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REVIEW

Effect of homologous or heterologous vaccine booster over two initial doses of inactivated COVID-19 vaccine

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ABSTRACT

Introduction: Inactivated vaccines were delivered to low- and middle-income countries during the early pandemics of COVID-19. Currently, more than 10 inactivated COVID-19 vaccines have been developed. Most inactivated vaccines contain an inactivated whole-cell index SARS-CoV-2 strain that is adjuvant. Whole virions inactivated with aluminum hydroxide vaccines were among the most commonly used. However, with the emerging of COVID-19 variants and waning of the immunity of two doses of after 3 months, WHO and many local governments have recommended the booster-dose program especially with heterologous platform vaccine.

Area Covered: This review was conducted through a literature search of the MEDLINE database to identify articles published from 2020 to 2023 covered the inactivated COVID-19 vaccines primary series with homologous and heterologous booster focusing on safety, immunogenicity, efficacy, and effectiveness.

Expert opinion: The inactivated vaccines, especially whole virion inactivated in aluminum hydroxide appeared to be safe and had good priming effects. Immune responses generated after one dose of heterologous boost were high and able to preventing severity of disease and symptomatic infection. A new approach to inactivated vaccine has been developed using inactivating recombinant vector virus-NDV-HXP-S vaccine.

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KEYWORDS
Primary series; inactivated COVID-19 vaccine; heterologous boost; variant of concerns; new generation inactivated vaccine

1. Introduction

The emergence of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became a global pandemic in early 2020 [1]. The pandemic of COVID-19 has caused serious impacts on the global economy and public health system. The development and implementation of vaccines have been key measure to control the pandemic. Various COVID-19 vaccines have been developed using different platforms, for example, inactivated, vector-based, and mRNA platforms.

Inactivated vaccines are safe and effective and had been distributed nearly 1 billion doses globally outside China. Using traditional manufacturing technologies, vaccines can be developed rapidly when a new infection emerges. This type of vaccine has to be stored at 2–8°C, which is logistically feasible, especially in low- to middle-income countries (LMICs). The advantages of inactivated COVID-19 vaccines are their safety and ability to induce strong immune responses (humoral and cell-mediated immune responses) to many antigens. These vaccines can be used in immunocompromised patients. The disadvantages of inactivated COVID-19 vaccines are the need for biosafety level 3 areas for their production and the potential for epitope alteration during the inactivation process [2]. There were theory concerns of immune enhancement effects of non-neutralizing antibodies generated by inactivated vaccine platform in general. However, there were no reports of this phenomenon after receiving currently authorized inactivated COVID-19 vaccines. A meta-analysis revealed that the primary series of inactivated COVID-19 vaccines effectively prevented SARS-CoV-2 infection and hospitalizations with short-term, mild-to-moderate adverse reactions and rare serious events [3].

Because vaccine protection and immune responses wane over time and new immune escape SARS-CoV-2 variants of concern (VOCs) emerge, a booster dose of vaccine is recommended [4]. After priming with two doses of inactivated vaccine, homologous or heterologous boosters have been used and evaluated. The heterogenous boosters seemed to yield better outcomes in terms of immune responses and effectiveness compared with homologous boosters [5,6].

This review focuses on the safety, immunogenicity, efficacy, and effectiveness of licensed and newly developed inactivated COVID-19 vaccines with homologous and heterologous booster regimens.

2. Primary series of inactivated COVID-19 vaccines: safety, immunogenicity, and efficacy

Currently, 11 inactivated COVID-19 vaccines have been developed (Table 1). Most inactivated vaccines contain an inactivated whole-cell index SARS-CoV-2 strain that is adjuvant. Various types of adjuvants have been used including aluminum hydroxide, Algel-IMDG, and CpG 1018. Two doses of

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Article highlights

- Inactivated vaccines - an aluminum-hydroxide-adjuvanted, inactivated whole virus vaccine(Coronavac/Sinovac) and BBIBP-CorV /Sinopharm were delivered to low- and middle-income countries during the early pandemics of COVID-19 in 2021.
- Two doses of immunity were waning after 3 months.
- The heterologous regimens include boosting with vector-based (Ad26.COV2-S, ChAdOx1 nCoV-19), mRNA-based (BNT162b2, mRNA-1273), and subunit and recombinant protein COVID-19 vaccines.
- The inactivated vaccine appeared to have good priming effects which were able to raised the immune responses up after one dose of heterologous boost especially in preventing severity of disease against both Delta and Omicron (BA.1) variants.
- New concept of inactivated vaccine by inactivating recombinant vector virus using a recombinant vector inactivated platform, the NDV-HXP-S COVID-19 (Wuhan-Hu-1 strain) vaccine has no safety concerns and able boost the immune response similar to the vector-based platform.

inactivated COVID-19 vaccines are recommended, usually with a 2–4 week interval between vaccinations.

