

Next-generation COVID-19 vaccines: Opportunities for vaccine development and challenges in tackling COVID-19

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SUMMARY The ongoing COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global threat. Although non-pharmaceutical interventions have been rigorously and widely implemented, living conditions caused by the pandemic will last until highly effective vaccines are successfully improved and globally administered. Several first-generation COVID-19 vaccines were approved at the end of 2020. However, the COVID-19 pandemic is persisting worldwide. To be clear, the efficiency and the coverage of current vaccines are insufficient, but newly emerging and rapidly spreading variants are the most pressing concern. A second-generation COVID-19 vaccine worth mentioning, NVX-CoV2373, has demonstrated 90% overall efficacy as well as a high level of efficacy against circulating variants in Phase 3 clinical trials. Currently, NVX-CoV2373 is the only vaccine that has proven successful against variants during Phase 3/4 trials. Therefore, developing the next generation of vaccines is a promising strategy to ultimately prevail against SARS-CoV-2. This review provides up-to-date information on COVID-19 vaccines in terms of their efficacy and new platforms and the progression of COVID-19 vaccination. Moreover, this review also summarizes the efficacy of approved COVID-19 vaccines against variants. Lastly, this review highlights the global challenges for COVID-19 vaccines in development and vaccination, and it discusses opportunities for development of future COVID-19 vaccines and vaccination coverage.

Keywords COVID-19, SARS-CoV-2, vaccines, NVX-CoV2373, vaccination, distribution

1. Introduction

As of June 25, 2021, more than 17 million confirmed cases of COVID-19 and 3,840,223 deaths have been reported by the WHO (1). The COVID-19 pandemic has posed a serious crisis to both health care systems and economies worldwide. Since there are no effective treatments for COVID-19, the chances of controlling the COVID-19 pandemic depend mainly on two main factors: *i*) public health interventions and *ii*) development and administration of safer and more effective vaccines (2).

Public health interventions such as non-pharmaceutical measures were obviously effective in reducing the spread of COVID-19 (3). Governmental measures including travel restrictions, border restrictions, quarantine of travelers, confirmed cases, and contacts, orders to avoid confined spaces and large gatherings, social distancing, compulsory mask wear, school closures, and establishment of designated hospitals were useful at preventing the spread of COVID-19. Individual interventions, such as use of protective equipment by

healthcare workers and attention to personal hygiene, were also effective in tackling COVID-19. Nevertheless, sporadic cases of COVID-19 continue to emerge even in countries with strict controls compared to countries with less stringent interventions (4,5).

More importantly, a number of newly emerged mutations have accelerated the rapid spread of SARS-CoV-2. There are 4 known major variants: the B.1.1.7 lineage (called the Alpha variant) that was first identified in the United Kingdom, the B.1.351 lineage (called the Beta variant) that was identified in South Africa, the P.1 lineage that was identified in Brazil (called the Gamma variant), and the B.1.617 lineage (called the Delta variant) that was verified in India. These variants have been labeled variants of concern (VOC) by the WHO (6). At the current point in time, the B.1.617 variant has been blamed for the current surge of COVID-19 in India (7). The variants have increased transmissibility or increased virulence compared to the original virus. Changes in those variants cause worse disease presentation and negatively impact COVID-19 epidemiology and public health measures. Therefore, strict control measures

alone are not effective enough to stop the COVID-19 pandemic, more efficacious vaccines need to be quickly developed to prevent the COVID-19 pandemic.

2. Strategies for the development of COVID-19 vaccines

As of June 25, 2021, a total of 574 vaccines have been developed, including 103 vaccines in clinical trials, and 184 vaccines in pre-clinical studies. Of the 103 vaccines in clinical trial, 23 are in Phase 3 or 4. Multiple platforms have been used to develop the 103 vaccines. Eighteen are inactivated and live attenuated vaccines, including BBIBP-CorV (COVIL0) from Sinopharm (Beijing and Wuhan) and CoronaVac from Sinovac (8). Thirty-three are recombinant protein vaccines, or recombinant subunit vaccines, such as NVX-COV2373 from Novavax and ZF2001 from Zhifei Biology. Twenty-six are nucleoid vaccines, such as BNT-162b2 from BioNTech and mRNA-1273 from Moderna. Twenty-one are viral vector vaccines, such as ChAdOx1-nCoV-19 from AstraZeneca, Ad5-nCoV from CanSino, Ad26.COV2.S from Janssen Pharmaceuticals, and Sputnik V from Gamaleya (9).

