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REVIEW

A review of the safety and efficacy of current COVID-19 vaccines

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Abstract **Vaccination is the most effective and feasible way to contain the coronavirus disease 2019 (COVID-19) pandemic. The rapid development of effective COVID-19 vaccines is an extraordinary achievement. This study reviewed the efficacy/effectiveness, immunogenicity, and safety profile of the 12 most progressed COVID-19 vaccines and discussed the challenges and prospects of the vaccine-based approaches in a global crisis. Overall, most of the current vaccines have shown safety and efficacy/effectiveness during actual clinical trials or in the real-world studies, indicating a development of pandemic control. However, many challenges are faced by pandemic control in terms of maximizing the effect of vaccines, such as rapid vaccine coverage, strategies to address variants with immune escape capability, and surveillance of vaccine safety in the medium- and long-terms.**

Keywords COVID-19; SARS-CoV-2; vaccine; safety; efficacy; effectiveness; immunogenicity

Introduction

The pandemic of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has substantially affected public health, the economy, and society worldwide. As of August 9, 2021, more than 200 million confirmed cases of COVID-19 and more than 4 million deaths had been reported to the World Health Organization (WHO) [1]. Non-pharmaceutical interventions (NPIs) are mainly employed for achieving control over the epidemic and suppressing SARS-CoV-2 transmission [2]. However, researchers believe that the world will not return to normal until safe and effective vaccines are widely available. Considering the unprecedented effect of the pandemic, scientists, vaccine manufacturers, and regulatory agencies in many countries quickly responded and launched a "saturated" research and development competition to generate COVID-19 vaccines, with all technological routes operating in tandem. Currently, more than 290 vaccines are being developed, and more than 100 vaccines are undergoing clinical trials [3].

As of July 2021, 12 COVID-19 vaccine manufacturers have released the results of phase 3 clinical trials, including four inactivated, four non-replicating viral vector, three RNA-based, and one protein subunit vaccines. Among these vaccines, three inactivated vaccines (BBIBP-CorV, CoronaVac, WIV04) and one adenoviral vector vaccine (Ad5-nCoV) received the conditional marketing authorization in China [4–7]. Two RNA-based vaccines (BNT162b2 and mRNA-1273) and one adenoviral vector vaccine (Ad26.COV2.S) received emergency use authorization for the first time in USA [8]. An adenoviral vector vaccine (AZD-1222) was first approved in the UK [9]. One adenovirus vector vaccine (Gam-COVID-Vac) registered in Russia [10]. An inactivated vaccine (COVAXIN) was first licensed in India [11]. After being licensed in the countries of origin, some vaccines were approved for use in other countries (details in Table 1). In addition, BBIBP-CorV, CoronaVac, BNT162b2, mRNA-1273, mRNA-1273, and Ad26.COV2.S are included in the WHO emergency use listings [12]. A two-dose immunization schedule is implemented for most vaccines (83%, 10/12), and a one-dose schedule is implemented for two vaccines (17%). The present review summarizes the safety and efficacy of the 12 current COVID-19 vaccines and discusses the challenges in developing vaccines against SARS-CoV-2 variants.

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Efficacy and effectiveness

Efficacy in clinical trials

In phase 3 clinical trials of COVID-19 vaccines, the two key efficacy endpoints are protection against symptomatic COVID-19 cases and protection against severe disease. The efficacy of each vaccine is summarized in Table 1. Reports on the efficacy are available for 12 vaccines, and all the vaccines except CVnCoV were above the criterion set by the WHO Target Product Profiles for COVID-19 vaccines (50%) [13]. The efficacies of RNA-based vaccines mRNA-1273, BNT162b2, and CVnCoV are 94.1%, 95.0%, and 48% against symptomatic COVID-19 cases and 100%, 88.9% (after dose 1), and 77% (in the age group of 18–60 years) against severe disease or moderate-to-severe disease, respectively [14–16]. The efficacies of adenoviral vector vaccines AZD-1222 and Gam-COVID-Vac with a two-dose regimen are 64.2% and 91.6% against symptomatic cases and 85.4% and 100% against severe disease or moderate-to-severe disease, respectively [17,18]. The efficacies of single-dose adenoviral vector vaccines Ad26.COV2.S and Ad5-nCoV are 66.5% and 68.83% against symptomatic cases and 85.4% and 95.47% against severe disease, respectively [7,19]. Efficacy Data have been reported for four inactivated vaccines. The efficacies of BBIBP-CorV against symptomatic and severe diseases were 78.1% and 100%, respectively [20]. Similar to BBIBP-CorV, the efficacies of COVAXIN were 77.8% and 93.4% for symptomatic and severe diseases, respectively [21]. In addition, the efficacies of WIV04 were 72.8% and 100% against symptomatic and severe diseases, respectively [20]. The efficacy of CoronaVac varies widely across countries. For symptomatic cases, the efficacies of CoronaVac are 83.5%, 65.30%, and 50.7% in Turkey, Indonesia, and Brazil, respectively, and 100% for severe cases in Brazil [22–25]. Among the protein subunit vaccines, only NVX-CoV2373 with the Matrix-M adjuvant has efficacy Data of 89.7%–90.4% against symptomatic cases and 100% against severe disease [26,27]. Notably, the efficacy of these vaccines may not be directly comparable because of differences in study design, population, sites, time, and cases surveillance systems.