2.1. Safety of the inactivated COVID-19 vaccines

Inactivated vaccines are generally very safe. The results from phase 1–3 clinical trials revealed mild-to-moderate adverse events without any major concerns (Table 1). A meta-analysis reported that two doses of COVID-19 inactivated vaccines caused more adverse events (total adverse events [Relative risk-RR 1.14, 95% CI (1.08, 1.21), $p < 0.00001$] and systemic adverse events [RR 1.22, 95% CI 1.09, 1.35, $p = 0.0002$] than placebo [3].

The common local adverse events included injection site pain and swelling, redness, and pruritus [24], which depended on the type of adjuvant used [3]. Common systemic adverse events included fatigue, headache, muscle pain, fever, and gastrointestinal symptoms (Table 1). There were no cases of anaphylaxis or vaccine-related deaths [14].

Serious adverse events were rare compared with adenoviral vector or mRNA-based COVID-19 vaccines. A phase 3 clinical trial of CoronaVac vaccine reported 0.1% serious adverse events in the CoronaVac and placebo groups and there were no deaths [7]. The vaccine-induced thrombotic thrombocytopenia (VITT) was very rare [25,26] after BBIBP-CorV vaccine administration. In contrast, the incidence of VITT in adenoviral vector-based COVID-19 vaccines was 28 per 100,000 administrations and with high mortality rate (32%) [27]. Myocarditis has been reported but is not a major severe adverse event of inactivated COVID-19 vaccines. In a case-control study, the incidence of carditis from CoronaVac and BNT162b2 vaccines was estimated to be 0.31 (95% CI, 0.13 to 0.66) and 0.57 (95% CI, 0.36 to 0.90) per 100,000 doses administered, respectively [28]. Overall, the inactivated vaccine platform is very safe with mild-to-moderate adverse events and serious adverse events are rarely reported.

2.2. Immunogenicity of the inactivated COVID-19 vaccines

Phase 2 immunogenicity data of inactivated COVID-19 vaccines are summarized in Table 1. The vaccine immune response peaked 14–28 days after the second vaccine dose before gradually waning. Regarding CoronaVac vaccine immunogenicity, a phase 2 clinical trial in healthy adults (aged 18–59 years) was conducted to study 3 μg vs. 6 μg doses and 14 vs. 28-day intervals. The study reported similar immunogenicity between the two doses and the longer interval induced higher immune responses [9]. The seroconversion rate of neutralizing antibodies to wild type (WT) live SARS-CoV-2 after two doses of 3 μg CoronaVac vaccine was 92% and the geometric mean titer (GMT) was 44.1 at day 28 after vaccination [9]. For the BBIBP-CorV vaccine, a phase 1 immunogenicity study reported a dose escalating response and a phase 2 trial reported a 100% seroconversion rate at day 42 after vaccination and that two doses of 4 μg at intervals of 21 and 28 days provided high neutralizing antibody titers (neutralizing antibody GMT of 282.7 (221.2–361.4) for 4 μg in the 0–21-day interval group and 218.0 (181.8–261.3) for 4 μg in the 0–28-day interval group) [12].

Although most inactivated vaccines use aluminum hydroxide as an adjuvant, the BBV152 vaccine (Covaxin) uses Algel-IMDG (an imidazoquinoline molecule chemisorbed on alum [Algel]), which stimulates cell-mediated responses [29]. A phase 2 trial of BBV152 in adults and adolescents to test 3 μg and 6 μg Agel-IMDG reported a significant increase in the GMT (PRNT50) at day 28 after the second vaccination in the higher dose group compared with the lower dose group (197.0 vs. 100.9; $p = 0{\cdot}0041$) [13]. Regarding cellular responses, a significant increase in the levels of Th1 cytokines (IFN-γ, IL-2, and TNF-α) was reported for both doses. Similar immune responses were obtained from other inactivated vaccines listed in Table 1.

Immune responses induced by inactivated vaccines wane 3–6 months after vaccination, especially during the emergence of VOCs. Therefore, higher levels of antibodies are required for protection against new viral variants. A study in Hongkong reported that among CoronaVac vaccinees at 3–4 months after the completion of vaccination, neutralizing antibody levels against the Delta and Omicron (BA.1) variants were – 3.18 and – 5.84-fold compared with levels against the WT virus [30]. Furthermore, neutralizing antibodies against VOCs were near the detection limit 3 months after vaccination [30]. This trend was also reported for other inactivated COVID-19 vaccines. For the BBIBP-CorV vaccine, neutralization IC50 titers against the Delta and Omicron (BA.1) variants were – 4.30 and – 6.0-fold compared with levels against the wild-type virus 1 month after complete vaccination and a significantly decreased neutralization IC50 was noted 5 months after vaccination, especially for the Omicron (BA.1) variant [31]. However, the humoral (anti-RBD, anti-nucleocapsid, and sVNT) and cellular (vaccine-induced memory B cells and antigen-specific CD4+ and CD8+ T-cells) immune responses induced by the BBV152 vaccine remained for up to 12 and 6 months post-vaccination, respectively [32,33]. The immune responses to VOCs were significantly decreased when compared with the ancestral strain: 1.7- and 2-fold reductions in sVNT titers for the beta and Delta strains, respectively [32]. Furthermore, the sVNT for Omicron (BA.1) was below the limit of detection [33].

