immunization on days 0 and 21, respectively, was conducted, and the resulting protective efficacy reached 91.6%.^[13] An ongoing trial assessing sequential vaccination with an adenovirus-vectored COVID-19 vaccine and the BNT162b2 vaccine, with a 12-week interval between the two vaccine doses, is currently being conducted in the United Kingdom. An interim analysis of this trial showed good safety and slightly strong immunogenicity of the heterologous AZD1222/BNT162b2 immunization schedule with 10 to 12 week vaccine intervals compared with homologous BNT162b2/BNT162b2 vaccination with 3-week vaccine intervals.^[35] The results of this study are expected to help improve the immunization program using existing COVID-19 vaccines and to enhance the protective efficacy of COVID-19 vaccination.^[36]

Owing to the extremely high worldwide demand for COVID-19 vaccines, the affordability and accessibility of these vaccines have attracted increasing attention. To ensure that low- and middle-income developing countries can also receive safe and effective COVID-19 vaccines, the

global alliance for vaccines and immunization (GAVI) has launched a multi-billion-dollar financing plan, known as the advance market commitment (AMC), to provide sufficient COVID-19 vaccines for these countries.^[37] AstraZeneca is the world's first vaccine manufacturer to sign an AMC; they are committed to providing 300 million COVID-19 vaccine doses in a non-profit manner. However, there are still countries or regions that are ineligible for GAVI or other assistance for various reasons, where they are unable to independently develop or produce COVID-19 vaccines. For these countries, controlling the price of COVID-19 vaccines may be an effective means of increasing vaccine accessibility. However, if such price control is implemented in only low- and middle-income countries, COVID-19 vaccine manufacturers may choose to supply insufficient doses to or not sell at all in these markets, or they may give priority to high-margin markets.^[38] Therefore, other measures, in addition to COVID-19 vaccine price control, must also be taken to ensure the fair distribution of COVID-19 vaccines worldwide.

Conflicts of interest

None.

References

- Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch MC. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science* 2020;368:860–868. doi: 10.1126/science.abb5793.
- World Health Organization. COVID-19—Landscape of novel coronavirus candidate vaccine development worldwide; 2021. Available from: <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>. [Last accessed on May 13, 2021]
- COVID-19 Vaccine Tracker. 14 Vaccines Approved By At Least One Country; 2021. Available from: <https://covid19.trackvaccines.org/vaccines/>. [Last accessed on April 26, 2021]
- Chinese Academy of Sciences. A Recombinant COVID-19 Vaccine (CHO cell) Was Approved for Emergency Use (in Chinese); 2021. Available from: http://www.im.cas.cn/xwzx/2018/jqyw/202103/t20210316_5975187.html. [Last accessed on April 21, 2021]
- Sinovac. Sinovac Receives Conditional Marketing Authorization in China for its COVID-19 Vaccine, 2021. Available from: <http://www.sinovac.com.cn/news/shownews.php?id=1153&lang=en>. [Last accessed on April 21, 2021]
- Sinopharm. NMPA Accepts the Application for Conditional Marketing Authorization of Sinopharm's COVID-19 Vaccine (in Chinese); 2020. Available from: https://www.cnbg.com.cn/content/details_12_5965.html. [Last accessed on June 22, 2021]
- NMPA. NMPA Accepts the Application for Conditional Marketing Authorization of CNVSI Wuhan's COVID-19 Vaccine (in Chinese); 2021. Available from: <http://www.nmpa.gov.cn/directory/web/nmpa/yaowen/ypjgyw/20210225184306142.html>. [Last accessed on April 21, 2021]
- CanSinoBIO. NMPA Accepts the Application for Conditional Marketing Authorization of CanSinoBIO's COVID-19 Vaccine (in Chinese); 2021. Available from: <http://www.cansinotech.com.cn/html/1/179/180/813.html>. [Last accessed on April 21, 2021]
- Yang ZN, Zhao YY, Li L, Gao HD, Cai Q, Sun XX, *et al.* Evaluation of safety of two inactivated COVID-19 vaccines in a large-scale emergency use (in Chinese). *Chin J Epidemiol* 2021;42:1–6. doi: 10.3760/cma.j.cn112338-20210325-00249.
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, *et al.* Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020;383:2603–2615. doi: 10.1056/NEJMoa2034577.
- Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, *et al.* Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384:403–416. doi: 10.1056/NEJMoa2035389.
- Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397:99–111. doi: 10.1016/s0140-6736(20)32661-1.
- Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, *et al.* Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet* 2021;397:671–681. doi: 10.1016/s0140-6736(21)00234-8.
- Janssen. Johnson & Johnson Announces Single-Shot Janssen COVID-19 Vaccine Candidate Met Primary Endpoints in Interim Analysis of Its Phase 3 ENSEMBLE Trial; 2021. Available from: <https://www.janssen.com/johnson-johnson-announces-single-shot-janssen-covid-19-vaccine-candidate-met-primary-endpoints>. [Last accessed on April 21, 2021]
- CanSinoBIO. MPA Accepts the Application for Conditional Marketing Authorization of CanSinoBIO's COVID-19 Vaccine ConvideciaTM; 2021. Available from: <http://www.cansinotech.com/html/1/179/180/651.html>. [Last accessed on April 21, 2021]
- Sinovac. Summary of Clinical Trial Data of Sinovac's COVID-19 Vaccine (CoronaVac®); 2021. Available from: <http://www.sinovac.com.cn/news/shownews.php?id=1154&lang=en>. [Last accessed on April 21, 2021]
- SINOVAC. World Health Organization Authorizes SINOVAC's CoronaVac® for Emergency Use; 2021. Available from: <http://www.sinovac.com.cn/news/shownews.php?id=1245&lang=en>. [Last accessed on June 10, 2021]
- Wuhan Institute of Biological Products Co., Ltd. Interim Analysis of Inactivated COVID-19 Vaccine of the Phase 3 Clinical Trial Developed by CNVSI Wuhan (in Chinese); 2021. Available from: <http://www.wibp.com.cn/ChsMobile/Detail.aspx?id=14670>. [Last accessed on June 22, 2021]
- Bharat Biotech. Bharat Biotech announces Phase 3 results of COVAXIN®: India's First COVID-19 Vaccine Demonstrates Interim Clinical Efficacy of 81%; 2021. Available from: https://www.bharatbiotech.com/press_releases.html. [Last accessed on April 21, 2021]
- Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, *et al.* Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. *N Engl J Med* 2020;383:2320–2332. doi: 10.1056/NEJMoa2026920.
- Richmond P, Hatchuel L, Dong M, Ma B, Hu B, Smolenov I, *et al.* Safety and immunogenicity of S-Trimer (SCB-2019), a protein subunit vaccine candidate for COVID-19 in healthy adults: a phase 1, randomised, double-blind, placebo-controlled trial. *Lancet* 2021;397:682–694. doi: 10.1016/s0140-6736(21)00241-5.
- Novavax. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial, 2021. Available from: <https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3>. [Last accessed on April 21, 2021]
- Yang S, Li Y, Dai L, Wang J, He P, Li C, *et al.* Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. *Lancet Infect Dis* 2021. doi: 10.1016/s1473-3099(21)00127-4.
- Zhang L, Cao L, Gao X, Zheng B, Deng Y, Li J, *et al.* A proof of concept for neutralizing antibody-guided vaccine design against SARS-CoV-2. *Natl Sci Rev* 2021. doi: 10.1093/nsr/nwab053.
- Moderna. First Participants Dosed in Phase 1 Study Evaluating mRNA-1283, Moderna's Next Generation COVID-19 Vaccine; 2021. Available from: <https://investors.modernatx.com/news-releases/news-release-details/first-participants-dosed-phase-1-study-evaluating-mrna-1283#:~:text=%20First%20Participants%20Dosed%20in%20Phase%201%20Study,Emergency%20Use%20Authorization%20%28EUA%29%20for%20active...%20More%20.> [Last accessed on April 22, 2021]
- Cines DB, Bussell JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. *N Engl J Med* 2021;384:2254–2256. doi: 10.1056/NEJMe21106315.