Vaccines developed using different platforms have pros and cons because of the different techniques used (10,11). *i*) Inactivated vaccines and live attenuated vaccines are quick to prepare and easy to produce but do not readily induce T-cell immunity and usually need to be administered 2-3 times to enhance immunity. In addition, the long-lasting immune response to inactivated vaccines relies more on adjuvants than other vaccines, and live attenuated vaccines against complex pathogens are challenging (12-13). *ii*) Nucleoid vaccines are easy to rapidly mass produce and confer long-term host immunogenicity but have potential genetic risks since mRNA is unstable and they remain ineffective when administered to humans with compromised immunity (14-15). *iii*) Viral vector vaccines can induce strong humoral and cellular immunity but are not able to induce immunogenicity in the face of preexisting immunity (16-18). *iv*) Recombinant vaccines such as NVX-COV2373 from Novavax and ZF2001 from Zhifei Biology have very clear advantages such as a distinct composition and a high level of safety and stability but also have weak immunogenicity and require adjuvants (19). (Table 1)

3. Progress of COVID-19 vaccination

Widespread vaccination is also required to end the COVID-19 pandemic. In mid-December 2020, the first reports of a COVID-19 vaccine outside of clinical trials were published in the UK, thus sparking a race for vaccine development. Waves of vaccination subsequently occurred daily around the world. With the successful development of the first-generation vaccine, the COVID-19 vaccination rate increased in a wide range of countries from January to May 2021 (20).

Thanks to the tremendous breakthrough in COVID-19 vaccine development, the WHO is working tirelessly with partners to manufacture vaccines and to promote their safety and effectiveness. As of June 25, 2021, a total of 471,786,361 persons were fully vaccinated and 1,031,602,050 persons were vaccinated with at least one dose, accounting for 22.4% of the world's population (1,21). Two-point-eight billion doses have been administered, and 40.8 million doses are administered each day (21). However, the vaccination rate (> and = 2nd dose) among people in low-income countries was less than 1%, which implies that the ongoing COVID-19 vaccination faces great challenges.

4. Challenges with COVID-19 vaccines in development and vaccination

4.1. Issues with the efficacy of COVID-19 vaccines against variants

SARS-CoV-2 is an enveloped virus with a positive-polarity single-stranded RNA genome that contains four major structural proteins: the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The trimeric S protein consists of a receptor-binding subunit (S1) and a membrane-fusion subunit (S2). The S1 subunit consists of the N-terminal domain (NTD), the receptor-binding domain (RBD), and two small subdomains. The role of the S protein is to mediate SARS-CoV-2's entry into host cells *via* surface receptor angiotensin-converting enzyme 2 (ACE2). The S1 subunit is involved in cell entry, and the RBD domain is responsible for direct binding. Thus, the S, S1, and RBD proteins are 3 major targets for vaccine development (22-24).

However, mutations in those target proteins represent a great challenge to the efficacy of COVID-19 vaccines (25). As reported, variants of concern (VOC) are associated with increased transmissibility and virulence due to notable mutations in key proteins. For example, mutations in the B.1.1.7 lineage involve multiple sites, such as a N501Y substitution in the RBD region, H69/V70 deletion in the N-terminal region, and P681H mutation adjacent to the furin cleavage site in the S protein. Mutations in the B.1.351 variant (20H/501Y.V2) include K417N, E484K, and N501Y. In the P.1 variant (B.1.1.28.1), mutations involve K417T, E484K, and N501Y substitutions in the RBD domain. B.1.617.2 is defined by more mutations in the S protein, including T19R, DEL157/158, T478K, and D950N. In addition, these variants share the D614G mutation, which has been found to increase the rapid spread of the virus. Therefore, inadequate public healthcare measures and vaccination coverage have accelerated the emergence of variants. Moreover, the rapid spread of variants has increased the global demand for more effective vaccines. Whether the 6 prototype vaccines in Phase III/IV trials will remain effective against variants

Table 1. Comparison of Novavax and other COVID-19 vaccines on the market (8)

