Immunogenicity, efficacy and safety of COVID-19 vaccines: an update of data published by 31 December 2021

Authors

Kun Xu\textsuperscript{1,2}, Chunxiang Fan\textsuperscript{3}, Yuxuan Han\textsuperscript{4}, Lianpan Dai\textsuperscript{2,4,5} and George F. Gao\textsuperscript{4,5}

Affiliations

\textsuperscript{1}Research Network of Immunity and Health (RNIH), Beijing Institutes of Life Science, Chinese Academy of Sciences, Beijing 100101, China

\textsuperscript{2}Key Laboratory of Tropical Translational Medicine of Ministry of Education, School of Tropical Medicine and Laboratory Medicine, The First Affiliated Hospital, Hainan Medical University, Hainan 571199, China

\textsuperscript{3}National Immunization Programme, Chinese Center for Diseases Control and Prevention, Beijing 100050, China

\textsuperscript{4}Savaid Medical School, University of Chinese Academy of Sciences, Beijing 101408, China

\textsuperscript{5}CAS Key Laboratory of Pathogen Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China

Correspondence to: G. F. Gao; E-mail: gaof@im.ac.cn
Abstract

The unprecedented coronavirus disease 2019 (COVID-19) pandemic has caused a disaster for public health in the last 2 years, without any sign of an ending. Various vaccines were developed rapidly as soon as the outbreak occurred. Clinical trials demonstrated the reactogenicity, immunogenicity and protection efficacy in humans, and some of the vaccines have been approved for clinical use. However, waves of infections such as the recently circulating Omicron variant still occur. Newly emerging variants, especially the variants of concern, and waning humoral responses pose serious challenges to the control of the COVID-19 pandemic. Previously, we summarized the humoral and cellular immunity, safety profiles and protection efficacy of COVID-19 vaccines with clinical data published by 21 May 2021. In this review, we summarize and update the published clinical data of COVID-19 vaccines and candidates up to December 31, 2021.

Keywords: antibody, SARS-CoV-2, vaccine effectiveness, vaccine efficacy, cellular immune response
Introduction

The coronavirus disease 2019 (COVID-19) pandemic is an unprecedented disaster for humans (1). To control and prevent the disease and reduce transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, vaccine development was rapidly initiated worldwide, using different targets and platforms (2-4). After the proof-of-concept and pre-clinical studies, clinical studies (Phase 1, 2 and 3) were conducted for vaccine safety and efficacy evaluation in humans.

Previously, we summarized the COVID-19 vaccine development progress up to May 2021, including the humoral and cellular immunity and safety of COVID-19 vaccines from published articles (5). Table 1 summarizes the protection efficacy in Phase 3 clinical trials and effectiveness in the real world studies for preventing COVID-19 about some of those vaccines and Table 2 summarizes findings from some newer vaccines. To date, 331 COVID-19 vaccine candidates have been developed, and 30 of them have been approved for use in at least one country or region worldwide under authorization (Fig. 1). Although large-scale vaccination campaigns were continued, new SARS-CoV-2 variants emerged, circulated and caused breakthrough infections. A waning humoral immune response to COVID-19 vaccines was observed and boost doses were administered. Therefore, we have updated the progress of the COVID-19 vaccines and candidates up to December 31, 2021 in this review.

mRNA vaccines

BNT162b2 (Comirnaty) is an mRNA vaccine expressing a prefusion-stabilized spike protein (S protein) with K986P and V987P substitutions (S-2P protein). Vaccination with BNT162b2 in adults induces innate and adaptive immune responses (6). Anti-viral polyfunctional and long-lived CD4 and CD8 T cells with T helper type 1 (Th1) polarization are induced (6-9). Two doses of BNT162b2 induce strong humoral immune responses in children, adolescents, younger adults and older adults (10-12). Six months after the second dose of the BNT162b2 vaccination, levels of receptor-binding domain (RBD)-binding antibodies and neutralizing-antibodies (NAbs) substantially decrease, especially among people aged 65 years or older (13,14). Therefore, a third dose can be administered to boost the antiviral immune response. The reports revealed that at 1 month after dose 3, NAb geometric mean titers (GMTs) against the prototype virus increased to more than 5–7 times as high as the GMTs at 1 month after dose 2. In addition, the breadth of neutralized SARS-CoV-2 variants also increased with dose 3 (15,16).

Immune responses induced by BNT162b2 against SARS-CoV-2 variants have been previously reported (5). The Omicron variant, defined as a new Variant of Concern (VOC) in late 2021, began to circulate globally and showed the highest resistance to NAbs induced by infection with ancestral SARS-CoV-2 (prototype and D614G) and by licensed COVID-19 vaccine immunization, including BNT162b2 (NAb GMT reduction of 22-fold compared with D614G) (17). Beta and Gamma VOCs also extensively escape NAbs induced by BNT162b2 in humans (18-21). In addition, Delta, Kappa, Epsilon and Iota variants show slight or moderate escape from BNT162b2-elicited NAbs (22-27). However, T cell-mediated immunity elicited by BNT162b2 was not affected by mutations in SARS-CoV-2 variants, such as Alpha and Beta VOCs (28).
The results of Phase 3 clinical trials of BNT162b2 revealed that vaccine efficacies against symptomatic COVID-19 and severe disease were 91.3% and 96.7%, respectively, after 6 months of follow-up (29) (Table 1). The effectiveness of two-doses of BNT162b2 in the real-world have been reported as follows: i) 91% and 96% against symptomatic COVID-19 infection and severe outcomes (hospitalization and death) respectively, in Canada (30); ii) 91.3% against COVID-19 in New York, USA (31); iii) 83.3% and 90.6% against SARS-CoV-2 infection and COVID-19-related mortality, respectively, in Hungary (32); iv) 83% against Alpha VOC infection in Italy (33); v) 93.7% and 88.0% against symptomatic disease caused by the Alpha and Delta VOCs, respectively, in the UK (34); vi) 90% against death from the Delta VOC in Scotland (35); and vii) 51.9% and 93.4% against Delta VOC infection and Delta-induced severe, critical or fetal disease, respectively (36) and 89.5% and 75.0% against infection with the Alpha and Beta VOCs, respectively, in Qatar (37).

