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Evidences on the efficacy and the effectiveness of the first generation COVID-19 vaccines in the clinical trials and real-world studies

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Abstract

More than 300 COVID-19 vaccine candidates have been developed or are still in development. COVID-19 vaccines in the World Health Organization Emergency Use Listing and some other COVID-19 vaccine products under conditional approval by national regulatory authorities are already in largescale use, preventing populations from severe illness or death and inducing herd immunity to impact the SARS-CoV-2 pandemic. In this review, we systemically assess the vaccine efficacy and effectiveness of COVID-19 vaccines in clinical trials or real-world studies, in various populations, including healthy adults, children, the elderly, pregnancy women, people with cancer, rheumatic and musculoskeletal diseases, chronic hemodialysis, solid organ transplantation, and so on. In addition, we reviewed the available effectiveness evidence on the immunization strategies of COVID-19 vaccines in those who have previous infection history of SARS-CoV-2, and the enhanced effectiveness associated with various boosting immunization. We also discuss the unmet gaps about the persistence and spectrum of vaccine protection provided by the current available COVID-19 vaccines.

Introduction

The COVID-19 pandemic caused by SARS-CoV-2 has led to more than 575 million confirmed cases and 6 million deaths worldwide till August 2nd, 2022[1]. Efficacious vaccine is an important preventive measure against COVID-19. According to the World Health Organization (WHO) data released on Jun 1st, 2022, more than 300 Covid-19 vaccine candidates have been developed or are still in development. Of these, 153 COVID-19 vaccine candidates have been evaluated in clinical trials. These vaccines mainly include inactivated vaccines (accounting for 14% of the total), live

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attenuated vaccines (1%), viral vector vaccines (replication and non-replication; 17% of the total), RNA vaccines (18%), DNA vaccines (11%), protein subunit vaccines (34%), and VLP vaccines (4%)[2].

The first generation COVID-19 vaccines were vaccines designed based on the the receptor-binding domain (RBD) or spike of prototype SARS-CoV-2 or the whole prototype virus. The WHO Emergency Use Listing (EUL) has authorized 11 vaccines for the emergency use up to Jun 13th, 2022, including Ad26.COV2.S developed by Janssen, COVAXIN developed by Bharat Biotech, BNT162b2 developed by Pfizer-BioNTech, AZD1222 Vaxzevria developed by Oxford-AstraZeneca, mRNA-1273 developed by Moderna, inactivated SARS-CoV-2 Vaccine BBIBP-CorV developed by Sinopharm, CoronaVac developed by Sinovac, NVX-CoV2373/Nuvaxovid developed by Novavax, ChAdOx1 nCoV-19 and NVX-CoV2373/Covovax developed by Serum Institute of India, and Ad5-nCoV developed by CanSino Biologics[3]. These vaccines in the WHO EUL, along with some other seven vaccine products under conditional approval by national regulatory authorities are already in largescale use [4,5], to impact on the SARS-CoV-2 pandemic by preventing populations from severe illness or death and inducing herd immunity.

Although all populations are susceptible to SARS-CoV-2 infection, including children, adults, the elderly, male and female, and people with underlying medical conditions. Some populations have higher risks of more severe COVID-19 disease or outcomes from SARS-CoV-2 infection than others do[6]. The large-scale vaccination campaigns worldwide inevitably lead to increasing researches on the application of the COVID-19 vaccines in some special populations with underlying medical conditions, such as cancer, pregnancy, rheumatic and/or musculoskeletal diseases, chronic hemodialysis, and solid organ transplantation [7,8]. Vaccine protection against

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COVID-19 could be different in these different populations.

In this review, we systematically summarize the efficacy and/or effectiveness about the first generation COVID-19 vaccines in clinical trials or real-world studies against prototype strain or various SARS-CoV-2 variants, and in generally healthy populations, as well as in those with underlying conditions or diseases. In addition, we compare the enhanced efficacy and/or effectiveness associated with different boosting immunization strategies with these COVID-19 vaccines. The unmet gaps about the persistence and spectrum of vaccine protection provided by the current available COVID-19 vaccines are also discussed.

Method

We searched PubMed with the key terms "(COVID-19[Title/Abstract] OR SARS-CoV-2[Title/Abstract]) AND (vaccine[Title/Abstract] OR vaccination[Title/Abstract]) AND (efficacy[Title] OR effectiveness[Title/Abstract] OR protection[Title/Abstract] OR effect[title/Abstract])" and "(Protection [Title/Abstract]) AND ((SARS-CoV-2 [Title/Abstract]) OR ("COVID-19 vaccination"[Title/Abstract]) OR ("breakthrough infection"[Title/Abstract]))" with article types restricted to "Clinical study" or "Clinical Trial" or "Observational Study", a total of 319 and 161 articles were found, respectively. Duplicated studies, and Meta analysis were excluded. Additional publications were identified searching manually the references sections of each of the articles identified using the above-mentioned keywords. Then we identified a total of 99 articles about phase 3 trial or real-world study that reported efficacy or effectiveness of COVID-19 vaccines, published before July 20, 2022, by reading the titles and abstracts.

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COVID-19 vaccines in the WHO EUL list

Inactivated vaccines

Three inactivated COVID-19 vaccines involved in WHO EUL list, including BBIBP-CorV and CoronaVac developed in China, which are β- propiolactone inactivated prototype vaccines adjuvanted with aluminium hydroxide[9], and BBV152 developed in India, which is also β-propiolactone-inactivated whole-virion SARS-CoV-2 vaccine but adjuvanted with Algel-IMDG, an imidazoquinoline class molecule (TLR7 and TLR8 agonist) adsorbed onto Algel[10].

The first efficacy phase 3 trial of the CoronaVac performed between July, 2020 and Jan, 2021 in Turkey, Brazil and Indonesia, reported an efficacy of 83.5% (95% CI 65.4-92.1), 50.7% (95% CI, 36.0-62.0), and 65.3% (not available for 95%CI) for preventing PCR-confirmed symptomatic COVID-19 at 14 days or more after the second dose, respectively (table 1) [11-13].

From January 2021 to February 2022, five retrospective or prospective cohort studies or test-negative case-control studies on CoronaVac reported moderate and high vaccine effectiveness against SARS-CoV-2 variants associated symptomatic infection and hospitalization or death (table 2). A countrywide mass vaccination campaign with CoronaVac was conducted in Chile from February to May, 2021, with predominant strain of Gamma (P.1), which showed an effectiveness of 65.9% (95% CI, 65.2-66.6) against COVID-19 and 87.5% (95% CI, 86.7-88.2) against hospitalization, and 86.3% (95% CI, 84.5-87.9) against COVID-19-related death [14]. However, the effectiveness of CoronaVac in later reported studies were comparable to or slightly lower in the setting of new epidemic variants transmission or involving more elderly population. A retrospective analysis involved all confirmed cases of COVID-19 in mainland China between May

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21, 2021 and February 28, 2022 were conducted, during which period the epidemic variants shifted from Delta (B.1.617.2) to Omicron (B.1.1.529) [15], demonstrating that fully vaccination reduced the risk of severe COVID-19 diseases by 83% and 69%, and booster vaccination reduced the risk of pneumonia by 86% and 69%, and the risk of severe disease by 98% and 91%, among cases aged 18-59 years and ⩾60 years, respectively. Another study in Hongkong also reported that the primary two-dose immunization of CoronaVac showed high protection (around 91.7%~93.3%) against severe, critical disease, and death in adults aged ⩽59 years, but the protection was lower (around 58.2%~63.0%) in the elderly adults aged 60 years or older, particularly for those aged over 80 years [16].