Effectiveness in real-world

The actual effectiveness of five vaccines (BNT162b2, mRNA-1273, AZD-1222, CoronaVac, and Ad26.COV2.S) has been reported in several countries, and the findings were all consistent with the efficacy observed in clinical trials. The majority of prospective studies of effectiveness were conducted in Israel, United States, and UK (Table 1). Israel's mass vaccination campaigns with BNT162b2 was launched on December 20, 2020. As of February 24, 2021, 68.7% of Israelis older than 16 years had received their first vaccine dose, making it one of the fastest vaccination campaigns in the world [28]. The efficacies of BNT162b2 against symptomatic cases, hospitalizations, and severe diseases were 94%, 87% and 92%, respectively, after the second dose in Israel [29]. In terms of the effect of vaccination campaigns at the population level, a large and early decrease in COVID-19 cases and hospitalizations were observed in elderly individuals who were prioritized and therefore received the vaccine earlier and in cities that started vaccination early [28]. The dynamic of the second wave of the pandemic (third lockdown plus vaccine campaigns) differed substantially across age groups, which was not observed in the first wave (second lockdown) [28]. This scenario demonstrates the effectiveness of nationwide vaccination campaigns in Israel. The CoronaVac study in Chile also showed effectiveness levels of 65.9%, 87.5%, 90.3%, and 86.3% against symptomatic cases, hospitalization cases, cases requiring admission to the ICU, and confirmed death [30]. Ad26.COV.S showed a similar efficacy (76.7% against SARS-CoV-2 infection) to that reported in the phase 3 clinical trial [31]. Furthermore, in the United States, the actual effectiveness of single-dose mRNA vaccines reached 80% [32], although most of the partially immunized results included Data between two doses and may not accurately reflect the effectiveness of a single dose of a vaccine. In addition to the effectiveness of the vaccine, the effects of vaccination campaigns nationwide depend on the vaccine coverage, the timing of vaccine campaign initiation, and the behavior of vaccinated individuals [33]. Earlier, more proactive, and larger-scale vaccine campaigns are urgently needed worldwide to control the COVID-19 pandemic.

Considering the lack of head-to-head clinical trials, the comparison of the efficacy of different vaccines is inappropriate. However, in the real world, when multiple vaccinations are used in the same region or country, the effectiveness of different vaccines may be compared. A study in the US revealed that the adjusted effectiveness of BNT162b2 and mRNA-1273 were 93% (95% CI 78%–98%) and 82% (95% CI 20%–96%) against SARS-CoV-2 infection, respectively [34]. One test negative case control study showed that the adjusted effectiveness of AZD-1222 was lower than that of BNT162b2 against symptomatic diseases caused by the Alpha (66.1% vs. 93.4%) or Delta variants (87.9% vs. 59.8%) [35]. However, the effectiveness of AZD-1222 and BNT162b2 against hospitalizations caused by the Alpha (86% vs. 95%) or Delta variants (92% vs. 96%) was similar with that in England [36]. Studies in Scotland also showed no substantial difference in the effectiveness of a single dose of AZD-1222 or BNT162b2 in hospital admission (88% vs. 91% at 28–34 days post-vaccination) [37].

The duration of protection also raises great concerns, which is best evaluated by ongoing blinded follow-up of placebo group in phase 3 trial [38]. However, ethical

Table 1 Efficacy, effectiveness, and basic information of vaccine

Vaccine (alternative name)	Sponsor	Vaccine type	Storage	Regimen	Countries in use [10,114]	Efficacy of phase 3		
						Days after vaccination	Sample size	Efficacy for COVID-19, VE (%) (95% CI)
Gam-COVID-Vac (Sputnik V) [17]	Gamaleya Research Institute; Health Ministry of the Russian Federation	Viral vector (Non-replicating)	Frozen: stable at –18 °C; Lyophilized: stable at 2–8 °C	2 doses, 0/21 days	70 countries including Hungary, Serbia, UAE, Belarus, Russia, etc.	21 days after dose 1	27 530	Symptomatic diseases: 91.6 (85.6–95.2) (RUS) Moderate to severe disease: 100 (94.4–100) (RUS)
AZD-1222 (Covishield, Vexzevria) [18,83,115]	Oxford Universty/ AstraZeneca		Stable at 2–8 °C	2 doses, 0/4–12 weeks	121 countries including Argentina, Brazil, India, Mexico, UK, etc.	14 days after dose 2	7548 (GBR) 4088 (BRA) 1467 (RSA)	Symptomatic diseases: 73.5 (55.5–84.2) (GBR) 64.2 (30.7–81.5) (BRA) 21.9 (–49.9 to 59.8) (RSA) 76 (68–82) (USA) Severe diseases: 100 (GBR)[a] 100 (USA)
Ad5-nCoV [7,116]	CanSino Biological Inc./Beijing Institute of Biotechnology		Stable at 2–8 °C	1 dose	8 countries including Chile, China, Hungary, Mexico, Pakistan, etc.	14 days after dose 1	Approximately 40 000	Symptomatic diseases: 68.83 Severe diseases: 95.47
Ad26.COV2.S [19]	Janssen Pharmaceutical		Stable at –20 °C; 2–8 °C for 3 months	1 dose	59 countries including Brazil, Italy, Spain, Thailand, USA, etc.	28 days after dose 1	39 058	Symptomatic diseases: 66.5 (55.5–75.1) (USA/BRA/RSA) Severe diseases: 85.4 (54.2–96.9) (USA/BRA/RSA)
BBIBP-CorV [20]	Sinopharm/China National Biotec Group Co./Beijing Institute of Biological Products	Inactivated virus	Stable at 2–8 °C	2 doses, 0/21 days	59 countries including Bahrain, China, Pakistan, Peru, UAE, etc.	14 days after dose 2	25 463	Symptomatic diseases: 78.1 (64.9–86.3) (UAE/BRN/EGY/JOR) Severe diseases: 100 (NE–100) (UAE/BRN/EGY/JOR)
WIV04 [20]	Sinopharm/China National Biotec Group Co./Wuhan Institute of Biological Products		Stable at 2–8 °C	2 doses, 0/21 days	China and UAE	14 days after dose 2	25 480	Symptomatic diseases: 72.8 (58.1–82.4) (UAE/BRN/EGY/JOR) Severe diseases: 100 (NE–100) (UAE/BRN/EGY/JOR)
COVAXIN (BBV152) [21]	Bharat Biotech International Limited		Stable at 2–8 °C	2 doses, 0/28 days	9 countries including India, Mexico, Nepal, Paraguay, Philippines, etc.	14 days after dose 2	25 753	Symptomatic diseases: 77.8 (65.2–86.4) (IND) Severe diseases: 93.4 (57.1–99.8) (IND)