Some studies compared the immune responses of COVID-19 vaccines across various platforms. CoronaVac vaccinees had

Table 1. Summary of inactivated COVID-19 vaccines.

Vaccine	Developer	Vaccine structure	Strain	Adjuvant	Administration	Clinical stage	Safety-related adverse events (AE %) reported	Immunogenicity (against index virus)	Vaccine efficacy (VE)/ effectiveness	Reference
Fully licensed inactivated COVID-19 vaccines										
CoronaVac	Sinovac Biotech, China	Whole-virion inactivated	CN02	Aluminum hydroxide	3 μg IM, 2–4 week interval	Phase 3 and real-world effectiveness	18.9%, most common systemic reaction was fatigue (8.2%)	At day 28 after vaccination - seroconversion rate: 92% - live virus neutralizing antibody generated - GMT was 44.1	VE: 83.5% (95% CI 65.4–92.1) against COVID-19 infection Vaccine effectiveness: 65.9% reduction in COVID-19 infection, 87.5% reduction in hospitalizations, 86.3% reduction in death	[7–9]
BBIBP-CorV	Sinopharm's Beijing Institute of Biological Products, China	Whole-virion inactivated	HB02	Aluminum hydroxide	4 μg IM, 3–4 week interval	Phase 3 and real-world effectiveness	23%, most common systemic reaction was fatigue (3.0%)	At day 28 after vaccination - seroconversion: 100% - live virus neutralizing GMT was 29.3	VE (HBO2): 78.1% (95% CI 64.8–86.3) Vaccine effectiveness: 79.6% reduction in hospitalizations, 84.1% reduction in death	[10–12]
BBV152	Bharat Biotech International, India	Whole-virion inactivated (vero cell)	NIV-2020-770 (spike variant Asp614Gly)	Algel-IMDG	6 μg IM, 4 week interval	Phase 3 and real-world effectiveness	12.4%	At day 28 after vaccination - seroconversion: 98.3% - neutralizing GMT (PRNT50): 197.0	VE: 77.8% (95% CI 65.2–86.4) against infection, 93.4% (95% CI 57.1–99.8) against severe COVID-19	[13,14]
VLA2001	Valneva Austria GmbH, Austria	Vero cell-based inactivated vaccines	No data	CpG 1018 and aluminum hydroxide	25 AU IM, 4 week interval	Phase 3	60.0%	At day 14 after vaccination - seroconversion: 97.4%, neutralizing GMR (MNA50): 1.39, (1.25–1.56; p<0·0001) compared with ChAdOx1-S	No data Immunobridging study: non-inferior to ChAdOx1-S	[15]
Emergency authorized inactivated COVID-19 vaccines										
ERUCOV-VAC	Turkish Ministry of Health and Erciyes University, Türkiye	Whole-virion inactivated	hCoV-19/Türkiye/ERAGEM-001/2020	Aluminum hydroxide	3 μg IM, 4 week interval	Phase 3	58.8%, most common systemic reactions were headache (16.7%) and fatigue (16.7%)	At day 32 after vaccination - seroconversion: 96.6%, neutralizing GMT (MNT50): 34.2	Non-inferior to CoronaVac at preventing symptomatic COVID-19	[16,17]
QazCovid-in/ QazVac	The Research Institute for Biological Safety Problems in Kazakhstan	Whole-virion inactivated	SARS-CoV-2 human/KAZ/KZ_Almaty/2020	Aluminum hydroxide	5 mg IM, 3 week interval	Phase 3	48.7%, most common systemic reaction was headache (2.4%)	At day 21 after vaccination - seroconversion: 99%, micro-neutralizing GMT (MNA): 109	VE: 82.0% (95% CI 71.1 −88.5) against symptomatic COVID-19	[18]
CoviVac	Chumakov Centre, Russia	Whole-virion inactivated	B.1.1 strain	No data	2 doses IM, 2 week interval	Phase 3 (NCT05407142)	35.2%	At day 14 after vaccination - seroconversion: 86.9%	VE: 49.0% against lung injury and 84% against severe lung injury	[19,20]

(*Continued*)

Table 1. (Continued).