Generally, CoronaVac provides a high protection against severe COVID-19 cases, hospitalization and intensive care (ICU) admission for children and adolescents [17]. In children aged 6 to 16 years, the effectiveness of CoronaVac against infection was 74.5% (95% CI, 73.8-75.2), against hospitalization was 91.0% (95% CI, 87.8-93.4), and against ICU was 93.8% (95% CI, 87.8-93.4). However, a population-based cohort of 490,694 children aged 3-5 years who were observed for the effectiveness of CoronaVac, during the Omicron (B.1.1.529) outbreak in Chile, indicated an obvious decrease of vaccine protection against the infection associated with Omicron (B.1.1.529) variant [18]. The estimated vaccine effectiveness was 38.2% (95% CI, 36.5-39.9) against symptomatic COVID-19, 64.6% (95% CI, 49.6-75.2) against hospitalization, and 69.0% (95% CI, 18.6-88.2) against ICU admission.

Another inactivated COVID-19 vaccine BBIBP-CorV manufactured by Beijing institute of Sinopharm, was developed based on a prototype SARS-CoV-2 HB02 strains. Efficacy study of BBIBP-CorV was conducted in the United Arab Emirates and Bahrain among adults 18 years and

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older without known history of COVID-19, from July, 2020 to December, 2020, yielding an efficacy of 78.1% (95% CI, 64.8-86.3) against symptomatic COVID-19 during a median follow-up of 77 days (range: 1-121), since 14 days after the second dose (table 1) [19]. Vaccine effectiveness of BBIBP-CorV were evaluated in China, Argentina, Hungary and The United Arab Emirates (table 2). In Argentina, a significant reduced risk of SARS-CoV-2 infection and COVID-19 deaths in people older than 60 years were reported with vaccine effectiveness of 44% (95% CI, 42-45) and 85.0% (95% CI, 84.0-86.0) for BBIBP-CorV, respectively [20]. A real-world effectiveness study conducted in Singapore, claimed that BBIBP-CorV was better than CoronaVac in preventing infection and severe disease, but both BBIBP-CorV and CoronaVac had significantly weaker protection than the mRNA vaccine did. Based on this evidence, Singapore requires vaccination with three doses of inactivated vaccine as the primary immunization series [21].

Both the efficacy and effectiveness of BBV152 were evaluated in India. The efficacy study involved in 25 Indian hospitals or medical clinics, and recruited adults (age ≥18 years) who were healthy or had stable chronic medical conditions between Nov 16, 2020, and Jan 7, 2021, with Delta (B.1.617.2) as the predominant pandemic strain [22]. An overall estimated BBV152 vaccine efficacy was 77.8% (95% CI, 65.2-86.4) for symptomatic cases and 93.4% (95% CI, 57.1-99.8) for severe cases (table 1). While, the efficacy was 67.8% (95% CI, 8.0-90.0) for older participants (⩾60 years) and 79.4% (95% CI, 66.0-88.2) for participants who were younger than 60 years. However, the effectiveness data showed that the protection of BBV152 against symptomatic COVID-19 diseases were decreased when facing the pandemic associated with Delta (B.1.617.2) [23].

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Viral vector vaccines

The ChAdOx1 nCoV-19 vaccine (AZD1222) was developed by Oxford University and consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural spike protein gene. In the phase 3 trials conducted in the UK and Brazil, two doses of ChAdOx1 nCoV-19 showed an overall vaccine efficacy of 62.1% (41.0-75.7) in adults aged 18 years and older (table 1) [24]. Then, another phase 3 trial in the United States, Chile, and Peru, estimated that two-dose of ChAdOx1 nCoV-19 vaccines provided an overall vaccine efficacy of 74.0% (95% CI, 65.3-80.5) in participants 18 years or older and 83.5% (95% CI, 54.2-94.1) in participants 65 years of age or older[25]. However, in a multicenter, double-blind, randomized, controlled trial in South Africa, the two-dose regimen of ChAdOx1 nCoV-19 vaccine demonstrated nearly no protection (10.4% (95% CI, 76.8-54.8)) against mild-to-moderate COVID-19 due to the Beta (B.1.351) variant [26]. With the massive administration of the ChAdOx1 nCoV-19 vaccine in populations, the vaccine effectiveness was assessed in UK, Scotland, Canada, Brazil, Argentina, and Hungary (table 2). Surveillance data on symptomatic cases of COVID-19 in England revealed that the effectiveness of two doses of ChAdOx1 nCoV-19 vaccine was 74.5% (95% CI, 68.4-79.4) among persons with the Alpha (B.1.1.7) variant and 67.0% (95% CI, 61.3-71.8) among those with the Delta (B.1.617.2) variant [27]. During the Omicron (B.1.1.529) epidemic, two-dose immunization of ChAdOx1 vaccine induced a protection about 48.9 (95% CI, 39.2-57.1) against the symptomatic infections in 2-4 weeks after second dose and waned over time. Two doses of ChAdOx1 vaccine had little or no protection against Omicron (B.1.1.529)-related infection after 6 months since the second vaccination [28].

The Ad26.COV2.S (Johnson & Johnson) vaccine is a recombinant, replication-incompetent

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human adenovirus type 26 vector encoding full-length SARS-CoV-2 spike protein in a prefusion-stabilized conformation, developed by Janssen. In the phase 3 trials, single dose of Ad26.COV2.S provided protection of 66.9% (95% CI, 59.1-73.4) and 55.9% (95% CI, 51.0-60.5) against symptomatic COVID-19 of any severity, 76.7% (95% CI, 54.6-89.1) and 73.7% (95% CI, 63.9-80.5) against severe to critical COVID-19 disease with onset at least 14 days after vaccination (table 1) [29,30]. The Ad26.COV2.S provided significant protection against Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1), but not Delta (B.1.617.2) [30].The effectiveness of a single dose of the Ad26.COV2.S vaccine was evaluated in South Africa from November 2021 to January 2022 (table 2). The results showed an effectiveness of 75% (95% CI, 69-82) to prevent COVID-19-related hospital admissions requiring critical or intensive care, and 62% (95%CI, 42-76) and 67% (95% CI, 62-71) to prevent COVID-19-related hospitalizations [31], during the epidemics dominated with Beta (B.1.351) and Delta (B.1.617.2) variants.