In addition, the decline in BNT162b2 vaccine effectiveness against SARS-CoV-2 infection between 1 month and 5 months after the second-dose vaccination was observed in other studies in the USA and Qatar, probably because of waning neutralizing antibody titers over time. However, the effectiveness of BNT162b2 against hospital admissions for severe disease was high until 6 months after vaccination (38-40). By analyzing the viral loads of breakthrough infections in Israel, it was found that the viral loads were lower in vaccinees who received single or full doses of BNT162b2 than those in unvaccinated individuals. This effect began to decline 2 months post vaccination and even vanished at 6 months or longer, as did vaccine effectiveness (41-43). The booster vaccine dose could restore the effect of BNT162b2 on reducing viral loads in breakthrough infections and significantly enhance the effectiveness against COVID-19-related hospitalization, severe disease and death (41,42,44).

Another mRNA vaccine, mRNA-1273 (SpikeVax) contains mRNA expressing the S-2P protein. Vaccine mRNA-1273 induces strong humoral and specific T-cell responses in adolescents, younger adults and older adults (45,46). Robust and rapid polyfunctional CD4 T cell generation, a gradual CD8 T-cell response and a durable T cell memory induced by mRNA-1273 have been observed (47-49). In addition, T cells of vaccinees effectively recognize variants, including Alpha, Beta, Gamma and Epsilon (50). Comprehensive analysis of neutralization of SARS-CoV-2 variants by plasma revealed that lineages with E484K and N501Y/T mutations were greatly reduced, followed by lineages with L452R (27).The NAb activity of sera from mRNA-1273 recipients against the prototype D614G virus decreased at 6 months post vaccination, and NAb titers against Beta, Gamma and Delta VOCs were low and even undetectable (13,51-53). A third dose of mRNA-1273 at 6 months induced increased NAb activity against the prototype virus and key VOCs and Variants of Interest (VOIs) (52).

The final analysis of Phase 3 clinical trials of mRNA-1273 revealed that the vaccine efficacies in preventing symptomatic COVID-19, severe disease and asymptomatic infection were 93.2%, 98.2% and 63.0%, respectively (54) (Table 1). The effectiveness of two doses of mRNA-1273 in the real world was reported as follows: i) 94% and 96% against symptomatic COVID-19 infection and severe outcomes (hospitalization and death), respectively, in Ontario, Canada (30); ii) 88.7% and 93.6% against SARS-CoV-2 infection and COVID-19-related mortality, respectively, in Hungary (32); iii) 73.1% and 96.1% against any Delta VOC infection and Delta-induced severe, critical or fetal disease, respectively, in Qatar (36); and iv) 86.7% and 97.5% against infection or hospital admission with the Delta
VOC, respectively, and the effectiveness against Delta VOC infection declined from 94.1% on Day 14–60 to 80.0% on Day 151–180 post vaccination in Southern California, USA (55).

CVnCoV is an mRNA vaccine candidate, developed by CureVac AG, Germany. It contains nucleotides without chemical modification, encapsulated in lipid nanoparticles (LNP), and also expresses the S-2P protein (56). The Phase 1 trial compared the immunogenicity of 2, 4, 6, 8 and 12 μg doses of CVnCoV and found that the humoral immune responses induced by CVnCoV were dosage-dependent (56). In addition, two doses of CVnCoV (12 μg) elicited similar RBD and S protein-binding IgG GMT levels and lower NAb GMT level in participants than those of human convalescent sera (HCS) (56). The results of a Phase 3 trial showed that two doses of CVnCoV (12 μg), 28 days apart, provided 48.2% and 70.7% protection efficacy against symptomatic COVID-19 and moderate-to-severe COVID-19, respectively (57) (Table 2). CVnCoV had an acceptable safety profile (56,57). Because of the emergence of SARS-CoV-2 variants and the other reasons, CureVac ceased the further development of CVnCoV candidate and focused on the next-generation vaccine candidates (57).

**Adenovirus-based vaccines**

AZD1222 (Vaxzevria) is a recombinant chimpanzee-adenovirus into which the gene encoding the SARS-CoV-2 full-length S protein was inserted and two doses were administered. Several new studies on the immunogenicity of AZD1222 have been published recently. A third dose (boost dose) of the AZD1222 vaccine elicited higher antibody titers and boosted T-cell responses (58). Although the NAb GMTs in AZD1222-elicted human sera were lower against the Delta VOC than against the prototype SARS-CoV-2, the levels of vaccine-induced CD4 and CD8 T-cell responses were similar to those against Delta and prototype viruses (59). After immunization with two doses of AZD1222, broad CD4 and CD8 T-cell coverage across the S protein was elicited, with polyfunctional Th1-dominated T-cell responses (60).