(*Continued*)

Vaccine (alternative name)	Sponsor	Vaccine type	Storage	Regimen	Countries in use [10,114]	Efficacy of phase 3		
						Days after vaccination	Sample size	Efficacy for COVID-19, VE (%) (95% CI)
CoronaVac [22–25]	Sinovac Research and Development Co., Ltd.		Stable at 2–8 °C	2 doses, 0/14 days	39 countries including Brazil, China, Chile, Turkey, Indonesia, etc.	14 days after dose 2	10 214 (TUR) 1603 (INA) 12 396 (BRA)	Symptomatic diseases: 83.5 (65.4–92.1) (TUR) 65.30 (18.95–85.10) (INA) 50.7 (35.9–62.0) (BRA) Severe diseases: 100 (16.9–100) (BRA)
BNT162b2 (Comirnaty) [15]	BioNTech/ Pfizer/ Fosun Pharma	RNA based vaccine	Stable at –80 °C to –60 °C; 2–8 °C for 1 month	2 doses, 0/21 days	97 countries including Argentina, Mexico, Saudi Arabia, Canada, USA, UK, etc.	7 days after dose 2	43 548	Symptomatic diseases: 95.0 (90.3–97.6) (USA) Severe diseases: 88.9 (20.1–99.7) (USA)[b]
mRNA-1273 [14]	Moderna/National Institute of Allergy and Infectious Diseases (NIAID)		Stable at –50 °C to –15°C; 2–8 °C for 30 days; 8–25 °C for 24 h	2 doses, 0/28 days	65 countries including Canada, Israel, Switzerland, USA, UK, etc.	14 days after dose 2	30 420	Symptomatic diseases: 94.1 (89.3–96.8) (USA) Severe diseases: 100 (NE–100) (USA)[a]
CVnCoV [16]	CureVac AG		Stable at 2–8 °C	2 doses, 0/28 days	Not approved	NA	Approximately 40 000	Symptomatic diseases: 48 Moderate to severe diseases: 77[c,d]
NVX-CoV2373 [26,27,94]	Novavax	Protein subunit	Stable at 2–8 °C	2 doses, 0/21 days	Not approved	7 days after dose 2	14 039 (GBR) 2684 (RSA) 29 960 (USA/MEX)	Symptomatic diseases: 89.7 (80.2–94.6) (GBR) 90.4 (82.9–94.6) (USA/MEX) 49.4 (6.1–72.8) (RSA) Moderate or severe disease: 100 (87–100) (USA/MEX) Severe diseases: 100 (GBR)[a] 100 (RSA)[a]

[a]Few cases of severe disease observed in the trial and all occurred in the placebo group.
[b]Severe COVID-19 occurrence after dose 1.
[c]Results of age group 18–60 years.
[d]This study was conducted in 10 countries including Argentina, Belgium, Colombia, Dominican Republic, Germany, Mexico, Netherlands, Panama, Peru, and Spain.
TUR, Turkey. BRA, Brazil. USA, United States of America. GBR, UK. RSA, Republic of South Africa. RUS, Russia. UAE, United Arab Emirates. BRN, Bahrain. EGY, Egypt. JOR, Jordan. INA, Indonesia. MEX, Mexico. NA, not available. NE, not estimable.

considerations require that vaccines are provided to the placebo group in a timely manner during the pandemic [39]. The blind crossover design would be the preferred way to assess the durability of COVID-19 vaccine efficacy even after placebo group participants receive the vaccine [40]. In addition, real-world studies are important to assess the long-term protective effects of vaccines. Currently, Data on the long-term efficacy of the vaccine are lacking because of the relatively short period of time since phase 3 studies are launched.

Immunogenicity

Neutralizing antibodies

Vaccine-elicited neutralizing antibody titers can offer a comparable protection as COVID-19 vaccines [41]. Neutralizing activity was assessed by live virus neutralization assays for most vaccines. The seroconversion rate was 96%–100% for all vaccines, except for Ad5-nCoV (47%) [42–54]. Considering the diversity in testing methodologies and lack of head-to-head clinical trials, vaccine-induced neutralizing antibody levels cannot be compared directly. Data are available on neutralizing antibody levels in both vaccinated and convalescent patients for nine vaccines, including Gam-COVID-Vac, AZD-1222, Ad26.COV2.S, COVAXIN, CoronaVac, BNT162b2, mRNA-1273, CVnCoV, and NVX-CoV2373. The relative levels of neutralizing antibodies are summarized in Fig. 1. For vaccines with a two-dose immunization schedule, the neutralizing antibody titers peaked at 7–21 days after the second dose.