The Convidecia is a single-dose Ad5 vectored vaccine expressing the SARS-CoV-2 spike protein (Ad5-nCoV vaccine) manufactured by CanSino Biologics, China. A phase 3 clinical trial which enrolled adults aged 18 years and older was performed in Argentina, Chile, Mexico, Pakistan and Russia, which found that one dose of Convidecia had a 57.5% (95% CI, 39.7-70.0) efficacy against symptomatic, PCR-confirmed, COVID-19 infection at 28 days or more post vaccination (table 1) [32]. Only one observational study in Yunnan province in China, reported the effectiveness of Ad5-nCoV vaccine Convidecia [33], showing a protection of 61.5% (95%CI, 9.5-83.6) against symptomatic COVID-19, and 67.9% (95% CI, 1.7-89.9) against COVID-19 pneumonia, and 100% (95%CI, 36.6–100) against severe/critical COVID-19 caused by the Delta (B.1.617.2) variant.

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Protein subunit vaccine

NVX-CoV2373 is the only recombinant protein vaccine involved in the WHO EUL currently, which contains recombinant nanoparticle prefusion spike protein of the prototype strain plus Matrix-M adjuvant. In a phase 3 trial, conducted at 33 sites in the United Kingdom, in adults between the ages of 18 and 84 years, two doses of NVX-CoV2373 showed an overall vaccine efficacy of 89.7% (95% CI, 80.2 to 94.6) against symptomatic disease largely caused by Alpha (B.1.1.7) [34].

Another phase 3 trial to evaluate the efficacy of NVX-CoV2373 in adults (≥18 years of age) was carried out in the United States and Mexico during the first half of 2021 [35]. Receiving two doses of NVX-CoV2373 yield an efficacy of 90.4% (95% CI, 82.9-94.6) against COVID-19, and an efficacy of 100% (95% CI, 87.0-100) against moderate-to-severe disease (table 1).

mRNA vaccines

BNT162b2 and mRNA-1273 are the only two mRNA vaccines listed in the WHO EUL, and are the most widely used COVID-19 vaccines against SARS-CoV-2 infection worldwide [36].

A randomized, double-blind study of BNT162b2 an mRNA vaccine was performed in the healthy population 16 years of age or older, reported some early protection 12 days after the first dose and 95% (95% CI, 90.3-97.6) efficacy at 7 days after the second dose (table 1). Similar vaccine efficacy was observed across subgroup defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions [37]. During 6 months of follow-up, the vaccine efficacy against COVID-19 was 91.3% (95% CI, 89.0-93.2), and against severe disease was 96.7% (95% CI, 80.3-99.9) among the participants. In South Africa, where the SARS-CoV-2

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variant of concern Beta (B.1.351) was predominant, a vaccine efficacy of 100% (95% CI, 53.5-100) was observed [38]. In a study involved participants without evidence of previous SARS-CoV-2 infection aged 12 to 15 years old, no COVID-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients, and 16 cases occurred among placebo recipients, resulting in a vaccine efficacy of 100% (95% CI, 75.3-100) .

Injections of two-dose mRNA-1273, 28 days apart, were evaluated in a clinical trial at 99 centers across the United States, which showed a vaccine efficacy in preventing COVID-19 illness was 94.1% (95% CI, 89.3-96.8) for adults ⩾18 years and 86.4 (61.4–95.2) for the elderly ⩾65 [39]. While, the efficacy in preventing severe disease was 98.2% (95% CI, 92.8-99.6), with 2 cases in the mRNA-1273 group and 106 in the placebo group, and the efficacy in preventing asymptomatic infection starting 14 days after the second injection was 63.0% (95% CI, 56.6-68.5) [40].

As a most wildly used COVID-19 vaccines, the effectiveness of BNT162b2 vaccines have been reported worldwide, from USA, UK., Israel, Italy, Qatar, Canada, France, Hungary, Scotland, South Africa and so on (table 2). Most of the studies found that the effectiveness of the two-dose BNT162b2 vaccines against COVID-19 diseases were high against various variants in adults, including the Delta (B.1.617.2) variant, though the effectiveness observed were decreased over time. However, studies found that two-dose BNT162b2 regimen became less effective against the Omicron (B.1.1.529) variant. For both Omicron (B.1.1.529) BA.1 and BA.2, two doses of BNT162b2 vaccine in the population without previous SARS-CoV-2 infection history showed no protection against symptomatic infections over a period of 200 days post-vaccination. While, three doses of BNT162b2 vaccine provided 59.6% (95% CI, 52.9-65.3) and 52.2% (95% CI, 48.1-55.9) against symptomatic infections caused by Omicron (B.1.1.529) BA.1 and BA.2 within 1 or 2

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months, respectively, but an over 95% protection against severe, critical, and fatal COVID-19 diseases [41]. High vaccine effectiveness of the mRNA-1273 provided for symptomatic, severe, critical, and fatal infections caused by various SARS-CoV-2 variants, which were similar to that of BNT162b2, but the mRNA-1273 also showed a consistently high protection against Omicron (B.1.1.529) BA.1 and BA.2 variants (table 2).

A real-world surveillance study in Slovenia based on the data collected from February, 2022 to March, 2022, reported an overall COVID-19 incidence of 98/100,000 in adults aged 18 years or older [42]. The incidence of COVID-19 varied according to the vaccination status, 343/100,000 in the unvaccinated population, 132/100,000 in the two-dose mRNA vaccinated population, and 74/100,000 in the three-dose mRNA vaccinated population. In the most vulnerable population aged 65 years and older, the protection induced by mRNA vaccines against hospitalization associated with SARS-CoV-2 infection caused by Omicron (B.1.1.529) was 95% (95% CI, 95-96) in three-dose recipients compared with 82% (95% CI, 79-84) in two-dose recipients. The level of vaccine protection was maintained for at least 6 months.

A case-control study in adolescents aged 12-18 years was carried out during the Delta (B.1.617.2) and Omicron (B.1.1.529) epidemics, which showed that two-dose BNT162b2 vaccines provided similar protections in those aged 12- to 15-year-old and 16- to 18-year-old (83% versus 82%). The vaccine efficacy during the Delta (B.1.617.2) epidemic was 96% (95% CI, 90-98) and 91% (95% CI, 86-94) among these adolescents for critical cases and non-critical hospitalization, respectively [43]. While, the vaccine efficacy during the Omicron (B.1.1.529) epidemic declined to 79% (95% CI, 51-91) for critical cases, and to 20% (95% CI, -25-49) for non-critical illness. Although the protection with two doses of BNT162b2 against Omicron (B.1.1.529)-related COVID-19 was

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lower than that with Delta (B.1.617.2) in adolescents, the vaccine protection against critical illness were sustained. In Denmark, a large observational study in adolescents also reported a vaccine effectiveness of 93% (95% CI, 92-94) 60 days post-vaccination of BNT162b2 vaccines during the Delta (B.1.617.2) epidemic [44]. Even so, 3.7-fold (95% CI, 2.7-5.2) lower rate of confirmed infection risk was observed after the boosting compared to the two-dose cohort up to 60 days post-vaccination in adolescents [45]. All COVID-19 infections are at risk of Long-COVID, but a study reported that vaccination with mRNA vaccines or Ad26.COV2.S before infection confers only 15% protection against post-acute sequelae compared to people with SARS-CoV-2 infection without prior vaccination [46].