The Phase 3 clinical trials in the USA, Chile and Peru showed that the overall estimated vaccine efficacy against symptomatic COVID-19 was 74.0%, and vaccine efficacy for preventing SARS-CoV-2 infection was 64.3% (61) (Table 1). Another Phase 3 trial in Brazil found that AZD-1222 vaccine efficacy was 69% against any symptomatic COVID-19 caused by the Zeta (P.2) variant and 64% against the Gamma VOC with fewer disease cases (62).

In the real world, the effectiveness of two doses of the AZD-1222 vaccine was as follows: i) 71.5% and 88.3% against SARS-CoV-2 infection and COVID-19-related mortality, respectively, in Hungary (32); ii) 74.5% and 67.0% against symptomatic disease caused by the Alpha and Delta VOCs, respectively, in the UK (34); iii) 91% against death from the Delta VOC in Scotland (35); and iv) 63.1% and 81.5% against virus infection and preventing moderate-to-severe COVID-19 during the delta VOC surge in India (59). In addition, at 2–3 and 18–19 weeks after the second dose of AZD-1222, vaccine effectiveness decreased from 83.7% to 63.7% in Scotland when the Delta VOC was the most widespread one and from 86.4% to 42.2% in Brazil when the Gamma VOC was common (63).

Ad26.COV2.S was designed as a single administration of recombinant type 26 adenovirus expressing the SARS-CoV-2 S-2P protein in addition to two mutations at the furin cleavage site (R682S and R685G). Ad26.COV2.S induces durable humoral and cellular immune
responses for at least 8 months post vaccination (13,64). In particular, the expansion of NAb breadth against SARS-CoV-2 variants over this time period has been observed (13). The median pseudovirus NAb titers induced by Ad26.COV2.S were 5.0-fold and 3.3-fold lower against the Beta and Gamma VOCs, respectively, compared with the prototype virus (WA1/2020) (65). The vaccine elicited CD8 and CD4 T-cell responses and the central and effector memory responses were comparable among the prototype virus and Alpha, Beta, Gamma and Epsilon variants (65).

Ad26.COV2.S protected against moderate to severe-critical COVID-19 with an efficacy of 66.9% in multi-center Phase 3 clinical trials, at least 14 days after vaccination (66) (Table 1). In the real world, the vaccine effectiveness of Ad26.COV2.S against SARS-CoV-2 infection in the USA was 73.6% (67). Recently, a decline in effectiveness against laboratory-confirmed COVID-19 was observed, possibly caused by waning immunity and circulating of Delta VOC (31).

Ad5-nCoV (Convidecia) is a recombinant human type 5 adenovirus expressing the SARS-CoV-2 full-length S protein. Previous reports on the results of Phase 1 and Phase 2 trials showed that a single dose of Ad5-nCoV administered intramuscularly induced specific humoral and cellular immune responses (68,69). Another Phase 1 trial was conducted to evaluate the safety, tolerability and immunogenicity of aerosolized Ad5-nCoV in adults. The immune responses induced by an intramuscular injection, aerosol inhalation or intramuscular injection prime followed by an aerosol inhalation boost were compared. The results indicated that aerosolized Ad5-nCoV was well tolerated, and two doses of aerosolized Ad5-nCoV elicited similar levels of NAb response to one dose of intramuscular injection. Priming by intramuscular injection and boosting by inhalation, which were separated by 28 days, induced stronger IgG and NAb responses than single-dose intramuscular injection and two-dose inhalation (70).

Recently, the final efficacy analysis of single-dose Ad5-nCoV (intramuscular administration) in Phase 3 was released, with 63.7% and 57.5% protection against symptomatic COVID-19 at 14 and 28 days or more post vaccination, respectively (71) (Table 1).

Gam-COVID-Vac (Sputnik V) is a two-dose vaccine regimen with a recombinant adenovirus 26 prime and a recombinant adenovirus 5 boost, both carrying the gene for the SARS-CoV-2 S protein. The kinetics of antibodies induced by Gam-COVID-Vac up to 6 months after immunization in Argentina were analyzed and it was found that anti-RBD titers began to decrease between 28 and 60 days post vaccination, remained stable between 60 and 90 days post vaccination, and decreased to a low level at 180 days post vaccination, with 31% of sera positive for anti-RBD antibody (72). The Gam-COVID-Vac-elicited sera neutralized the Alpha VOC with a similar level compared with the prototype but the Beta VOC partially escaped with a GMT reduction of 6.1-fold compared with the prototype (73). In addition, reduced neutralizing activities against the Gamma VOC compared with the prototype virus were observed (74).

In Phase 3 clinical trials, Gam-COVID-Vac provided 91.6% prevention efficacy against COVID-19 21 days after the first dose (Table 1). In Hungary, the effectiveness of Gam-COVID-Vac against SARS-CoV-2 infection and COVID-19-related mortality was 85.7% and 97.5%, respectively (32). In addition, the first dose of Gam-COVID-Vac could confer 78.6%
and 84.8% effectiveness for preventing SARS-CoV-2 infection and COVID-19-related death, respectively, in 60–79-year-old vaccinees as conducted in Argentina (75). Because of the shortage in the supply of vaccines, Sputnik Light was developed with a single-dose immunization of a recombinant adenovirus type 26 vector expressing the SARS-CoV-2 S protein. The results of the Phase 1/2 trial reported that Sputnik Light induced IFN-γ release from T cells, RBD-specific IgG and NAb production, with a GMT lower than that in a panel of convalescent plasma (76).