Based on the peak neutralizing antibody titer, the mRNA-1273, BNT162b2, and NVX-CoV2373 resulted in relatively high neutralizing antibody titers, reaching 3.4–4 times the GMT in convalescent serum [45,46,50]. Adenovirus vector vaccines with a two-dose schedule (Gam-COVID-Vac and AZD-1222) and COVAXIN resulted in peak neutralizing antibody titers approximately

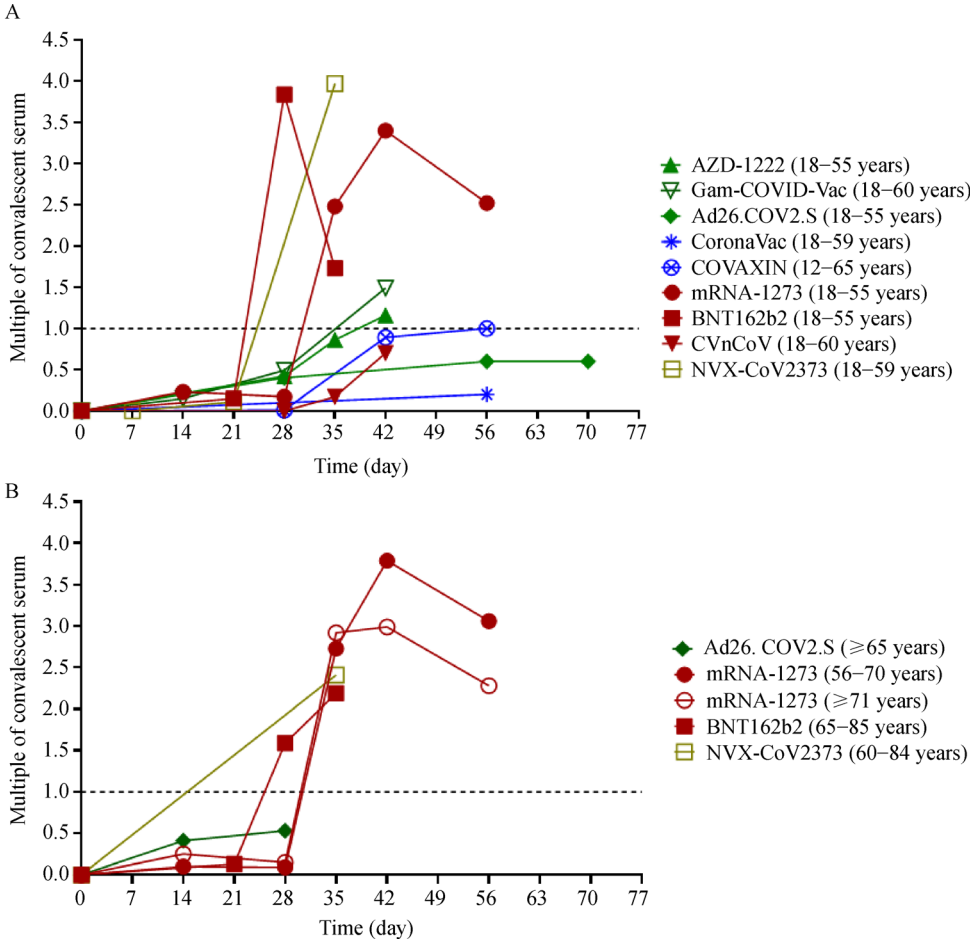

Fig. 1 Comparison of neutralizing antibody titers after vaccination with different vaccines in younger and older participants. (A) Comparison in younger adult participants. (B) Comparison in elderly participants. The colors green, red, blue, and mustard yellow represent adenovirus vector vaccines, RNA-based vaccines, inactivated virus vaccines, and protein subunit vaccines, respectively.

1–2 times that in convalescent serum [43,44,47]. The peak neutralizing antibody titers after vaccination with CoronaVac, Ad26.COV2.S, and CVnCoV were 0.3–0.7-fold that in convalescent serum [49,53,55] (Fig. 1A). One concern with the use of adenoviral vector vaccines is the pre-existing immunity to adenovirus. AZD-1222 had no relationship between the presence of low-level antibodies to ChAdOx1 at baseline and the ELISA titer to SARS-CoV-2 spike protein after vaccination in phase 2 clinical trial, but Data from subjects with high-level antibodies are lacking [44]. The presence of pre-existing immune responses to vaccine vectors components (rAd26 and rAd5) does not affect the titer of RBD-specific antibodies in the serum of participants in the phase 1/2 study of Gam-COVID-Vac [47]. However, in participants who received the Ad5-nCoV vaccine, RBD-specific enzyme-linked immunosorbent assay (ELISA) antibody and neutralizing antibody levels in participants with low pre-existing Ad5 antibodies ($\leqslant$1:200) were approximately two-fold higher than that in participants with high pre-existing Ad5 antibodies ($>$1:200) [54]. The effect of pre-existing immunity on the immune response after AD26.COV2.S immunization has not been reported.