Vaccine	Developer	Vaccine structure	Strain	Adjuvant	Administration	Clinical stage	Safety-related adverse events (AE %) reported	Immunogenicity (against index virus)	Vaccine efficacy (VE)/ effectiveness	Reference
KCONVAC	Shenzhen Kangtai Biological Products Co. Ltd. and Beijing Minhai Biotechnology Co. Ltd., China	Vero cell-based inactivated vaccines	CQ01	Aluminum hydroxide	5 and 10 µg IM,2 and 4 week intervals	Phase 3 (NCT04852705)	25–26%	At day 28 after vaccination - seroconversion: 83.0–99.0%%, neutralizing GMT (PNA): 37.2–44.5	No data	[21]
BIV1-CovIran/ CovIran-Barkat	Barkat Pharmaceutical Group, Iran	Whole-virion inactivated	B4 lineage (PANGO lineage)	Alhydrogel	5 µg IM, 4 week interval	Phase 1/2	54.0%	At day 14 after vaccination - seroconversion: 82.8%, neutralizing GMT: 17.1 µg/mL	No data	[22]
IMBCAMS COVID-19/ Covidful	Institute of Medical Biology, Chinese Academy of Medical Sciences, China	Whole-virion inactivated (Vero cell)	No data	No data	2 doses IM, 2 week interval	Phase 3 (NCT04659239)		No published data		
Inactivated COVID-19 vaccines under development in clinical trials										
NDV-HXP -S/HXP-GPO vac	Icahn School of Medicine at Mount Sinai	Inactivated egg-based recombinant Newcastle disease virus vaccine expressing the spike protein	Not applicable	CpG 1018	3,3+cpG, and 10 µg IM, 4 week interval	Phase 1/2, Phase 2 (TCTR20220804007), Phase 3 (TCTR20221026004)	Local AE: 22.9–65.7% Systemic AE: 22.9–54.3%	At day 14 after vaccination - seroconversion: 93.9–100%, neutralizing GMC (PNA): 122.2–474.4 IU/mL	No data	[23]

Based on access to www.clinicaltrial.gov on 27 August 2023.

AE = adverse event, VE = vaccine efficacy, GMT = geometric mean titer, GMR = geometric mean ratio, GMC = geometric mean concentration, PRNT = plaque reduction neutralization test, MNA = microneutralization assay, PNA = pseudovirus neutralization assay, IM = intramuscular, CI = confidence interval.

significantly lower humoral immune responses against the wild-type virus compared with the BNT162b2 mRNA vaccine [30,34]. The GMT measured by PRNT50 1 month after completed vaccination among those who received the BNT162b2 mRNA vaccine was significantly higher than that of those who received the CoronaVac vaccine (251.6 vs 69.45, $p = 1.24 \times 10^{-9}$) [34]. Similar results were reported by a study in Serbia that compared the immunogenicities of BBIBP-CorV, BNT162b2, and Gam-COVID-Vac vaccines: the BNT162b2 vaccine had the highest anti-spike IgG level followed by the Gam-COVID-Vac and BBIBP-CorV vaccines [35].

2.3. Efficacy and effectiveness of the inactivated COVID-19 vaccines

Overall, the completed primary series of inactivated COVID-19 vaccinations showed moderate efficacy against symptomatic COVID-19, and good efficacy and effectiveness against severe COVID-19 (Table 1). However, the vaccine efficacy decreased in the context of VOCs. Phase 3 efficacy and real-world effectiveness data are available for the initial vaccines including CoronaVac, BBIBP-CorV, and BBV152.

Placebo-controlled COVID-19 efficacy studies were no longer ethically acceptable when the VLA2001 phase 3 study was initiated [15]. Thus, only an immunobridging study was performed and no efficacy and effectiveness data are available for VLA2001.

For the CoronaVac vaccine, phase 3 studies conducted in adults aged 18–59 years showed 83.5% (95% CI, 65·4% to 92·1%) efficacy against symptomatic COVID-19 during a mean follow-up of 43 days in Turkey and 65.3% at approximately 3 months of follow-up in Indonesia [7,36]. A nationwide vaccine effectiveness study in Chile reported the adjusted vaccine effectiveness was 65.9% (95% CI, 65.2% to 66.6%), 87.5% (95% CI, 86.7% to 88.2%), 90.3% (95% CI, 89.1% to 91.4%), and 86.3% (95% CI, 84.5% to 87.9%) for the prevention of COVID-19, hospitalization, Intensive Care Unit (ICU) admission, and COVID-19–related deaths, respectively, in fully vaccinated adults aged ≥16 years [8]. A phase 3 study of the BBIBP-CorV vaccine was conducted in the United Arab Emirates and Bahrain among 40,382 adults aged ≥18 years to evaluate the efficacy and adverse events of two inactivated COVID-19 vaccines, WIV04 (5 µg/dose) and HB02 (4 µg/dose) [10]. In the interim analysis, both vaccines demonstrated good vaccine efficacy against symptomatic COVID-19 (72.8% (95% CI, 58.1% to 82.4%) for the WIV04 group and 78.1% (95% CI, 64.8% to 86.3%) for the HB02 group) during a median (range) follow-up duration of 77 (1–121) days. A retrospective study to evaluate the real-world efficacy of BBIBP-CorV in the United Arab Emirates reported the vaccine effectiveness at 3 months was 79.6% (95% CI, 77.7 to 81.3) against hospitalization, 86% (95% CI, 82.2 to 89.0) against critical care admission, and 84.1% (95% CI, 70.8 to 91.3) against death due to COVID-19 [11].