**Protein subunit vaccines**

ZF2001 (ZIFIVAX) is a protein subunit vaccine jointly developed by us and Anhui Zhifei Longcom Biopharmaceutical Co., Ltd. ZF2001 contains the SARS-CoV-2 tandem-repeat dimeric RBD protein, which showed higher immunogenicity than monomeric RBD protein, and the aluminum hydroxide adjuvant (77). In the Phase 1 and 2 clinical trials, we demonstrated that ZF2001 induced robust humoral immune responses and balanced cellular immune responses in humans, with low reactogenicity (78). In addition, we also found that the ZF2001-elicited sera efficiently neutralize the SARS-CoV-2 variants with a range of GMT reduction folds between 1.1 and 2.1 for Beta, Gamma, Epsilon, Eta, Kappa and Delta variants, demonstrated by pseudotyped-virus neutralization assays (79). Humoral immune responses in ZF2001 vaccines exhibit higher tolerance to Beta VOC than convalescents do, because the induced anti-RBD NAbs display a high diversity and are unaffected by the N-terminal domain (NTD) of the S protein mutations, characterized by neutralization assays of plasma and high-throughput single-cell VDJ sequencing of peripheral blood mononuclear cells (PBMCs) from vaccinees and convalescents (80).

Following the circulating of Omicron VOC, we tested the ZF2001-elicited human sera and found that three doses of ZF2001 administration with a long interval (4-6-month) between the second and third doses elicited higher NAb levels against the Omicron VOC than those with a short interval (less than 2-month) (81). The NAb GMTs against the Omicron VOC were 3.1 and 10.6 folds lower than those against the prototype in the recipients with long interval and short interval vaccination, respectively (81). Therefore, a boost strategy with an extended interval would be beneficial for enhanced and broad humoral immune responses against SARS-CoV-2 variants, including Omicron. In addition, recently, we released the data of Phase 3 clinical trials, which showed that ZF2001 conferred efficacies in preventing symptomatic and severe-to-critical COVID-19 of 81.4% and 92.9%, respectively, with short-term (~50 days) follow-up, and of 75.7% and 87.6% respectively, with long-term (6 months) follow-up (Table 1). The vaccine efficacies preventing Alpha and Delta VOCs were 92.7% and 81.4% in the short-term follow-up, and 88.3% and 76.1% in the long-term follow-up, respectively (82).

NVX-CoV2373 (Nuvaxovid) is composed of a trimeric full-length S-2P protein with another three mutations at the furin cleavage site (R682Q, R683Q and R685Q), adjuvanted with Matrix-M1 (83). A Phase 2 trial found that a two-dose regimen of 5-μg NVX-CoV2373 was immunogenic and well tolerated in both younger and older adults, with serum neutralization GMTs exceeding those seen in a panel of HCS (84). In Phase 3 clinical trials, two 5-μg doses of NVX-CoV2373 provided 90.4% efficacy protection against COVID-19 in the USA and Mexico, in which most cases were caused by VOCs and VOIs (largely Alpha) (85).
Another study in South Africa showed that the efficacy of the NVX-CoV2373 vaccine was 60.1% in HIV-negative participants during circulation of the Beta VOC in South Africa (86). In the UK, 89.7% protection was observed, with an efficacy of 86.3% against the Alpha VOC (87).

Seasonal influenza epidemics occur globally. An annual influenza vaccination is recommended for prevention in many countries. This continued large-scale COVID-19 vaccination campaign will certainly coincide with the influenza vaccination. A sub-study was conducted in the UK to evaluate the safety, immunogenicity and efficacy of NVX-CoV2373 co-administered with licensed seasonal influenza vaccines. The results showed that the incidence of adverse events was low and balanced between the co-administration group and the NVX-CoV2373-alone group. Although a reduction in antibody responses to the NVX-CoV2373 vaccine was observed in the co-administration groups, the NVX-CoV2373 vaccine efficacy in the sub-study was 87.5%, similar to the efficacy in the main study (88).

Another recombinant COVID-19 vaccine developed by West China Hospital of Sichuan University, China (89) (Table 2) contains the SARS-CoV-2 RBD protein and has an aluminum hydroxide adjuvant. Both this RBD immunogen and the previously described spike immunogen used in the NVX-CoV2373 vaccine were grown in Sf9 cells. The results of Phase 1 and 2 trials showed that the levels of humoral immune responses induced by this vaccine were highest in the participants receiving three doses (0, 14, 28 days) at a high dose (40 μg) among all the groups (90). In addition, cellular immune responses (IFN-γ release) could be elicited by this vaccine and the magnitude was highest in the 14 days after the last immunization. The most common adverse reactions were pain, fatigue, cough, sore throat, fever and headache, which were mild or moderate in severity (90). The results of Phase 1 and 2 trials demonstrated that this vaccine is safe and immunogenic in humans with three doses of administration (90).