Only four vaccine manufacturers have reported comparable neutralizing antibody results in the elderly population [42,45,49,50]. The immune response in the elderly population is weaker than that in younger adult participants. The peak neutralizing antibody titers after vaccination with RNA vaccines and NVX-CoV2373 were 2–4-fold that in convalescent serum [42,45,50], whereas those after vaccination with Ad26.COV2.S were approximately 0.5-fold that in convalescent serum [49] (Fig. 1B).

The currently available vaccines cannot induce a high level of neutralizing antibodies within 3 weeks after the priming vaccination. Vaccines that can induce a rapid response of neutralizing antibodies may be one of the key targets of future vaccine development. In addition, the indirect comparison of the relative levels of neutralizing antibodies was influenced by the composition of the convalescent serum panels, which varies across studies.

Cell-mediated immunity

Considering that SARS-CoV-2 is a mucosal pathogen, adaptive T cell immunity is also important for control and clearance [56]. Flow cytometry and IFN-γ ELISpot are mainly used to assess the cellular immune response. Cellular immunoassay indicators vary among different vaccine clinical trials, including $CD8^+$ T cell, $CD4^+$ T cell, and IFN-γ. Most vaccines invoke a significant T cell immune response with a Th1 response bias, yielding a balanced Th1/Th2 response [42,43,46–49,51–54,57,58]. Considering the differences in assay methods and indicators, we failed to compare the T cell responses of different vaccines.

Safety

Pre-licensure evaluation

The safety profile is critical to evaluating a vaccine, because these vaccines are administered to healthy populations. For mRNA vaccines, the most common adverse reactions include short-term mild-to-moderate pain at the injection site, fatigue, headache, myalgia, arthralgia, and chills. The incidence and severity of adverse reactions increase after the second dose [14,15]. Adverse reactions are less common and less severe in older participants than in younger participants. A proportion of subjects have experienced grade 3 or above adverse reactions. The frequency of grade 3 pain, fever, fatigue, headache, chills, and muscle pain after a second dose of BNT162b2 is higher than 1% [59]. In the phase 3 clinical trial of mRNA-1273, 5.6% and 19.5% of the subjects experienced grade 3 adverse reactions after the first and second doses, respectively [14]. Notably, four and six serious vaccine-related adverse reactions were encountered in the phase 3 clinical trials of BNT162b2 and mRNA-1273, respectively [14,15]. Pain, fever, chills, muscle ache, headache, and malaise were the most common adverse reactions in subjects who received adenoviral vector vaccines [17–19,54]. Prophylactic paracetamol can effectively reduce adverse reactions. In subjects receiving AZD-1222 who did not use paracetamol, the incidences of grade 3 feverishness, chills, malaise, fatigue, and headache could exceed 5% [44]. One vaccine-related severe adverse event (transverse myelitis) occurred in subjects who received AZD-1222 [18]. Seven serious adverse events were considered to be related to Ad26.COV2.S [19]. Inactivated vaccines have a good safety profile with few grade 3 adverse reactions, and two serious vaccine-related adverse events were considered to be related to CoronaVac, BBIBP-CorV, and COVXIN [20–22,25].

Post-licensure evaluation

Post-licensure safety surveillance allows the timely detection of rare or delayed adverse reactions and those that only occur in certain subgroups [60]. COVID-19 vaccine safety surveillance is critical for the rapid mass immunization campaigns implemented during the pandemic to detect potential safety problems early and thus implement corrective measures [61]. Cerebral venous and dural sinus thrombosis (CVST) with thrombocytopenia after vaccination with Ad26.COV2.S and ADZ-1222 were monitored by the Vaccine Adverse Event Reporting System (VAERS) in the US and the Pharmacovigilance Risk Assessment Committee in Europe [62,63]. The estimated incidence rate of CVST following AZD-1222 vaccination is 5.0 per million people in Europe [64]. Based on the US CDC, the incidence of thrombosis with

thrombocytopenia syndrome is approximately 7 per 1 million Ad26.COV2.S vaccinated women between 18 and 49 years old [65]. The National Health Service of the UK recommends that people under the age of 40 years without other health conditions should not be administered with AZD-1222 [66]. The risk of thrombocytopenic, thromboembolic, and hemorrhagic events significantly increase after the first dose of AZD-1222 [67]. Two mRNA vaccines (BNT162b2 and mRNA-1273) are associated with the risk of anaphylaxis, delayed large local reactions [68–70], and the risk of myocarditis/pericarditis especially in adolescents [71]. The reported rates of anaphylaxis following BNT162b2 and mRNA-1273 vaccination were 4.7 and 2.5 per 1 million doses administered, respectively [72]. Post-vaccination myocarditis/pericarditis occurs mainly in young men, and the reported rate in males aged 12–17 years after the second dose of BNT162b2 or mRNA-1273 was 66.7 per million doses [71]. No serious adverse reactions of inactivated vaccines (BBIBP-CorV and WIV04) were observed in the large-scale safety surveillance after emergency use [73]. The medium- and long-term safety of the newly developed COVID-19 vaccines require ongoing evaluation.

Vaccines versus new variants

Multiple SARS-CoV-2 variants have emerged globally. Four variants, namely, Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2), are classified as variants of concern (VOC) by the WHO. In addition to VOC, the other variants of interest (VOI) include Epsilon (B.1.429) and Iota (B.1.526), which were first detected in the United States, and many more [74].