For the BBV152 vaccine, a phase 3 randomized, double-blind, placebo-controlled study of 25,798 Indian adults aged >18 years reported the efficacy against any severity of COVID-19 with onset 14 days after the second vaccination was 77.8% (95% CI, 65.2 to 86.4), and efficacy against severe COVID-19 was 93.4% (95% CI 57.1 to 99.8) at a median follow-up of 99 days [14]. Furthermore, the vaccine efficacy against Delta VOCs was 65.2% (95% CI, 33.1 to 83.0). The real-world effectiveness of the BBV152 vaccine using a test-negative design revealed the adjusted effectiveness of two doses administered before testing was 46% (95% CI, 22 to 62) and 57% (95% CI, 21 to 76) administered at least 28 days and 42 days before testing, respectively, in health care workers during the second wave of COVID-19 (predominately Delta variants) in India [37].

Several phase 1 and phase 2 clinical trials of a chimeric Newcastle Disease Virus (NDV) vaccine platform, developed by three different vaccine manufacturers, GPO (Thailand), IVAC (Vietnam), and Butantan (Brazil), have been completed. The vaccine has been demonstrated to be safe and highly immunogenic across a range of doses, and GPO has decided to continue development of the product using the highest dose level, 10 mcg, to maximize the magnitude and duration of responses in the face of the continuing challenges of variants [23]. The 10 mcg dose was chosen for use as a primary regimen among those who have not been vaccinated as well as a booster immunization in subjects primed with the same (HXP-GPO Vac) or other available vaccines. A phase 3 trial will provide data on the safety and immunogenicity of HXP-GPO Vac used as a booster for those already primed with other vaccines.

3. Booster effect of heterologous or homologous boosters on those receiving an inactivated primary series vaccinations

3.1. The first booster dose, third dose effects

Homologous and heterologous booster COVID-19 vaccines have been used as the third dose in those who received an inactivated COVID-19 primary series of vaccinations. The heterologous regimens include boosting with vector-based (Ad26.COV2-S, ChAdOx1 nCoV-19), mRNA-based (BNT162b2, mRNA-1273), and subunit and recombinant protein COVID-19 vaccines (Table 2). There were no safety concerns for the homologous and heterologous booster regimens [5,50–53].

Regarding immunogenicity, the homologous and heterologous COVID-19 booster vaccinations strongly enhanced humoral immune responses. A homologous CoronaVac booster at 5 months after the 28 schedules of CoronaVac in a cohort from Chile revealed enhanced neutralizing antibody levels, which were greater than those at the peak immune response 2–4 weeks after the second dose and there was a sustained CD4+ T cell response [54]. Moreover, both neutralizing antibodies and cellular immunity induced by the booster showed activity against Delta and Omicron (BA.1) VOCs with seropositivities of 93% and 76.7%, respectively [54].

Table 2 summarizes studies that compared the immunogenicity (focusing on neutralizing antibodies) of homologous and heterologous booster regimens over the primary inactivated COVID-19 vaccines in healthy adults. Many studies have reported that heterologous boosters provided greater immunogenicity than homologous boosters over the primary inactivated series. For example, in a phase 4 study from Brazil, a heterologous booster with adenoviral vector vaccines (Ad26.

Table 2. Immunogenicity of homologous vs. heterologous boosters over the primary inactivated series in healthy adults.