MVC-COV1901 vaccine, developed by Medigen Vaccine Biologics Corporation, Taiwan, China, contains the S protein ectodomain with two proline substitutions at residues 986 and 987, a “GSAS” substitution at residues 682–685 to abolish the furin cleavage site and a T4 fibrin trimerization motif; it is adjuvanted by aluminum hydroxide and CpG 1018 (91,92).

MVC-COV1901 has a good safety profile in Phase 1 and 2 clinical trials (91,92). Two doses of 15 μg and 25 μg MVC-COV1901 vaccine both induced higher NAb levels than those of a panel of HCS (91). In the antibody titration assays, The World Health Organization (WHO) reference standard National Institute for Biological Standards and Control (NIBSC) was used to convert the NAb and binding-antibody GMTs to international units (IU)/ml and binding-antibody units (BAU)/ml, respectively (92). To confront the SARS-CoV-2 variants, the NAb activity against a pseudovirus with Beta VOC S protein declined significantly, compared with the prototype S protein pseudovirus (93). In addition, enzyme-linked immunospot (ELISpot) assays showed that MVC-COV1901 vaccine elicited IFN-γ-producing cells, but minimal IL-4-producing cells (91) (Table 2).

The Sclamp subunit vaccine contains the prefusion S ectodomain, replaces the furin cleavage site 680–690 with a glycine–serine–glycine linker, trimerized by a molecular clamp sequence from human immunodeficiency virus 1 (HIV-1) glycoprotein 41 (gp41) and is adjuvanted by MF59; it was developed by University of Queensland and CSL Limited, Australia (94). The results of a Phase 1 trial showed that Sclamp was well tolerated with
similar frequencies of adverse events to the placebo group (94). Two doses of Sclamp vaccine induced strong antigen-specific polyfunctional CD4 T-cell responses and NAb responses. The NAb GMTs were at similar levels among the 5, 15 and 45 μg groups (94) (Table 2). However, humoral responses against HIV-1 gp41 were elicited by the Sclamp vaccine, which could be detected by commonly used HIV diagnostic tests, posing the potential to impact existing HIV screening programmes. Therefore, studies are ongoing with alternative trimerization domains to ameliorate this response (94).

FINLAY-FR-1 and FINLAY-FR-1A contain a recombinant SARS-CoV-2 dimeric RBD protein adjuvanted by aluminum hydroxide (FINLAY-FR-1A) or adjuvanted by the outer membrane vesicles from Neisseria meningitidis group B (OMVs) plus aluminum hydroxide (FINLAY-FR-1); they were developed by Finlay Vaccine Institute and Centre of Molecular Immunology, Cuba (95). The recombinant dimeric RBD protein has two copies of the RBD protein (amino acid residues 319–541 with a poly-histidine fusion tag at its C-terminus) connected by a Cys538–Cys538 interchain disulphide bridge (95).

The NAb GMT induced by three doses of FINLAY-FR-1 (50 μg) was higher than those of FINLAY-FR-1A (25 and 50 μg), indicating that OMVs improved the immune response induced by the dimeric RBD protein (Table 2). The adverse events reported by participants who received FINLAY-FR-1 vaccine were higher than those reported by FINLAY-FR-1A vaccine, though serious adverse events were not found (95). Another study demonstrated that a booster dose of FINLAY-FR-1A (50 μg) to COVID-19 convalescents enhanced the magnitudes of NAb titers and cellular immune responses (96). These results of Phase 1 trials showed that both FINLAY-FR-1 and FINLAY-FR-1A were safe and immunogenic, and the addition of OMVs adjuvant increased the NAb responses (95,96).

Inactivated virus vaccines

BBIBP-CorV (Covilo) is an inactivated whole virus, adjuvanted with aluminum hydroxide. BBIBP-CorV is safe, well tolerated and immunogenic in participants aged 3–17, 18–59 and ≥ 60 years (97,98). The results of the Phase 3 trial showed that BBIBP-CorV conferred 78.1% protection against COVID-19 (99). The effectiveness of BBIBP-CorV against SARS-CoV-2 infection and COVID-19-related mortality in Hungary was 68.7% and 87.8%, respectively (32) (Table 1).

CoronaVac is composed of an inactivated virus and an aluminum hydroxide adjuvant. A study in Chile demonstrated that immunization with CoronaVac in a 0–14 day schedule induced IFN-γ-producing cellular responses and generation of NAbs with higher titers in participants aged 18–59 years than in adults aged ≥ 60 years (100). In addition, a Phase 1/2 clinical trial of CoronaVac conducted in China showed that two doses of CoronaVac were well tolerated and induced humoral responses in children and adolescents aged 3–17 years (101). However, vaccine-elicited circulating NAb titers declined substantially six months after the second dose.