27. FDA. Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020; 2020. Available from: <https://www.fda.gov/media/144245/download>. [Last accessed on April 21, 2021]
 28. Ozonoff A, Nanishi E, Levy O. Bell's palsy and SARS-CoV-2 vaccines. *Lancet Infect Dis* 2021;21:450–452. doi: 10.1016/s1473-3099(21)00076-1.
 29. World Health Organization. WHO Coronavirus (COVID-19) Dashboard; 2021. Available from: <https://covid19.who.int/>. [Last accessed on May 13, 2021]
 30. Mallapaty S. Vaccines are curbing COVID: data from Israel show drop in infections. *Nature* 2021;590:197. doi: 10.1038/d41586-021-00316-4.
 31. Liu Y, Liu J, Xia H, Zhang X, Fontes-Garfias CR, Swanson KA, *et al*. Neutralizing activity of BNT162b2-elicited serum. *New Engl J Med* 2021;384:1466–1468. doi: 10.1056/NEJMc2102017.
 32. Wu K, Werner AP, Koch M, Choi A, Narayanan E, Stewart-Jones GBE, *et al*. Serum neutralizing activity elicited by mRNA-1273 vaccine. *New Engl J Med* 2021;384:1468–1470. doi: 10.1056/NEJMc2102179.
 33. Yao H, Song Y, Chen Y, Wu N, Xu J, Sun C, *et al*. Molecular architecture of the SARS-CoV-2 virus. *Cell* 2020;183:730–738.e13. doi: 10.1016/j.cell.2020.09.018.
 34. He L, Lin X, Wang Y, Abraham C, Sou C, Ngo T, *et al*. Single-component, self-assembling, protein nanoparticles presenting the receptor binding domain and stabilized spike as SARS-CoV-2 vaccine candidates. *Sci Adv* 2021;7:eabf1591. doi: 10.1126/sciadv.abf1591.
 35. Hillus D, Schwarz T, Tober-Lau P, Hastor H, Thibeault C, Kasper S, *et al*. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1-nCoV19 and BNT162b2: A prospective cohort study. *medRxiv* 2021; 2021.2005.2019.21257334. doi: 10.1101/2021.05.19.21257334.
 36. Yahoo News. Britain Trial to Test Combining Pfizer and AstraZeneca Vaccines in Two-shot reGimen, 2021. Available from: <https://news.yahoo.com/britain-trial-test-combining-pfizer-001145361.html>. [Last accessed on April 23, 2021]
 37. Usher AD. COVID-19 vaccines for all? *Lancet* 2020;395:1822–1823. doi: 10.1016/S0140-6736(20)31354-4.
 38. Karim SA. COVID-19 vaccine affordability and accessibility. *Lancet* 2020;396:238. doi: 10.1016/S0140-6736(20)31540-3.
-
- How to cite this article:** Jiang HD, Tao YY, Jia SY, Li JX, Zhu FC. Coronavirus disease 2019 vaccines: landscape of global studies and potential risks. *Chin Med J* 2021;134:2037–2044. doi: 10.1097/CM9.0000000000001688