As shown in Table 2, variants have varying degrees of resistance to neutralizing activity of serum from vaccinated individuals. The neutralization activity of vaccines against the Alpha variant shows little change [75–81]. The Beta variant is relatively more affected by the neutralization response induced by the vaccine with a 2- to 11-fold decrease [75,76,78,79,81–85]. The Gamma variant may be less resistant to vaccine-induced antibodies than the Beta variant but is more resistant than the Alpha variant [75,81,86]. The decrease in neutralization activity against the Delta variant may differ among different vaccines. The neutralization activity of the inactivated vaccine COVAXIN against the Delta variant decreased by 1.95-fold [80]. For the mRNA-1273 and BNT162b2 vaccines, the neutralization activity could decrease by 1.4- to 5.8-fold [87–89]. The neutralization activity of AZD-1222 against the Delta variant decreased by 3.2-fold [90]. Limited Data are available on the immunization escape for the VOI. The neutralization activities of the mRNA-1273, NVX-CoV2373, and CoronaVac vaccines against the Epsilon variant decreased by approximately 1- to 2-fold [81,84]. The effect of neutralization against the Iota variant may be predominantly concentrated in the version carrying E484K [85].

The efficacy or effectiveness of AZD-1222, NVX-CoV2373, Ad26.COV2.S, BNT162b2, mRNA-1273, COVAXIN, and CVnCoV against the COVID-19 variants has been reported. The efficacies of AZD-1222, NVX-COV2373, and CVnCoV against symptomatic cases caused by infection with the Alpha variant were 70.4% (95% CI 43.6%–84.5%) [91], 86.3% (95% CI 71.3%–93.5%) [26], and 55% (95% CI 24%–74%) [16], respectively (Table 2). In actual studies in Qatar, the effectiveness of BNT162b2 and mRNA-1273 against infection with the Alpha variant was 89.5% (95% CI 85.9%–92.3%) and 100% (95% CI 91.8%–100%), respectively [92,93]. The efficacy of some vaccines against the Beta variant is significantly lower than that against the wild-type virus in clinical trials. The efficacies of AZD-1222 and NVX-CoV2373 against the Beta variant were 10.4% (95% CI –76.8% to 54.8%) [83] and 60.1% (95% CI 19.9%–80.1%) [94], respectively, which did not meet the WHO standard for COVID-19 vaccines [13]. The efficacy of Ad26.COV2.S in South Africa was 64.0% (95% CI 41.2%–78.7%) against moderate-to-severe disease, similar to the result obtained in the United States [19]. The efficacies of BNT162b2 and mRNA-1273 against infection with the Beta variant in Qatar were 75.0% (95% CI 70.5%–78.9%) and 96.4% (95% CI 91.9%–98.7%), which were relatively lower than those obtained against the Alpha variant [92,93]. However, the effectiveness of BNT162b2 against the development of severe, critical, or fatal disease caused by infection with the Beta variant was 100.0% (95% CI 73.7%–100.0%) [92]. The clinical trial of CVnCoV shows an efficacy of 67% (95% CI 30%–58%) against symptomatic cases of infection with the Gamma variant [16]. A study in Manaus, Brazil showed that at least one dose of CoronaVac was associated with an effectiveness of 49.6% (95% CI 11.3%–71.4%) against symptomatic Gamma variant infection [95]. As for the Delta variant, a study in UK revealed that the efficacies of BNT162b2 and AZD-1222 against symptomatic diseases were 87.9% (95% CI 78.2%–93.2%) and 59.8% (95% CI 28.9%–77.3%), respectively [35]. A clinical trial of COVAXIN in India also indicated that the efficacy against symptomatic diseases was 65.2% (95% CI 33.1%–83.0%) [21].

Notably, a comprehensive comparison of the neutralizing activity of the different variants may be difficult because of the differences in sample size, sample selection, and assay methods. For vaccines with large differences in neutralization activity against the original strains, even if the decrease in the neutralization activity against the mutant strains is similar, the ultimate level of effectiveness will still differ. Furthermore, the effectiveness of the vaccines against the variants is not only affected by