COVID-19 vaccines not in WHO EUL yet

Some COVID-19 vaccines have not been included in the WHO EUL yet, but have vaccine efficacy or effectiveness data in trials or observational studies been reported.

Gam-COVID-Vac (Sputnik V) is a heterologous two-dose regimen against COVID-19 approved for emergency use in Russia, with a recombinant of adenovirus type 26 (rAd26) vector-based vaccine as the first dose, and a rAd5 vector-based vaccine as the second dose, of which both vectors carrying the gene for the full-length SARS-CoV-2 glycoprotein S. Sputnik V provided an overall efficacy was 91.6% (95% CI, 85.6-95.2) and 100% (95% CI, 94.4-100.0) against severe diseases in the phase 3 trial in Russia [47]. A vaccination campaign against COVID-19 involved with the rAd26-rAd5 Sputnik V vaccine was carried out in Argentina in people older than 60 years, demonstrating an effectiveness of 64% (95% CI, 63-65) against infection, and 93.1% (95% CI, 92.6-93.5) against death during the epidemics associated with Gamma (P.1), Lambda (C.37), and

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Alpha (B.1.1.7) variants [20] (table 2). Another retrospective cohort study in Argentina reported the effectiveness of the first component of Sputnik V on reduction of SARS-CoV-2 laboratory-confirmed infections, hospitalizations and mortality by 78.6% (95% CI, 74.8-81.7), 87.6% (95% CI, 80.3-92.2) and 84.8% (95% CI, 75.0-90.7), respectively, in the elderly population aged 60-79 years in a Gamma (P.1) variant dominated period [48].

WIBP-CorV (developed by Wuhan institute of Sinopharm, China), is a similar β-propionolactone inactivated prototype vaccine adjuvanted with aluminium hydroxide to BBIBP-CorV (developed by Beijing institute of Sinopharm, China). The efficacy of WIBP-CorV was evaluated in the United Arab Emirates and Bahrain among adults 18 years and older, which demonstrated a protection of 72.8% (95% CI, 58.1-82.4) against symptomatic COVID-19 at the time when the variants were not common [19].

While, ZF2001, a protein subunit COVID-19 vaccine, using the tandem-repeat dimeric RBD of the SARS-CoV-2 spike protein (from the original Wuhan-Hu-1 strain) as antigen, manufactured by Anhui Zhifei Longcom Biopharmaceutical, has been authorized for emergency use in China. In the recently reported phase 3 trial, a total of 12625 ZF2001 recipients reported 158 cases of symptomatic COVID-19, while 12568 placebo recipients reported 580 cases, resulting in an efficacy of 75.7% (95% CI, 71.0-79.8) during the Delta (B.1.617.2) predominated period. Among them, three-dose of ZF2001 provided a protection of 76.0% (95% CI, 71.2-80.1) in the younger adults aged 18 to 59 years old, and a protection of 67.6% (95% CI, 21.9-87.8) to the old aged over 60 years [49]. Three-dose of ZF2001 provided 87.6% (70.6-95.7) against severe or critical ill cases.

SCB-2019 is a S protein subunit vaccine against SARS-CoV-2 consisting of the trimeric structure of the S protein adjuvanted with CpG-1018 and alum, developed by Clover Biopharmaceuticals.

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An efficacy trial was conducted in adults aged 18 years and older in Belgium, Brazil, Colombia, Philippines, and South Africa from March 24, 2021, until Aug 10, 2021 [50]. Two doses of SCB-2019 provided protection of 67.2% (95.72% CI, 54.3-76.8) against any severity COVID-19, 83.7% (97.86% CI, 55.9-95.4) against moderate to severe COVID-19, and 100% (97.86% CI, 25.3-100.0) against severe COVID-19.

CoVLP+AS03 vaccine consists of Coronavirus-like particles (CoVLP) that are produced in plants and display the prefusion spike glycoprotein of the original strain of SARS-CoV-2, which is combined with an AS03 adjuvant (Adjuvant System 03). In a phase 3 trial, vaccine efficacy was 69.5% (95% CI, 56.7-78.8) against any symptomatic COVID-19 caused by five variants (Alpha, Gamma, Delta, Lambda and Mu), and 76.9% (51.5-90.0) against moderate diseases and 100.0% (95% CI, -63.7-NA) against severe diseases [51].

ZyCoV-D is comprised of a DNA plasmid vector pVAX1 carrying gene-expressing spikeS protein of SARS-CoV-2 and IgE signal peptide, administered intradermally via a needle-free injection system (table 1). In a multicentre, double-blind, randomised, controlled trial at 49 hospitals in India, ZyCoV-D showed a vaccine efficacy of 66.6% (95% CI 47.6–80.7) for all COVID-19 associated cases, 64.9% (95% CI 44.9–79.8) for mild cases, and 100% for severe cases [52].

CVnCoV is formulated with the RNActive mRNA vaccine platform, a containing 12 μg of mRNA per dose, which is evaluated in a phase 2b/3, clinical trial in 47 public and private hospitals and clinics across four countries in Europe (ie, Belgium, Germany, the Netherlands, and Spain) and six countries in Latin America (ie, Argentina, Colombia, Dominican Republic, Mexico, Panama, and Peru) (table 1). CVnCoV provided protection of 48.2% (95.826% CI, 31.0–61.4) against COVID-19 of any severity and 70.7% (95% CI, 42.5-86.1) against moderate-to-severe

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COVID-19 [53].

The boosting immunization with COVID-19 vaccines

Third dose

During the Omicron (B.1.1.529) epidemic, there was a substantial decrease in vaccine protection. The primary two-dose immunization schedule with BNT162b2, mRNA1273, or ChAdOx1 only induced about 50% protection against symptomatic COVID-19 diseases between 14 days and 3 months, while the protection against infections were somewhat lower around 37%. Besides, the effectiveness of all the three vaccines were below 50% for both symptomatic diseases and infections after 3 months of the primary series. Similarly, two-dose regimen of the inactivated COVID-19 vaccines also could not protect recipients regardless of age from the symptomatic COVID-19 diseases [54]. Boosting with the third dose of COVID-19 vaccine, with mRNA, vector-based vaccine, or inactivated vaccine, could provide more than 79% protection against all clinically symptomatic infections within 3 months of booster vaccination [55].