Developer	Representative	Type	Platforms	Advantages and disadvantages	Approval	Vaccine Efficacy in clinical trails
Pfizer/BioNTech	BNT 162b2	3 LNP-mRNAs	Nucleoid vaccines	1). Easy to rapidly mass produce and confer long-term host immunogenicity; 2). but have potential genetic risks since mRNA is unstable and remain ineffective when administered to humans with compromised immunity	EUA	95% effective against COVID-19 beginning 28 days after the first dose; efficacy in adults over 65 years of age was over 94%
Moderna mRNA-1273	mRNA-1273	LNP-encapsulated mRNA			EUA	94.1% efficacy at preventing Covid-19 illness
AstraZeneca	ChAdOx1-nCoV-19 (AZD1222)	ChAdOx1-S	Viral vector vaccine	1). Can induce strong humoral and cellular immunity; 2). but are not able to induce immunogenicity in the face of preexisting immunity	EUA	90-0% effective after the 2nd dose. Overall vaccine efficacy across both groups was 70-4%
Johnson & Johnson	Ad26.COV2.S	Adenovirus Type 26 vector (Non-Replicating Viral Vector)			EUA	52.0-81.7% efficacy
CanSino Biologics	Ad5-nCoV	Adenovirus Type 5 Vector (Non-Replicating Viral Vector)			EUA	65.7% efficacy
Gamaleya Research Institute Gam-COVID-Vac	Sputnik V	Adeno-based (rAd26-S+rAd5-S) (Non-Replicating Viral Vector)			On the market (Russian)	vaccine efficacy is 91.6%
Sinovac CoronaVac	Corona Vac	Inactivated	Inactivated vaccines and live attenuated vaccines	1). Quick to prepare and easy to produce; does not readily induce T-cell immunity, needs to be administered 2-3 times to enhance immunity; 2). The long-lasting immune response to inactivated vaccines relies more on adjuvants than other vaccines; live attenuated vaccines against complex pathogens are challenging.	On the market (China)	50.4-60.7% efficacy
Wuhan Institute of Biological Products/Sinopharm	Sinopharm	Inactivated			On the market (China)	72.5% efficacy
Sinopharm (Beijing)	BBIBP-CoV	Inactivated			On the market (China)	78.1% efficacy
Bharat Biotech	BBV152	Whole-Virion Inactivated			Emergency use (India)	77.8% efficacy
Novavax	NVX-CoV2373	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Recombinant vaccines	Have a distinct composition and a high level of safety and stability, but weak immunogenicity and require adjuvants.	Phase 3	overall 95.6% efficacy

Source: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines>

Table 2. Vaccine efficacy against variants of concern (5)

WHO label	Lineage	First discovery place	Date of confirmation	Mutations	Vaccine Efficacy against variants
Alpha	B.1.1.7	United Kingdom	18-12-2020	N501Y substitution in the RBD region, H69/V70 deletion in the N-terminal region, and P681H mutation adjacent to the furin cleavage site in the S protein. D614G mutation	NVX-CoV2373 (85.6%)
Beta	B.1.351	South Africa	18-12-2020	K417N, E484K, N501Y, and D614G mutation	NVX-CoV2373 (49.4%) ChAdOx1 nCoV-19 (10%)
Gamma	P.1	Brizal	11-01-2021	K417T, E484K, and N501Y substitution in the RBD domain, and D614G mutation	unknown
Delta	B.1.617.2	India	11-05-2021 labeled as VOC	more mutations in the spike protein, namely T19R, DEL157/158, T478K and D950N, D614G mutation	unknown

Source: <https://www.ctynews.ca/health/coronavirus/b-1-617-variant-first-identified-in-india-classified-as-variant-of-global-concern-1.5421363>

is also a great concern (26). (Table 2)

4.2. The challenges of globally promoting and distributing vaccines

As of June 25, 2021, 60% of people are fully vaccinated against COVID-19 in Israel, and only 4.3% were partly vaccinated. A high level of vaccination coverage was noted in China (51% had received the 2nd dose, 13% had received the 1st), the United Kingdom (47% had received the 2nd dose, 17% had received the 1st), and the United States (45% had received the 2nd dose, 8.1% had received the 1st). The cumulative number of doses administered per 100 people was 123.44 in Israel. In some areas, however, such as South Africa countries, the total number of vaccinated per 100 people was less than 1 (21). The large differences in the rate vaccination coverage between countries imply significant inequality in vaccine distribution, which may be caused by different national economics, difficulties with logistics and storage, lower rates of vaccination, the extent to which vaccination has been promoted by the government (27).

Moreover, different countries have taken markedly different approaches to vaccination. European Union countries like the United Kingdom have adopted a 'first dose first' approach. This vaccination strategy priority promotes wider coverage with the first dose while delaying administration of the second dose. Other countries, such as Israel, the United States, and China taken the approach of fully vaccinating smaller populations first. Different approaches also led to different rates of vaccination coverage among different populations worldwide (20,28-31). The rapid development of COVID-19 vaccines within one year has been a great breakthrough in scientific and economic cooperation among countries. However, now that vaccines are being developed, the question is whether the global distribution of vaccines can match the speed of the COVID-19 pandemic, *i.e.* whether those vaccines can be administered quickly and widely

distributed around the world (32).