To reduce the decrease in antibody levels after vaccination, a third dose was administered (102). Recently, the results showed that a third dose of CoronaVac in adults administered 8 months after the second dose effectively induced a remarkable increase in antibody levels (102). Specially, in the group of recipients received 3 μg CoronaVac, which is the licensed
formulation, with a 0-28 days-8 months schedule, the induced NAb GMTs were 45.9, 6.8 (slightly below the seropositive cutoff) and 143.1 at 28 days after the second dose, 6 months after the second dose and 28 days after the third dose, respectively. (102). The immune responses induced by CoronaVac against variants were evaluated and showed that 50% pseudovirus-neutralization titers in sera collected 14 days after the second dose decreased by 1.51-, 1.25-, 3.92-, 4.03- and 5.27-fold for Alpha, Epsilon, Gamma, Iota and Beta, respectively, compared with NAb levels against wild-type S pseudovirus (103). For the currently emerging and circulating Omicron VOC, all 25 tested sera samples from CoronaVac-vaccinees, with neutralization activity against the prototype virus, could not neutralize the Omicron VOC (104). Although SARS-CoV-2 variants (especially Beta, Gamma and Omicron) escape vaccine-elicited NAbS, the elicited IFN-γ-secreting T cells exhibit similar responses to the prototype and VOCs of SARS-CoV-2 (105,106).

Phase 3 clinical trials revealed that vaccine efficacy against symptomatic COVID-19 was 83.5% in Turkey (107) (Table 1). In the real world, two doses of CoronaVac immunization were associated with 46.8% protection against symptomatic COVID-19 in older adults (≥ 70 years old) in the setting of widespread transmission of the Gamma VOC in Brazil (108). The effectiveness of vaccine CoronaVac was 65.9% for the prevention of COVID-19 analyzed in a cohort that included approximately 10 million persons in Chile (109). In addition, the overall effectiveness of two-dose BBIBP-CorV and CoronaVac during the outbreak of the Delta VOC in May 2021 in Guangzhou, China was 59.0% against COVID-19 and 70.2% against moderate disease (110).

BBV152 (Covaxin) is another inactivated virus vaccine with a toll-like receptor 7 (TLR7)/TLR8 agonist molecule adsorbed to alum (Algel-IMDG) adjuvant. Following the two-dose schedule vaccination, both antibody responses and cellular immune responses were activated (111), as well as innate immune responses, characterized by profound changes in plasma cytokine and chemokine levels (112). In the Phase 3 trial, two doses of immunization with BBV152 were immunogenic and conferred efficacies of 77.8% and 63.6% in preventing symptomatic COVID-19 and asymptomatic infections, respectively (113) (Table 1).

QazCovid-in vaccine contains inactivated whole-virion and an aluminum hydroxide adjuvant; it was developed by the Research Institute for Biological Safety Problems, Kazakhstan (114). The results of Phase 1 and 2 trials showed that this vaccine was safe and well-tolerated in adults aged from 18 to 70 years and caused predominantly mild adverse events. Two doses of QazCovid-in vaccine (5 μg) promoted pronounced humoral immune responses, with higher antibody titers in young participants aged 18-49 years than in participants aged ≥50 years. In addition, multifunctional cellular responses (induction of IFN-α, IFN-γ, TNF-α, IL-4 and IL-6) were elicited (114) (Table 2).

DNA vaccine

A DNA vaccine, ZyCoV-D, expresses full-length S protein and was developed by Zydus Cadila, India (115). ZyCoV-D was administered with three doses through the intradermal route via a needle or needle-free injection system (NFIS) by the Pharmajet Tropis® device. The NAb GMT level induced in the NFIS 2 mg group was the highest among needle 1/2 mg
and NFIS 1/2 mg groups, similar to a panel of HCS (Table 2). In addition, cellular responses (IFN-γ production) were induced (115). Further Phase 2 and 3 studies are ongoing.

Sequential heterologous immunization

In order to mitigate intermittent COVID-19 vaccine supply shortages and enhance safety and immunogenicity, heterologous COVID-19 vaccine regimens have been studied. Compared with the two doses of AZD1222 immunization, AZD1222-prime and BNT162b2-boost induced significantly higher frequencies of S-specific T cells and higher titers of NAbs against prototype, Alpha, Beta, Gamma and Delta VOCs (116-120).

A real-world study in Denmark showed that the vaccine effectiveness of heterologous immunization with AZD1222 and an mRNA vaccine (BNT162b2 or mRNA-1273) against SARS-CoV-2 infection was 88% 14 days after the second dose and onwards (121). Two doses of inactivated virus vaccine followed by a third boost dose of AZD1222 or BNT162b2 were studied and showed that the NAb titers in recipients significantly increased after the boost immunization (122-124). In addition, heterologous immunization with two doses of inactivated virus vaccine and a third dose of subunit protein vaccine ZF2001 induced higher generation of NAbs against prototype virus and variants than three doses of inactivated virus vaccine (125,126).

Safety and AEFI

Following the large-scale COVID-19 vaccine inoculation campaign, several rare adverse events have been reported, including myocarditis, thrombotic thrombocytopenia and others.

The occurrence of myocarditis was rare and mainly observed in the vaccinees receiving the mRNA COVID-19 vaccines within the first week, especially after the second dose, in which case it usually resolves within days or weeks. After the second-dose immunization of COVID-19 mRNA vaccines in the USA, the myocarditis reporting rates were 40.6 and 2.4 cases per million doses in males aged 12–29 and ≥30 years, respectively, and 4.2 and 1.0 cases per million doses in females aged 12–29 and ≥30 years, respectively. It was highest in males aged 12–17 years, with 62.8 cases per million doses (127-130).

One explanation for myocarditis following mRNA vaccine immunization is that the human immune system detects exogenous mRNA as an antigen and activates inflammatory cascades and immunologic pathways, which may contribute to the development of myocarditis as a systemic reaction in certain individuals. Another explanation is the cross-reaction between the anti-S-protein antibodies and self-antigens. In addition, sex hormone differences may contribute to the male predominance in myocarditis cases (131).