In an observational cohort study in over 3000 health care workers in the United States, three doses of mRNA vaccines showed an effectiveness of 91% (95% CI, 84-95) in preventing Delta (B.1.617.2) infection, with a relative vaccine effectiveness of 86% (95% CI, 69-94) versus that of two doses of mRNA vaccine. While, the effectiveness of the two doses of mRNA vaccine were 46% (95% CI, 25-61) in preventing Omicron (B.1.1.529) infection, and showed a relative vaccine effectiveness of 60% (95% CI, 40-73)[56].The results indicated that two- or three-dose vaccinations with mRNA vaccines are less effective against mild or asymptomatic infections caused by Omicron (B.1.1.529) compared with Delta (B.1.617.2). From November 27, 2021 to

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January 12, 2022, a test-negative design study in England found that a booster vaccination with BNT162b2 or mRNA1273 increased the effectiveness against severe disease to more than 75%, and maintained until about 6 months, while the effectiveness against symptomatic infections increased to 55-78% within first 3 month after the third dose, but then dropped to 29-64% by 3-6 months [28]. Among adolescents aged 12-15 years, a protection of 71.1% (95% CI, 65.5-75.7) was observed from 2 to 6.5 weeks after booster injection of BNT162b2 [57]. Although BNT162b2 or mRNA-1273 booster dose provided significantly higher protection against Omicron (B.1.1.529), but that still waned with time soon.

A large-scale prospective cohort study in Chile, has found that a third dose of the CoronaVac could enhance the vaccine protection against Omicron (B.1.1.529). Compared with only two doses of CoronaVac, the effectiveness of booster vaccination of CoronaVac was 63.8% (95% CI, 60.4-67.0) in preventing laboratory-confirmed COVID-19 infection and 59.3% (95% CI, 51.5-65.9) in preventing hospitalization, and 62.7% (95% CI, 44.9-74.7) in preventing deaths [58]. In Tianjin, China, a retrospective study also found that 3 doses of inactivated vaccines were associated with a significantly lower risk of ICU hospitalization [OR 0.023 (95% CI, 0.002-0.214)], re-positive nucleic acid tests [OR 0.240 (95% CI, 0.098-0.587)], and a shorter hospitalization and recovery time [OR 0.233 (95% CI, 0.091-0.596)] in breakthrough infection adults [59].

All these evidences supported the massive boosting vaccination campaign for the previous immunized population to increase the protection against COVID-19 diseases associated with Omicron (B.1.1.529) infection.

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Fourth dose

Since the protection against Omicron (B.1.1.529) waned rapidly after the third dose, a fourth dose of COVID-19 vaccine seemed inevitable in order to defeat the SARS-CoV-2 variants circulating.

In Israel, as one of the first country completed the implement of national immunization with three doses of COVID-19 vaccines, a study to investigate the boosting effects of the fourth dose of the COVID-19 vaccine was launched [60]. The fourth dose reduced the SARS-CoV-2 infection by 2 folds, and severe diseases by 4.3 folds in the old population, compared with those who only received three doses. Although fourth dose of BNT162b2 and mRNA-1273 elicited 9-10 folds higher neutralizing antibodies versus baseline before the boosting, but no significant increase were noted compared with the peaking level of neutralizing antibodies after the third dose [61]. In addition, the fourth dose provided effectiveness of 30% (95% CI, -8.8-50) with BNT162b2, and 10.8% (95% CI, -43-44) with mRNA-1273 against the SARS-CoV-2 infection, whereas 43.1% (95% CI, 6.6-65.4) with BNT162b2, and 31.4% (95% CI, -18.4-64.2) with mRNA-1273 against symptomatic diseases.

Although the fourth dose of the COVID-19 vaccines could only provide limited additional protection against the symptomatic diseases associated with SARS-CoV-2 infection, but the potential benefits in the high-risk populations against severe cases or death might be higher. In Ontario, Canada, a test-negative control study with a database estimated the relative effectiveness of a fourth dose of vaccination versus three-doses was conducted among the population aged 60 years and older, who were living in long-term care centers between December 30, 2021 and March 2, 2022 [62]. The results showed that the fourth dose of COVID-19 mRNA vaccine could enhance the protection of COVID-19-related morbidity and mortality caused by the Omicron

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(B.1.1.529) variant strain in elderly people in long-term care centers, an interval more than 84 days after vaccination of the third dose.

Heterologous versus homologous prime-boost vaccination

Different COVID-19 vaccines with different antigens or vaccine vectors were administrated in populations for the massive immunization, giving a unique opportunity to study the heterologous and homologous boost vaccination with the COVID-19 vaccines.

A series of trials or studies reported that heterologous priming-boost immunization with two different COVID-19 vaccines, particularly a heterologous mRNA vaccine or viral vectored vaccine, could elicit response of B cells to the pre-fusion sub-structural domains such as RBD, NTD, and an increased affinity of the neutralizing antibodies and broader reactivity than homologous immunization with a single COVID-19 vaccine did [63-65].

A nationwide test-negative studies in Brazil involving the population aged 18 years or older, whom have received two doses of CoronaVac as primary immunization and followed by a booster dose of CoronaVac or BNT162b2, investigated the vaccine protection during the Omicron (B.1.1.529) predominated period [66]. Homologous booster of CoronaVac increased the vaccine protection against hospitalization or death with a relative vaccine effectiveness of 42%, but with little or no increase in protection against symptomatic infections. Whereas, the heterologous booster of BNT162b2 increased protection against hospitalization or death significantly with a relative vaccine effectiveness of 66.9%, which maintained for at least 3 months. Compared with the younger adults, CoronaVac homologous boosting demonstrated lower effectiveness against hospitalization or death in people aged 75 years or older (46-54%), while BNT162b2 heterologous

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boosting elicited high protection in all age groups. These results supported heterologous booster vaccination to reduce severe illness and death associated with COVID-19 during the Omicron (B.1.1.529) epidemic.

A test-negative design conducted in the United States between January 2 and March 23, 2022, reported that one-dose of Ad26.COV2.S provided an effectiveness of 17.8% (95% CI, 4.3-29.5) between 14 days and 1 month, and then decreased to 8.4% (95% CI, 1.5-14.8) at 2-4 months, while two-dose of Ad26.COV2.S enhanced the protection to 27.9% (95% CI, 18.3-36.5), 29.2% (95% CI, 23.1-34.8), respectively. One-dose of Ad26.COV2.S plus a heterologous booster of mRNA enhanced the vaccine protection to 61.3% (95% CI, 58.4-64.0) and 54.3% (95% CI, 52.2 - 56.3), respectively, which was similar to that induced by three-dose of mRNA vaccines[67].

In a population immunized with 1 dose of adenovirus vaccine as a base, a single dose of mRNA vaccine heterologous booster provided nearly the same protection as 3 doses of mRNA vaccine.

A prospective observational, nationwide, large cohort study in Chile reported that, people aged 16 years and older who had completed the primary immunization with two-dose of CoronaVac was performed to evaluate the vaccine effectiveness of a booster injection with CoronaVac, AZD1222 or BNT162b2 vaccine [58]. Heterologous boost immunization with BNT162b2 increased the effectiveness to 96.5% (95% CI, 96.2-96.7), and AZD1222 increased the effectiveness to 93.2% (95% CI, 92.9-93.6), versus 78.8% (95% CI, 76.8-80.6) after the homologous boosting with CoronaVac.