	Population	Primary series	Duration	Booster	Neutralizing antibodies: Test virus and GMT at Day 14–28	Neutralizing antibodies: GMR	Reference
1	Age ≥18 years, Brazil, *N*=1240	CoronaVac	6 months	CoronaVac	ND	Reference	[5]
				Ad26.COV2-S		8·7	
				BNT162b2		21·5	
				ChAdOx1 nCoV-19		10·6	
2	Age ≥18 years, China, *N*=198	CoronaVac	3–6 months	CoronaVac	WT 33.6 and Delta 8.2	ND	[38]
				Convidecia	WT 197.4 and Delta 55		
3	Age ≥18 years, China, *N*=1,440 (immune subset *N*=450)	CoronaVac	90 days	Placebo	WT 202.8	ND	[39]
				CoronaVac	WT 2935.7		
				Ad26.COV2-S	WT 16,242.3		
				BNT162b2	WT 44,035.7		
4	Age ≥18 years, China, *N*=37	BBIBP-CorV	4–8 months	BBIBP-CorV	WT 285.6, beta 215.7, Delta 250.8, and Omicron (BA.1) 48.73	ND	[40]
				ZF2001 (subunit)	WT 1436.00, beta 789.6, Delta 1501.00, and Omicron (BA.1) 95.86		
5	Age 18–59 years, China, *N*=235	CoronaVac	5–7 months	Placebo	ND	-	[41]
				CoronaVac		0.73 (Delta: WT), 0.11 (Omicron(BA.1): WT)	
				ChAdTS-S (adenovirus vector)		0.79 (Delta: WT), 0.14 (Omicron(BA.1): WT)	
				RQ3013 (mRNA)		0.84 (Delta: WT), 0.27 (Omicron(BA.1): WT)	
				ZR202-CoV (Recombinant protein)		0.79 (Delta: WT), 0.17 (Omicron(BA.1): WT)	
6	Age ≥18 years, Bahrain, *N*=305	BBIBP-CorV	3–6 months	BBIBP-CorV	No GMT data GMC WT 63 ± 25 BAU/ml	ND	[42]
				BNT162b2	GMC WT 97 ± 2.3 BAU/ml		
7	Age ≥18 years, Thailand, *N*=179	CoronaVac	2–3 months	BBIBP-CorV	Delta 24.31, and Omicron (BA.1) 0.70	2.89 (post-: pre-boosting against Delta)	[43]
				ChAdOx1 nCoV-19	Delta 586.65, and Omicron (BA.1) 169.59	12.79 (post-: pre-boosting against Delta)	
				BNT162b2 half dose	Delta 1,512.7, and Omicron (BA.1) 551.29	19.39 (post-: pre-boosting against Delta)	
				BNT162b2 full dose	Delta 1,584.8, and Omicron (BA.1) 542.6	23.54 (post-: pre-boosting against Delta)	
8	Age ≥60 years, China, *N*=199	CoronaVac	3–6 months	CoronaVac	WT 286.4	ND	[44]
				Ad5-nCOV	WT 48.2		
9	Age 18–72 years, Philippines, *N*=430	CoronaVac	≥3 months	CoronaVac	WT 161, Delta 170, and Omicron (BA.1) 67.1	Booster SCB-2019: CoronaVac 5.03, 3.16, 3.33 against WT, Delta, and Omicron(BA.1)	[45]
				SCB-2019 (recombinant protein vaccine)	WT 811, Delta 538, and Omicron (BA.1) 223		
10	Age ≥18 years, United Arab Emirates, *N*=1800	BBIBP-CorV	1–3, 4–6, and ≥6 months	BBIBP-CorV	WT 296.20, 327.81, 449.30 for 1–3, 4–6, and ≥6 months	ND	[46]
				NVSI-06-07 (recombinant protein)	WT 1335.43, 1812.82, 1906.60 for 1–3, 4–6, and ≥6 months		
11	Age 18–70 years, Thailand, *N*=224	CoronaVac	5–7 months	BBIBP-CorV	Delta 69.6, and Omicron (BA.1) 24.6	ND	[47]
				ChAdOx1 nCoV-19	Delta 1003, and Omicron (BA.1) 250		
				BNT162b2	Delta 1285, and Omicron (BA.1) 277		
				mRNA-1273	Delta 2168, and Omicron (BA.1) 512		
12	Age 34–73 years, China, *N*=60	CoronaVac	61–160 days	CoronaVac	Delta 65, and Omicron (BA.1) 8.9	ND	[48]
				BNT162b2	Delta 305.5, and Omicron (BA.1) 59.2		
13	Age 22–72 years, Türkiye, *N*=52	CoronaVac	3–5 months	CoronaVac	WT 21.44	ND	[49]
				BNT162b2	WT 78.69		

ND = no data, WT = wild type, GMT = Geometric Mean Titer, GMR = Geometric Mean Ratio.

COV2-S, ChAdOx1 nCoV-19) or an mRNA vaccine (BNT162b2) over primary CoronaVac vaccination provided superior immune responses associated with anti-S and neutralizing antibodies, than a homologous booster with CoronaVac [5].

A similar trend was reported in a study from Chile using ChAdOx1 or BNT162b2 compared with the CoronaVac homologous booster in participants previously primed with CoronaVac [39].

NVX-CoV2373 vaccine manufactured by Serum Institute of India was also studied using as a heterologous booster which induced non-inferior immune responses as compared to homologous boosters in adults primed BBV152 [55].