Table 2 Vaccine implications of variants

Vaccine (reference)	VOC				VOI		
	Alpha (B.1.1.7)	Gamma (P.1)	Beta (B.1.351)	Delta (B.1.617.2)	Epsilon (B.1.429)	Iota (B.1.526) (E484K)	Iota (B.1.526) (S477N)
Neutralization							
Gam-COVID-Vac [76]	Increase by 1.8×	NA	Decrease by 6.1×	NA	NA	NA	NA
BBIBP-CorV [78,82]	Increase by 1.4×	NA	Decrease by 1.55× Decrease by 2.5 ×	NA	NA	NA	NA
BNT162b2 [75,79,85–88]	Increase by 1.3×	Decrease by 3.8×	Decrease by 10.3×	Decrease by 1.4×	NA	Decrease by 3.6×	Similar to D614G
	Decrease by 3.3×	Decrease by 2.6×	Decrease by 7.6×				
			Decrease by 3.4×	Decrease by 5.8×			
mRNA-1273 [77,79,84–86,89]	Increase by 1.6×	Decrease by 4.8×	Decrease by 9.7×	Decrease by 2.1×	Decrease by 2.0×	Decrease by 3.6×	Similar to D614G
	Decrease by 2.0×		Decrease by 12.4×				
	Decrease by 1.2×	Decrease by 3.2×	Decrease by 3.8×				
AZD-1222 [75,83,90]	Decrease by 2.3×	Decrease by 2.9×	Decrease by 11× Decrease by 9×	Decrease by 3.2×	NA	NA	NA
COVAXIN [80]	Decrease by 1.06×	NA	NA	Decrease by 1.95×	NA	NA	NA
CoronaVac [78,81]	Decrease by 2×	Decrease by 3.92×	Decrease by 3.3×	NA	Decrease by 1.25×	Decrease by 4.03×[a]	
	Decrease by 1.51×		Decrease by 5.27×				
WIV04	NA	NA	NA	NA	NA	NA	NA
Ad5-nCoV	NA	NA	NA	NA	NA	NA	NA
Ad26.COV2.S [117]	Decrease by 0.9×	Decrease by 3.4×	Decrease by 3.6×	Decrease by 1.6×	NA	NA	NA
NVX-CoV2373 [77,84]	Decrease by 2.1×	NA	Decrease by 14.5×	NA	Decrease by 2.5×	NA	NA
CVnCoV	NA	NA	NA	NA	NA	NA	NA
Efficacy/effectiveness							
Ad26.COV2.S [19]	NA	NA	Moderate to severe COVID-19: 64.0% (95% CI 41.2%–78.7%) Severe COVID-19: 81.7% (95% CI 46.2%–95.4%)	NA	NA	NA	NA
NVX-CoV2373 [94,118]	Symptomatic COVID-19: 86.3% (95% CI 71.3%–93.5%)	NA	Symptomatic COVID-19: 60.1% (95% CI 19.9%–80.1%)[c]	NA	NA	NA	NA
AZD-1222 [35,36,83,91]	Symptomatic COVID-19: 70.4% (95% CI 43.6%–84.5%) Hospitalization: 86% (95% CI 53%–96%)	NA	Mild-to-moderate COVID-19: 10.4% (95% CI –76.8% to 54.8%)	Symptomatic COVID-19: 59.8% (95% CI 28.9%–77.3%) Hospitalization: 92% (95% CI 75%–97%)	NA	NA	NA

(*Continued*)

Vaccine (reference)	VOC				VOI		
	Alpha (B.1.1.7)	Gamma (P.1)	Beta (B.1.351)	Delta (B.1.617.2)	Epsilon (B.1.429)	Iota (B.1.526) (E484K)	Iota (B.1.526) (S477N)
CoronaVac [95]	NA	Symptomatic COVID-19: 49.6% (95% CI 11.3%–71.4%)[b]	NA	NA	NA	NA	NA
BNT162b2 [35,36,92]	SARS-CoV-2 infection: 89.5% (95% CI 85.9%–92.3%) Symptomatic COVID-19: 92% (95% CI 88%–94%) Severe, critical, or fatal COVID-19: 100.0% (95% CI 81.7%–100.0%) Hospitalization: 95% (95% CI 78%–99%)	NA	SARS-CoV-2 infection: 75.0% (95% CI 70.5%–78.9%) Severe, critical, or fatal COVID-19: 100.0% (95% CI 73.7%–100.0%)	Symptomatic COVID-19: 87.9% (95% CI 78.2%–93.2%) Hospitalization: 96% (95% CI 86%–99%)	NA	NA	NA
mRNA-1273 [93]	SARS-CoV-2 infection: 100% (95% CI 91.8%–100%)	NA	NA	SARS-CoV-2 infection: 96.4% (95% CI 91.9%–98.7%)	NA	NA	NA
COVAXIN [21]	NA	NA	NA	Symptomatic COVID-19: 65.2% (95% CI 33.1%–83.0%)	NA	NA	NA
CVnCoV [16]	Symptomatic COVID-19: 55% (95% CI 24%–74%)[d]	Symptomatic COVID-19: 67% (95% CI 30%–85%)[d]	NA	NA	NA	NA	NA

[a]The study did not specify the version of B.1.526.
[b]Results from participants who received at least one dose vaccine.
[c]HIV-negative participants.
[d]Results from the 18–60 years age group.
NA, not available.

neutralization activity. In terms of immune response, the influence of variants on cellular immunity may also cause changes in vaccine effectiveness. The Y453F and L452R mutations result in HLA-A24-mediated cellular immune escape [96]. In addition, outside the immune response, the enhanced ability of the variants to bind to the receptor may also enhance the replication and infectivity than those of the wild-type strain, as observed in the Alpha and Delta variants [97]. This phenomenon could lead to more infections and resource limitations or strain placed on clinical care, thus affecting vaccine effectiveness. Cohort studies in the UK confirmed that the Alpha variant does not increase the risk of severe illness or death [98], which contradicted previous studies [99]; early cases were selected to exclude any substantial resource limitation or strain on clinical care. In combination with the current situation in India, these findings may suggest that the variants affect vaccine effectiveness through enhanced replication and transmission and not merely immune escape. Moreover, at the regional level, different levels of NPI implementation may also affect the protection afforded by vaccines.

Challenges and perspectives

Benefiting from the accumulation of knowledge about vaccines, parallel development based on multiple vaccine platforms, and unprecedented close collaboration among scientific research institutions, enterprises, governments, and regulatory agencies worldwide, COVID-19 vaccines have achieved rapid success in the initial stage, suggesting the possibility of future control over the pandemic. Most countries are scrambling to implement vaccination programs, as several vaccines have been approved for marketing or emergency use. However, achieving control over the pandemic is still hindered by many challenges. Global vaccine production and the rational distribution of the vaccines are major short-term issues. In addition, while attempting to improve the speed and capacity of vaccine development, issues such as approval policies for subsequent vaccines, surveillance of variant viruses, vaccine safety surveillance, and infrastructure for vaccine management and vaccination in low-income countries are also critical.