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COVID-19 vaccines in population with underlying medical conditions

Cancer

A retrospective cohort study based on electronic health records of cancer patients from a multicenter, national database in the United States between December 2020 and November 2021, found a significantly higher risk of breakthrough infection in the cancer patients than that in non-cancer patients after receivingtwo doses of BNT162b2, or mRNA-1273, or one dose of AZD1222 [68]. Among 45,253 vaccinated patients with the 12 specific cancer types, the highest risk was associated with liver cancer [hazard ratio 1.78 (95% CI, 1.38-2.29)], followed by lung cancer [hazard ratio 1.73 (95% CI, 1.50-1.99)], pancreatic cancer [hazard ratio 1.64 (95% CI, 1.24-2.18)], and colorectal cancer [hazard ratio 1.53 (95% CI, 1.32-1.77)], and the lowest risk was for thyroid cancer [hazard ratio 1.07 (95% CI, 0.88-1.30)], skin cancer [hazard ratio 1.17 (95% CI, 0.99-1.38)], breast cancer [hazard ratio 1.16 (95% CI, 1.07-1.25)], and prostate cancer [hazard ratio 1.19 (95% CI, 1.10-1.29)]. Breakthrough infections with SARS-CoV-2 in cancer patients are also associated with a significant and substantial risk of hospitalization and death.

A retrospective, cross-sectional study involving 2,578 cancer patients from March 2020 to December 2021 to assess the effectiveness of vaccination with BNT162b2 or CoronaVac vaccine against COVID-19 [69]. No significant difference of COVID-19 risks between the recipients of two doses of BNT162b2 and three doses of CoronaVac vaccine was noted. While two doses of CoronaVac with one boost dose of BNT162b2 were more effective than two doses of BNT162b2, or three doses of CoronaVac; and two doses of BNT162b2, or three doses of CoronaVac provided

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significantly higher protection compared to two doses of CoronaVac did in these cancer patients. A population-based test-negative case-control study in 377,194 cancer patients showed that, BNT162b2 vaccines provided an effectiveness of 72.1% (95% CI, 71.6-72.7) against COVID-19, while the ChAdOx1 nCov-19 vaccine provided 59.0% (95% CI, 58.5-59.6) [70]. Compared with general healthy population, decreased vaccine effectiveness was found in patients with cancer or treated with radiotherapy or systemic anticancer therapy within the past 12 months. Besides, vaccine effectiveness declined more rapidly in patients with hematologic tumors like lymphoma or leukemia than did in patients with solid tumors.

Pregnancy

An observational cohort study of 10,861 vaccinated pregnant women aged 16 years or older were matched to 10,861 unvaccinated pregnant controls estimated vaccine effectiveness was 96% (95%CI 89-100) for any documented symptomatic infection, 97% (95%CI 91-100) for infections with documented symptoms and 89% (95%CI 43-100) for COVID-19-related hospitalization [71]. In addition, vaccination of pregnant women may also provide protection against SARS-CoV-2 for their newborns.

Chronic hemodialysis

In 6,076 patients with chronic hemodialysis, the vaccine effectiveness were 68.9% (95% CI, 61.9-74.7) for two-dose BNT162b2, and 66.7% (95% CI, 58.9-73.0) for two-dose mRNA-1273, which were lower than those observed in healthy adults [72]. A systematic review of reported that 396,062 hemodialysis patients suffered from a higher risk of COVID-19, with 15-fold increase of COVID-19 incidence and associated death risk compared to that in the general population [73].

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Solid organ transplantation

The COVID-19 mRNA vaccines were less effective in recipients of solid organ transplantation against COVID-19-related hospitalizations. However, three doses of mRNA vaccines produced higher protection than two doses of mRNA vaccine did among the solid organ transplantation recipients. Effectiveness of mRNA vaccines against hospitalization associated with COVID-19 among 440 recipients of solid organ transplantation were 29% (95% CI, -19-58) for two-dose regimen and 77% (95% CI, 48-90) for the three-dose regimen, respectively [74].

In liver transplant patients, the immune response to two doses of BNT162b2 was low, but the third dose significantly improved the humoral and cellular immune response [75]. Further studies are needed to evaluate the persistence of immune response to three doses in the liver transplant patients to determine the optimal number of doses and an interval between the booster dose and the primary doses.

The unmet gaps

The ranking of vaccine regimens with effectiveness were revealed in a living systematic review with network meta-analysis involving a total of 53 studies and 24 combinations of COVID-19 vaccine regimens with or without boosting in preventing COVID-19 related symptomatic infection, hospital admission, and death [111]. In this review, a three-dose mRNA COVID-19 vaccine regimen was reported as the most effective against asymptomatic and symptomatic COVID-19 infections with vaccine effectiveness of 96% (95% CI, 72-99), and against COVID-19 related hospital admission with effectiveness of 95% (95% CI, 90-97). Following that, heterologous boosting using two-dose adenovirus vector COVID-19 vaccines plus one booster of mRNA vaccine also showed a satisfactory vaccine effectiveness of 88% (95% CI, 59-97). Then,

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decreasing of vaccine effectiveness was noted in two-dose mRNA vaccines, two-dose adenovirus vectored vaccine, one-dose adenovirus vectored vaccine, one-dose mRNA vaccine, and two-dose inactivated vaccines. These data also supported that higher protection could be associated with more doses of vaccination, and a heterologous boosting with COVID-19 vaccines.

However, we should be aware that vaccine effectiveness, particularly the protective effects of COVID-19 vaccines on significant clinical outcomes including severe, critical disease, and death, may be somewhat overestimated due to the "healthy vaccinee bias". The vaccinated population in the observational studies are potentially healthier than the unvaccinated population, so the vaccinated population are protected by the vaccination, as well as their good health condition, leading to a bias towards a higher vaccine effectiveness. The mRNA vaccine BNT162b2 are relatively more widely used worldwide with application in the immunocompromised populations, and collected more data on the vaccine protection in various populations, but evidences on the effectiveness of most COVID-19 vaccines in the presence of underlying medical conditions were limited.

In addition, most reported vaccine efficacy and/or effectiveness were obtained in a short-term after administration of the vaccination. Even with highly effective COVID-19 vaccines, the waning of antibodies over time as well as the vaccine-induced protection against infection of SARS-CoV-2 may be obvious. In addition, the breakthrough infection associated with new emerging variants of SARS-CoV-2 are constantly being reported. These emerging strains of the Omicron (B.1.1.529) subtypes such as BA.4/5 pose a significant challenge to the first generation of vaccines based on the antigen of prototype SARS-CoV-2, as well as the herd immunity constructed to infection with previous SARS-CoV-2 variants [112].