The effects of a fractional dose booster have also been evaluated. The immune responses of a half dose of heterogenous booster with the ChAdOx1 nCoV-19 or BNT162b2 vaccines over a CoronaVac primary series were non-inferior to the full-dose booster [43,51,56]. However, the immunogenicity seemed to wane more quickly in the half-dose group compared with the full-dose booster [43,51]. Regarding the interval of the booster dose, a longer interval between the second dose of the primary series and the first booster dose provided more robust immune responses. A homologous booster of CoronaVac at an 8-month interval markedly increased neutralizing antibody levels compared with a 2-month interval [50]. Similarly, a heterologous booster study using an Ad26.COV2.S booster dose following two doses of BBIBP-CorV appeared to have a higher GMT increase in those with a longer booster interval.

Regarding efficacy and effectiveness, many studies have reported high vaccine efficacy and effectiveness for the homologous booster of inactivated vaccines over an inactivated primary series. A homologous booster of CoronaVac had an adjusted vaccine effectiveness of 78.8% (95% CI, 76.8 to 80.6), 86.3% (95% CI, 83.7 to 88.5), 92.2% (95% CI, 88.7 to 94.6), and 86.7% (95% CI, 80.5 to 91.0) against symptomatic COVID-19, hospitalization, ICU admission, and death, respectively, in a large prospective study from Chile during the surge of the Delta variant [57]. The homologous BBIBP-CorV vaccine efficacy was 86.3% (95% CI, 79.6 to 91.1) and 94.1% (95% CI 79.6 to 91.1) against symptomatic and severe COVID-19 in a phase 3 cohort from Abu Dhabi [53].

In line with immunogenicity, a heterologous booster also had better effectiveness than a homologous booster [57]. A systematic review and meta-analysis of 28 studies reported the effectiveness against COVID-19 infection was 89.19% (95% CI, 78.49 to 99.89) for heterologous mRNA vaccine boosters, 87.00% (95% CI, 82.14 to 91.85) for non-replicating vector vaccine boosters, 69.99% (95% CI, 52.16 to 87.82) for homologous boosters, and 51.48% (95% CI, 41.75 to 61.21) for two doses of an inactivated vaccine as shown in Figure 1 [6]. Furthermore, homologous and heterologous booster regimens still provided high vaccine effectiveness against severe outcomes related to Omicron(BA.1) COVID-19 with an efficacy of 88.00% (95% CI, 82.15 to 93.85) and 90.47% (95% CI, 86.49 to 94.44), respectively [6]. Recent data showed that the effectiveness of homologous boost against Omicron (BA.5) was marginal [58].

3.2. The effects of a second or further booster dose

The protective effect of a third dose wanes over time, especially in the context of the Omicron (BA.1) era; a half-life of 111 days (95% CI, 88 to 155 days) was estimated for vaccine efficacy against Omicron (BA.1) symptomatic COVID-19 [59]. A second booster or a fourth vaccine dose was suggested and administered to a special population [60,61]. A second mRNA booster over an mRNA primary series showed marginal benefit related to vaccine efficacy against Omicron (BA.1) COVID-19 infection in healthy healthcare workers; 30% (95% CI, −9 to 55) for BNT162b2 and 11% (95% CI, −43 to 44) for mRNA-1273 [62]. However, a fourth dose substantially reduced hospitalizations and deaths from COVID-19 in the elderly aged >60 years [63]. The adjusted hazard ratios for hospitalization and death due to COVID-19 in a second BNT162b2 booster group compared with the first booster group were 0.36 (95% CI, 0.31 to 0.43) and 0.22 (95% CI, 0.17 to 0.28), respectively [63].

There are limited data for those receiving a fourth dose or more of an inactivated COVID-19 vaccine primary series. A study of a cohort from Chile reported that a second booster of CoronaVac at 6 months after a homologous CoronaVac booster and primary series (four doses of CoronaVac) enhanced neutralizing antibodies against the WT virus but provided inadequate protection against the Omicron (BA.1) variant; GMT of 33 and 3.7 ($p < 0.001$), respectively [64]. However, a sustained robust CD4+ T cell response was observed after a CoronaVac booster, which conferred protection against VOCs [64]. A fourth dose of BBIBP-CorV given 6 months after the third dose increased neutralizing antibodies than that after the third vaccination dose by 19- and 2.9-fold against the WT and Omicron (BA.1) viruses [65]. The administration of a fourth dose soon after the third dose is not recommended because the immune response generated from the third dose is still present. The greatest benefit of a booster dose is obtained when it is administered during the waning of immune responses.

The role and optimal interval of additional booster doses for the general population remains unclear. An additional booster at 6 or 12 months after the last dose is recommended by Strategic Advisory Group of Experts (SAGE)-WHO in high-priority groups (elderly, people with significant comorbidities, those who are immunocompromised, pregnant women, and frontline health workers). SAGE recommends a primary series and only first booster doses for medium priority groups (healthy adults, children and adolescents with comorbidities). COVID-19 vaccine is not recommended for the low priority group (healthy children and adolescents aged 6 months to 17 years) [66].