Accelerated vaccination should be prioritized

Globally, the access to and distribution and speed of vaccination are key factors in achieving herd immunity. As of May 16, 2021, 1.47 billion doses of COVID-19 vaccine had been administered globally [100]. Interestingly, in countries with high coverage rates such as Israel, the vaccine has shown good results in terms of controlling the pandemic, not only in the aspect preventing serious disease and death but also reducing infections [28]. In terms of limited vaccine supplies, some countries have adjusted immunization intervals to maximize vaccine coverage [101–103] to enhance the coverage of the vaccine and limit viral replication and infection and thus reduce viral mutations. Furthermore, the storage conditions of vaccines should be considered. Strict storage and transportation conditions may remarkably affect vaccine accessibility, especially in underdeveloped regions. At present, most vaccines such as inactivated, recombinant protein, and some adenovirus vector vaccines can be stored stably at 2–8 °C (Table 1), and the more temperature-sensitive mRNA vaccine (BNT162b2 and mRNA-1273) are currently available store at 2–8 °C for one month [104,105]. The improvement of vaccine storage and transportation conditions is another key point in vaccine development. In addition, vaccination hesitancy or resistance negatively affects mass vaccination campaigns. Dealing with vaccine hesitancy is complex, and experts recommend comprehensive multi-component approaches tailored to the local population combined with good communication at the individual level [106,107]. Specific strategies for addressing vaccine hesitancy include offering tailored communication from trusted sources, improving access to vaccines, community engagement, and training and education activities [107]. In some strongly hesitant populations, health knowledge highlighting personal benefit may be more effective than emphasizing collective benefit [108].

Escaped variants make pandemic control uncertain

Variants that pose threats to pandemic control may enhance transmissibility and elude the immune response induced by a vaccine. The current VOCs include Alpha, Beta, Gamma, and Delta [74]. Beta variant, which was first discovered in South Africa, has shown the most significant capacity for immune escape, and some vaccine-induced neutralizing antibody titers decreased by up to 10-fold [79,83]. AZD-1222 and NVX-COV2373 are less efficacious in South Africa than in other regions, in which AZD-1222 has no significant protective effect against the Beta variant [83,94]. Notably, both vaccines showed decreased efficacy in terms of preventing symptomatic COVID-19 cases, although severe cases occurred in the placebo group and not in the vaccine group. Studies on BNT162b2 in Qatar have shown similar results, indicating that the vaccine may be less effective against infection with the Beta variant, but the effectiveness against severe disease remains extremely robust [92]. The effect of the variants, especially the variants with immune escape capacity, on vaccine efficacy is still controversial, and manufacturers and research institutions are considering different ways of addressing the situation. The development of vaccines against variants and intensive vaccination with the prototype strain vaccine

are the key pandemic responses. The clinical immunogenicity results for the Moderna prototype vaccine and the variant vaccine in terms of enhancing immunity suggest the feasibility of this strategy [109]. However, the success of these two approaches are not guaranteed. The proliferation of variants and the time required to verify efficacy pose challenges for the development and implementation of variant vaccines. By contrast, the most rapid and effective way to deal with the current variants is the immediate vaccination of as many people as possible, creating an immune barrier that reduces the risk of mutation.

The extensive replication and transmission of the virus in hosts with low immunity may lead to more mutations, posing a greater challenge to vaccine effectiveness. In response to emerging variants, the US Food and Drug Administration (FDA) issued guidance in late February 2021 on how to evaluate the Emergency Use Authorization application for COVID-19 vaccine against emerging variants [110]. The FDA could accept Data from smaller clinical trials, similar to those for seasonal flu vaccines. This issuance could accelerate the review process for improved versions of vaccines, and its previous versions have exhibited acceptable safety and efficacy. A coalition of regulators from Australia, Canada, Singapore, Switzerland, the UK, and the European Union has issued similar guidelines [111–113]. If COVID-19 becomes endemic, vaccine updates could also follow a process similar to that for seasonal influenza vaccines.

In addition, research on new vaccines and vaccine immunization strategies to improve the broad spectrum of vaccine efficacy and convenience will also be focuses of future research.

Medium-to-long-term safety and rare serious adverse events after vaccination need to be closely followed up

The unprecedented speed and scale of vaccination against COVID-19 have magnified the safety risks of vaccines and even lead to unacceptable consequences for some vaccinated individuals. Adenovirus-vector vaccines AZD-1222 and Ad26.COV2.S did not cause serious adverse events in clinical trials, but CVST occurred after mass vaccination, arousing substantial concern worldwide [62,63]. Sample size and observation time constraints in clinical trials may cause medium-to-long-term and rare safety risks to be underrepresented. Therefore, after licensing, the medium-to-long-term safety of all types of vaccines should be followed up, and rare serious adverse events should be focused on.

Conclusions

Most of the current COVID-19 vaccines have shown satisfactory efficacy or effectiveness in actual clinical trials, suggesting that the pandemic can be controlled. However, some limitations are still encountered. More efforts are needed to facilitate rapid vaccine coverage, defense against variants capable of immune escape, and the surveillance of medium- and long-term safety risks and rare serious adverse events.

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Compliance with ethics guidelines

Zehong Huang, Yingying Su, Tianying Zhang, and Ningshao Xia declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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