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Although receiving a fourth dose of the prototype COVID-19 vaccines repeatedly could be feasible to restore the vaccine protection against SARS-CoV-2, theoretically, a variant-specific vaccine has the capacity to generate more optimal immune memory to both conserved and new epitopes. But, a phenomenon of 'original antigenic sin' may inhibit the capacity of the vaccine to elicit responses to the new variants [113]. A more ideal solution would be having a next generation of COVID-19 vaccines which have a wild epitope coverage to provide cross-immunity against SARS-CoV-2 variants, and could confer a longer duration of protection.

Efficacy and safety are two core characters for a vaccine, but when considering massive administration of vaccines in routine programs, ease of schedules, vaccine effectiveness, need and frequency of boosters, cost, other factors regarding cold-chain logistics, manufacturing scalability, acceptability by communities, and scope for local or regional production are additional important characters. Dr Hanna Nohynek, chair of the COVID-19 Vaccine Working Group of the WHO Strategic Advisory Group of Experts, and Dr Annelies Wilder-Smith, Coordinator of the COVID-19 Vaccine Working Group believe that countries around the world need multiple vaccines tailored to their national conditions due to different population structure, clinical practice, and level of economic development [6]. With more vaccine platforms available, we can possibly improve decision making regarding the selection of a vaccine, since different vaccine platforms may be more suitable for certain age groups, certain subpopulations (e.g., those with underlying immune-compromising or other medical conditions), and pregnant women. We may increasingly need to mix and match vaccines to leverage the benefits of each of these platforms.

Although more than 4.6 billion people in the world were already been vaccinated with at least one dose of COVID-19 vaccine approval for use, according to WHO's database collected by 200

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countries out of 222 countries [114], the unmet gaps about the persistence and spectrum of vaccine protection provided by the current available COVID-19 vaccines are need to be investigated in the future. Pancoronavirus COVID-19 vaccines or polyvalent COVID-19 vaccines with broader antigenic composition, improvement of adjuvants, and heterologous prime boost regimens might provide efficient strategies to confer longer term protection and increase resistance of immune responses to new SARS-CoV-2 variants.

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Table 1. The efficacy of COVID-19 vaccines observed in phase 3 randomized controlled clin

Sponsor/ country	Vaccine	Dose/ regimen	Region/ country	Study period	VE (any variant)	VE against Covid-19 of any severity (any variant)		VE against older population	
						Mild/ moderate	Severe/ critical		
Sinovac/ China	Corona Vac	2 doses/14 days apart	Turkey[11]	September 2020 to January 2021	83.5% (65.4-92.1)	-	-	-	
			Brazil[12]	July to December 2020	50.7% (36.0-62.0)	100% (56.4-100.0)*	100% (16.9-100.0)	51.1% (-166.9-91.0)†	-
			Indonesia[13]	August to October 2020	65.30%		-	-	
Beijing CNBG/ China	BBIBP-CorV	2 doses/21 days apart	United Arab Emirates and Bahrain[19]	July to December 2020	78.1% (64.8-86.3)	-	100%	-	-
Bharat Biotech/ India	BBV152	2 doses/28 days apart	India[22]	November 2020 to January 2021	77.8% (65.2-86.4)	-	93.4% (57.1-99.8)	67.8% (8.0-90.0)†	-
AstraZeneca/ UK	AZD1222	2 doses/21 to 35 days apart	UK and Brazil[24]	April to November 2020	62.1% (41.0-75.7)	-	-	-	-
			USA, Chile and Peru[25]	-	74.0% (65.3-80.5)	-	100%	83.5% (54.2-94.1)‡	-
			South Africa[26]	June to December 2020	-	21.9% (-49.9-59.8)	-	-	-
			UK[76]	May to November 2020	-	-	-	-	7 (-
			Brazil[77]	June to December 2020	-	-	-	-	-
Janssen/ USA	Ad26.COV2.S	1 dose	Argentina, Brazil, Chile, Colombia,	September 2020 to January 2021[29]	66.9% (59.1-73.4)	64.8% (55.8-72.2)	76.7% (54.6-89.1)	76.3% (61.6-86.0) †	-

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			Mexico, Peru, South Africa, and USA	September 2020 to July 2021[30]	55.9% (51.0 - 60.5)	29.4% (-64.6-70.7) 52.1% (46.1-57.4)	73.3% (63.9-80.5)	55.0% (42.9 - 64.7)†	7
CanSino/ China	Convidecia	1 dose	Argentina, Chile, Mexico, Pakistan, and Russia[32]	September 2020 to January 2021	57.5% (39.7-70.0)	-	-	17.5% (-127.6-70.1)†	-
Novavax/ USA	NVX-CoV2373	2 doses/21 days apart	UK[34]	September to November 2020	89.7% (80.2-94.6)	-	-	88.9% (20.2-99.7) ‡	8
			USA and Mexico[35]	December 2020 to February 2021	90.4% (82.9-94.6)	-	100% (87.0-100)	-	9
Pfizer/ BioNTech / USA/ Germany	BNT162b2	2 doses/21 days apart	USA, Argentina, Brazil, South Africa, Germany and Turkey	July to November 2020[37]	95.0% (90.3-97.6)	-	75.0% (-152.6-99.5)	94.7% (66.7-99.9) ‡	-
				July to October 2020[38]	91.3% (89.0-93.2)		96.7% (80.3-99.9)	94.5% (88.3-97.8) ‡ 96.2% (76.9-99.9)‖	1 1
Moderna/ USA	mRNA-1273	2 doses/28 days apart	USA[39]	July to October 2020	94.1% (89.3-96.8)	-	100%	86.4% (61.4-95.2) ‡	
			USA[40]	July to October 2020	93.2% (91.0-94.8)		98.2% (92.8-99.6)	91.5% (83.2-95.7) ‡	-
			USA and Canada[78]	March to August 2021	-		-	-	
Gamaleya / Russia	Sputnik V	2 doses/21 days apart	Russia[47]	September to November 2020	91.6% (85.6-95.2)	-	100% (94.4-100.0)	91.8% (67.1-98.3) §	-

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Wuhan CNBG/ China	WIBP-CorV	2 doses/21 days apart	United Arab Emirates and Bahrain[19]	July to December 2020	72.8% (58.1-82.4)	-	100%	-	-
Zhifei Longcom/ China	ZF2001	3 doses/30 days apart	Uzbekistan, Indonesia, Pakistan and Ecuador[49]	December 2020 to December 2021	75.7% (71.0-79.8)	-	87.6% (70.6-95.7)	67.6% (21.9-87.8) †	8 ((
Clover Biopharmaceuticals/ Hong Kong, China	SCB-2019	2 doses/21 days apart	Belgium, Brazil, Colombia, Philippines and South Africa[50]	March to August 2021	67.2% (54.3-76.8)¶	83.7% (55.9-95.4)*	100% (25.3-100.0)**	58.4% (-73.4-92.9)†	-
GSK+ Medicago /USA +Canada	CoVLP +AS03	2 doses/21 days apart	Argentina, Brazil, Canada, Mexico, UK and USA[51]	March to September 2021	69.5% (56.7-78.8)	76.9% (51.5-90.0) 78.8% (55.8-90.8)*	100.0% (-63.7-NA)	12.9% (-3295.5-97.8)‡	1 N
Cadila Healthcare/ India	ZyCoV-D	3 doses/28 days apart	India[52]	January to June 2021	66.6% (47.6-80.7)	64.9% (44.9-79.8)	100%	-	
CureVac/ Germany	CVnCoV	2 doses/28 days apart	Europe and Latin America[53]	December 2020 to April 2021	48.2% (31.0-61.4)††	70.7% (42.5-86.1)*	-	-	5 (1

VE (vaccine efficacy) are represented with point estimates and their 95% confidence intervals. * represents moderate to severe disease. † represents ol population aged≥65 years. § represents older population aged＞60 years. || represents older population aged≥75 years. ¶ represents 95.72% CI. ** rep represents children aged 6 to 11 years receiving one dose mRNA-1273.