The benefits of using mRNA COVID-19 vaccines under the Food and Drugs Administration (FDA) Emergency Use Authorization (EUA) clearly outweigh the risks in all populations, including adolescents and young adults, for the following reasons: i) the occurrence ratio of myocarditis after an mRNA vaccine vaccination is more than 100-fold lower than that caused by COVID-19, and the mRNA vaccines protect vaccinees against COVID-19; and ii) the mRNA vaccine-related myocarditis is generally mild or moderate, but
the symptoms of COVID-19-related myocarditis are much more severe and the risks of hospitalization and death associated with COVID-19 are much greater (130,131).

Thrombosis with thrombocytopenia syndrome is a rare but potentially fatal complication that occurs after vaccination with COVID-19 vaccines, particularly AZD1222 and Ad26.COV2.S. (132-136). The incidence of vaccine-induced immune thrombotic thrombocytopenia (VITT) is 14.9 cases per million vaccinees after the first or unknown dose and 1.8 cases per million vaccinees after the second dose (137).

Antibodies against platelet factor 4 (PF4) and low platelet levels were observed in patients with VITT. Immune complexes are formed with these anti-PF4 antibodies and bind to platelet FcγRIIa receptors, consequently activating platelets and the coagulation system (138,139).

The link between vaccination with COVID-19 vaccines and the formation of anti-PF4 antibodies is a critical focus. One explanation is that PF4 interacts with adenoviral vectors or other vaccine components (such as culture cell-derived proteins), becoming immunogenic and triggering the formation of autoantibodies against PF4 (138,140). In addition, the possibility of cross-reactivity between anti-PF4 antibodies and SARS-CoV-2 S protein was excluded (141). The exact mechanism has yet to be determined.

Conclusions and perspectives

The published clinical trials data show that most of the COVID-19 vaccines and candidates are safe, with a very low incidence of rare adverse events, and they are immunogenic and confer substantial protection against COVID-19, including that caused by SARS-CoV-2 variants. However, following the ongoing COVID-19 vaccine immunization campaigns, adverse events — especially rare adverse events with low incidence and vaccine effectiveness in the real world — should be monitored continuously, which will provide valuable advice for policy making.

Although high immunization coverage has been achieved in some countries, the uneven distribution of COVID-19 vaccines has led to limited access to vaccines and low vaccination coverage rates in some countries. In the era of globalization, solidarity and cooperation are necessary to control the unprecedented COVID-19 pandemic. In addition to increasing the supply of vaccines to countries with low vaccination coverage, immunization strategies could be optimized to build an effective immune barrier rapidly. These include: i) increasing the coverage of single-dose immunization, because the high seroconversion rate after a single dose in naïve participants could benefit the prevention of COVID-19 and delay the administration of the second dose to increase the number of people vaccinated (142-144); ii) an extended vaccine interval, which contributes to higher antibody levels compared with those vaccinated with standard or short intervals, as well as vaccine efficacies (58,81,145,146); and iii) sequential heterogeneous vaccination.

Currently, decreased vaccine effectiveness has been observed. One major factor is the newly emerging and circulating SARS-CoV-2 variants, particularly the Omicron VOC, which are resistant to the immune responses induced by COVID-19 vaccines. The other is the waning of antibody responses, especially half a year after the last dose of vaccination, and NAb titers were correlated with vaccine protection efficacy (147). Therefore, boost
immunization is performed to overcome the decline in vaccine effectiveness. Meanwhile, the development of vaccines with the advantages of broad cross-reactivity to SARS-CoV-2 variants and the induction of mucosal immune responses will contribute to higher efficacy in boosting immunization.
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Table 1. Updated results of the efficacy and effectiveness in preventing COVID-19 of early vaccines.