5. Strategies for development of future COVID-19 vaccines and vaccination coverage

5.1 Optimizing the vaccine platform, learning from Novavax

Thus far, only a few clinical trials have investigated the effects of COVID-19 vaccines on variants. A phase 3 trial was conducted in South Africa to assess the efficacy of a single dose of the Ad26.COVS vaccine (Johnson & Johnson/Janssen). Efficacy was reported to be 52% at 14 days and 64% at 28 days after the first dose of Ad26.COVS vaccine. The trial was contemporaneous with 95% of subjects being infected with the B.1.351 variant, but no vaccine is reported to be effective against the B.1.351 variant (33,34). Another phase 2 trial was also conducted in South Africa to evaluate the efficacy of the ChAdOx1 nCoV-19 vaccine (AstraZeneca). However, overall efficacy was only 22% and efficacy against the B.1.351 variant was only 10% (35).

Most recently, the efficacy of the NVX-CoV2373 vaccine against variants was examined in a phase III clinical trial. Results indicated that the efficacy of the NVX-CoV2373 vaccine against SARS-CoV-2 was 95.6%, that against the UK variant was 85.6%, and that against the South African variant was 49.4%. NVX-CoV2373 is the only vaccine effective against COVID-19 variants, but the next generation of vaccines will presumably be developed worldwide. A point worth noting is that the platform for NVX-CoV2373 used recombinant nanoparticle technology to generate an antigen from the spike (S) protein. The patented saponin-based Matrix-M™ adjuvant in Novavax was designed to promote a humoral and cellular immune response (35). (Table 2)

The efficacy of NVX-CoV2373 in clinical trials implies that the next generation of vaccines, and especially protein vaccines, need to optimize their

protein targets to enhance immunogenicity and to cover emerging and potential mutation sites. Moreover, appropriate adjuvants are useful at enhancing the immune response, and especially at inducing high levels of humoral immunity. As SARS-CoV-2 variants emerge, their surveillance, detection of neutralization antibodies, and the immune response to them in clinical trials are also crucial.

5.2. Optimizing vaccination strategies combined with non-pharmaceutical interventions

In rich countries such as Israel, promising vaccines are easier to develop and vaccination strategies are easier to optimize, and the country has done remarkably well with its vaccination efforts. In developing countries, however, vaccines are uncertain, so non-pharmaceutical interventions to combat COVID-19 was useful at limiting the spread of the virus and its variants. Under such conditions, the best strategies are social distancing, attention to personal hygiene, frequently handwashing, and mask wear while awaiting vaccines and affordable drugs (2).

Overall, vaccination strategies should be optimized in combination with non-pharmaceutical interventions to control the epidemic. Non-pharmaceutical interventions should be implemented as much as possible in developing or low-income countries. In the war against viruses, the faster the public health interventions and the more optimal the vaccine options, the more likely we are to win.

6. Discussion

Given problems with the efficacy of COVID-19 vaccines against variants, NVX-CoV2373 was a great scientific breakthrough, marking the first human victory in the battle against the virus and its variants. However, countries cannot rely on vaccines alone. Appropriate vaccination strategies and sufficient vaccination coverage, combined with non-pharmaceutical interventions, are key steps in controlling the global COVID-19 pandemic.

For a more complete and rapid future public health response to a disease like COVID-19, several aspects should be taken into account. First, the design of and clinical trials on next-generation vaccines have to take emerging variants into account. Second, countries where vaccines are lacking should to adopt a more flexible vaccination strategy since "administering a second dose of another vaccine is better than not administering one at all". As an example, further evidence is need to verify which types of vaccines can be mixed and which vaccines have sufficient safety and efficacy to cope with a temporary shortage of a given vaccine (36,37). Third, special populations, including the elderly, infants, and immunocompromised patients such as those with AIDS or cancer, are not yet fully covered in clinical trials on

COVID-19 vaccines and should be considered in the future (35,38).

Once COVID-19 vaccines are developed, widespread vaccine distribution and adequate vaccination coverage are also crucial steps. Thus, a plan for widespread vaccine distribution is needed based on different demographics, logistics, and acceptance and with the cooperation of various levels of government (39,40). Lastly, non-pharmaceutical interventions should be implemented more rigorously, and especially in countries with insufficient COVID-19 vaccination coverage.

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