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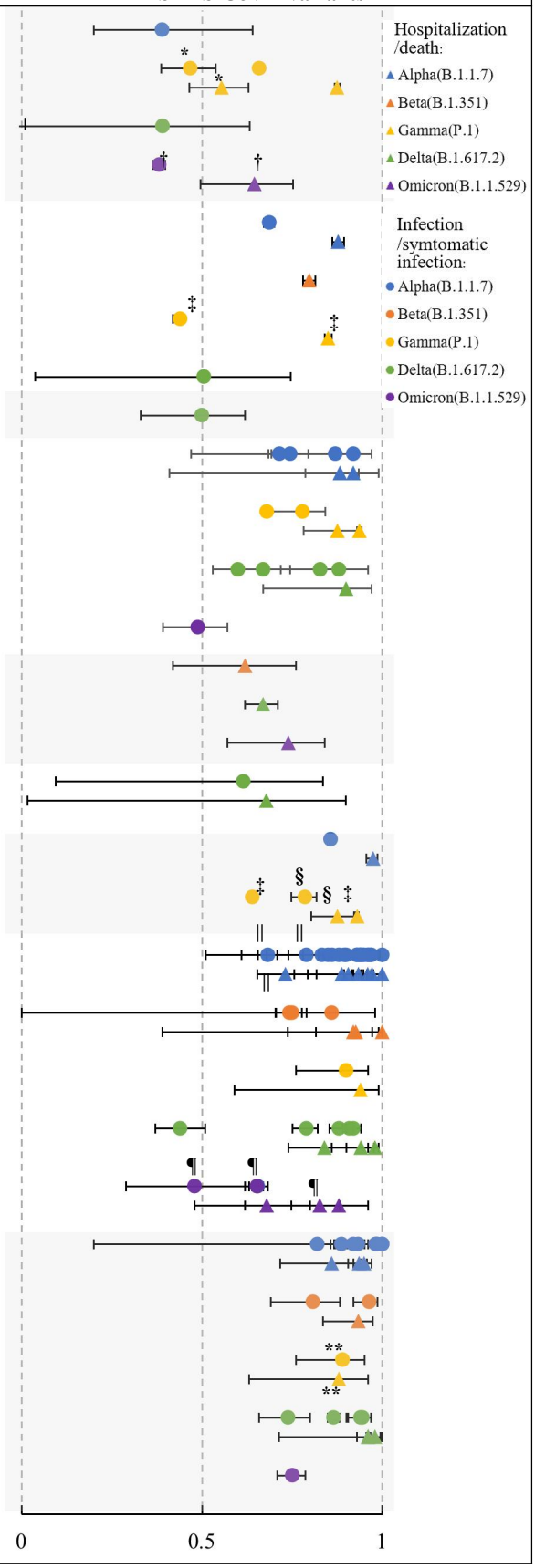
Table 2. Effectiveness of the COVID-19 vaccines against SARS-CoV-2 variants in the real-world studies.

Sponsor/ country	Name of vaccine	Study design	Country/ countries	Study period	Effectiveness against SARS-CoV-2 variants
Sinovac/ China	CoronaVac [14,79-82]	2 retrospective cohort studies; 2 prospective cohort studies; 1 test-negative case-control study	Chile, China, Turkey and Brazil	From January 2021 to February 2022	
Beijing Institute of Biological/ China	BBIBP-CorV [20,82-84]	2 retrospective cohort studies; 1 test-negative, case-control study; 1 retrospective, observational study	China, Argentina, Hungary and The United Arab Emirates	From September 2020 to September 2021	
Bharat Biotech/ India	BBV152 [23]	1 test-negative, case-control study	India	From April 2021 to May 2021	
AZD1222/ UK	AZD1222 Vaxzevria [20,27,28,84-88]	6 test-negative case-control studies; 1 large community-based survey; 1 retrospective, observational study	UK, Scotland, Canada, Brazil, Argentina, and Hungary	From December 2020 to January 2022	
Janssen/ USA	Ad26.COV2.S [31,89]	1 test-negative design study; 1 matched cohort design study	South Africa	From November 2021 to January 2022	
CanSino/ China	Convidecia [33]	1 retrospective cohort study	China	In July 2021	
Gamaleya/ Russia	Sputnik V [20,84]	1 test-negative, case-control study; 1 retrospective, observational study; 1 retrospective cohort study	Argentina and Hungary	From December 2020 to September 2021	
Pfizer/ BioNTech/ USA/ German	BNT162b2 [27,28,84,86-108]	11 test-negative case-control studies; 6 retrospective cohort studies; 5 prospective cohort study; 3 observational study	USA, UK., Israel, Italy, Qatar, Canada, France, Hungary, Scotland, South Africa and Germany	From February 2020 to February 2022	
Moderna/ USA	mRNA-1273 [28,84,86,92,100,101,104,106,108-110]	6 test-negative case-control studies; 2 retrospective cohort studies; 2 prospective cohort study; 1 observational study	USA, Qatar, Canada, France, Hungary and UK.	From December 2020 to January 2022	



Real-world vaccine effectiveness as assessed by case-control and observational studies of authorized two-dose regimens for CoronaVac, BBIBP-CorV, BBV152, AZD1222, Sputnik V, BNT162b2 and mRNA-1273, and one-dose regimen for Ad26.COV2.S and Ad5-nCoV. The point estimates and their 95% confidence intervals reported in studies of different vaccines were shown on the right, with circles representing vaccine effectiveness against infection/symptomatic infection and triangles representing severe disease, including hospitalization or death. Some studies only reported vaccine effectiveness in older adults or children, which have been marked in the figure. * Older adults aged ≥70 years; † children

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aged 3-5 years;

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‡ older adults aged ≥60 years; § older adults aged 60-79 years and after the first component of Sputnik V; || older adults aged ≥80 years; ¶ children aged 5 to 11 years; ** one-dose mRNA-1273 effectiveness.

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Competing interests

The authors declare no competing interests.

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