| Vacci1ne                  | Efficacy in preventing COVID-19 in Phase 3 clinical trials | Effectiveness in preventing COVID-19 in real-world | References |
|---------------------------|-----------------------------------------------------------|-----------------------------------------------------|------------|
| BNT162b2 (Comirnaty)      | 91.3% (symptomatic) 96.7% (severe)                       | USA: 91.3% (symptomatic) 96% (hospitalization/death) 83.3% (infection); 90.6% (death) UK: 93.7% (symptomatic caused by Alpha); 85.0% (symptomatic caused by Delta); 90% (death caused by Delta in Scotland) Italy: 83% (infection caused by Alpha) Qatar: 51.9% (infection); 93.4% (severe/critical/fetal disease caused by Delta) | (29-34,35,36) |
| mRNA-1273 (SpikeVax)      | 63.0% (infection) 93.2% (symptomatic) 98.2% (severe)    | Canada: 94% (symptomatic); 96% (hospitalization/death) Hungary: 88.7% (infection); 93.6% (death) USA: 86.7% (infection); 97.5% (hospitalization caused by Delta) Qatar: 73.1% (infection); 96.1% (severe/critical/fetal caused by Delta) | (30,32,36,54,55) |
| AZD12222 (Vaxzevria)      | 74.0% (symptomatic) 100% (severe or critical symptomatic) | UK: 74.5% (symptomatic COVID-19 caused by Alpha); 67.0% (symptomatic COVID-19 caused by Delta); 91% (death caused by Delta in Scotland) Hungary: 71.5% (infection); 88.3% (death) India: 63.1% (infection); 81.5% (moderate-to-severe) | (32,34,35,59,61) |
| Ad26.COV2.S               | 66.9% (symptomatic) 76.7% (severe or critical symptomatic) | USA: 73.6% (infection) 86.6% (symptomatic) | (31,66,67) |
| Ad5-nCoV (Convidecia)     | 57.5% (symptomatic) 91.7% (severe)                       | NA                                                  | (71)       |
| Gam-COVID-Vac (Sputnik V) | 91.6% (symptomatic) 100% (moderate or severe)            | Hungary: 85.7% (infection); 97.5% (death)          | (32,148)   |
| ZF2001 (ZIFIVAX)          | Short-term (~50 days) follow-up: 81.4% (symptomatic) 92.9% (severe or critical) Long-term (6 months) follow-up: 75.7% (symptomatic) 87.6% (severe or critical) | NA                                                  | (82)       |
| NVX-CoV2373 (Nuvaxovid)   | NA                                                        | US and Mexico: 90.4% (symptomatic); 100% (moderate-to-severe) South Africa: 60.1% (symptomatic) UK: 89.7% (symptomatic) | (85-87)    |
| BBIBP-CorV (Covido)       | 78.1% (symptomatic)                                       | Hungary: 68.7% (infection); 87.8% (death)         | (32,99)    |
| CoronaVac                 | 83.5% (symptomatic)                                       | Brazil: 46.8% (symptomatic); 55.5% (hospital admission); 61.2% (death) Chile: 65.9% (symptomatic); 87.5% (hospitalization); 86.3% (death) | (107-109)  |
| BBV152 (Covaxin)          | 83.6% (asymptomatic infection) 77.8% (symptomatic) 83.4% (severe) | India: 50% (symptomatic) | (113,149) |

1In the setting of widespread transmission of Delta VOC.
Arizona, Iowa, Minnesota, Florida, and Wisconsin.  
New York State.  
In the setting of widespread transmission of the Alpha VOC.  
Largely caused by Beta VOC.  
The interim efficacy results of phase 3 clinical trial in Turkey.  
In the setting of widespread transmission of the Gamma VOC.  
NA, not applicable.
Table 2. Features of recent vaccines and candidates against COVID-19.

| Vaccine                        | Platform          | Developer                                      | Formulation                                                                 | NAb level in humans                                                                 | Cellular responses in humans | Efficacy                     | References |
|-------------------------------|-------------------|-----------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------|-----------------------------|------------|
| Recombinant COVID-19 vaccine  | Protein subunit   | West China Hospital of Sichuan University, China | RBD protein + aluminum hydroxide adjuvant                                  | Induction of NAb in humans and no comparison with HCS                              | Induction of IFN-γ T-cell responses | NA                          | (90)       |
| MVC-COV1901                   | Protein subunit   | Medigen Vaccine Biologics Corporation, Taiwan, China | S protein with two proline substitutions (K986P and V987P), 682-685 “GSAS” substitution at the furin cleavage site and T4 fibrin trimerization motif + aluminum hydroxide and CpG 1018 adjuvants | Higher GMT levels than HCS in 15 μg and 25 μg groups                               | Induction of IFN-γ T-cell responses | NA                          | (91,92) |
| Sclamp                        | Protein subunit   | University of Queensland and CSL Limited, Australia | Prefusion trimeric S protein with molecular clamp domain from HIV-1 gp41 protein + MF59 adjuvant | Similar titers among 5, 15 and 45 μg groups, and generally similar to HCS          | Predominantly Th1 phenotype     | NA                          | (94)       |
| FINLAY-FR-1 (SOBERANA 01) and FINLAY-FR-1A (SOBERANA Plus) | Protein subunit | Finlay Vaccine Institute and Centre of Molecular Immunology, Cuba | Dimeric RBD protein with Cys538–Cys538 interchain disulfide bridge + OMVs and aluminum hydroxide adjuvants (for FINLAY-FR-1) or aluminum hydroxide adjuvant (for FINLAY-FR-1A) | Higher GMT level than HCS in FINLAY-FR-1 (50 μg) group; Lower GMT levels than HCS in FINLAY-FR-1A (CS and 50 μg) groups | NA in naïve participants | NA                          | (95)       |
| CVnCoV                         | mRNA              | CureVac AG, Germany                           | LNP-mRNA expressing full-length S protein with two proline substitutions (K986P and V987P) | Generally lower GMT levels for all dose groups than HCS                             | NA                          | 48.2% overall vaccine efficacy against symptomatic COVID-19 | (56,57) |
| ZyCoV-D                       | DNA               | Zydus Cadila, India                           | DNA plasmid expressing full-length S protein                               | Generally similar (NFIS 2 mg group) to or lower (NFIS 1 mg and Needle 1/2 mg groups) than HCS | Induction of IFN-γ cellular responses | NA                          | (115)      |
| QazCovid-in                   | Inactivated virus | Research Institute for Biological Safety Problems, Kazakhstan | Inactivated whole virus + aluminum hydroxide adjuvant                       | Induction of NAb in humans and no comparison with HCS                              | Induction of IFN-γ, TNF-α, IL-4, IL-6 T-cell responses | NA                          | (114)      |

NA, not applicable.
Figure legend

Fig. 1. The 30 authorized COVID-19 vaccines.