4. Future considerations

Inactivated COVID-19 vaccines are very safe and can be used over a wide range of ages, including the young. However, at least two doses have to be administered to obtain optimal effects. Because immune responses wane over a short period, adjuvanted formulations should be explored. Using new technologies, a recombinant vector inactivated platform, the NDV-HXP-S COVID-19 (Wuhan-Hu-1 strain) vaccine, is now being investigated in a phase 3 trial in Thailand. A new approach using different routes of administration such as the intranasal administration of the NDV-HXP-S bivalent (VoC strains) COVID-19 vaccine is now in phase 1/2 development [23,67]. However, there are many challenges related to new COVID-19 vaccine

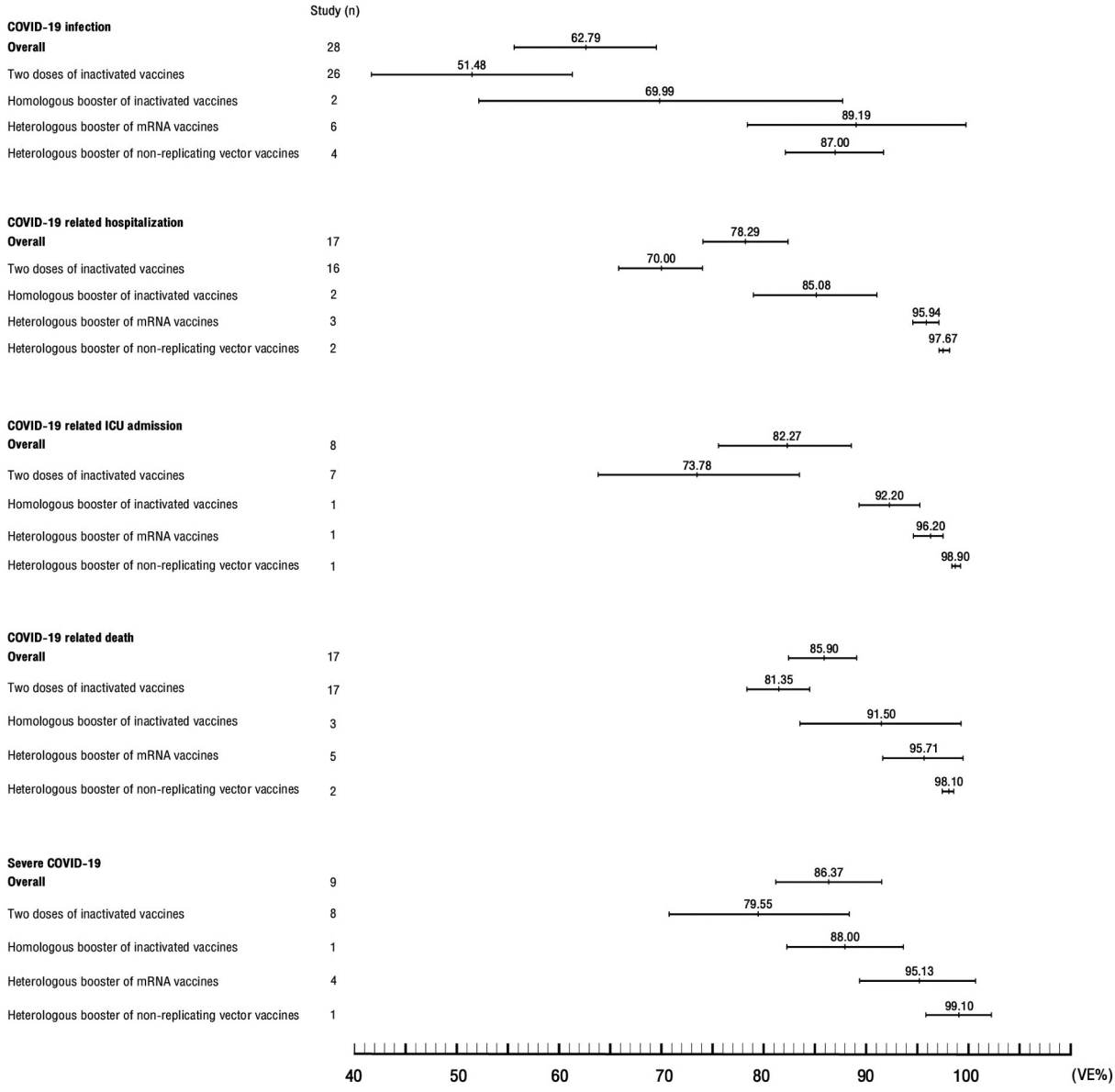

Figure 1. Vaccine effectiveness (VE) of booster regimens: results from a systematic review and meta-analysis. Adapted from zhang et al., 2023 [6] with permission.

trials to determine the direct effects of the vaccine on the immune responses as the immunity generated during a period of high circulating VoCs consists of hybrid immunity to COVID-19 infection that occurred prior or post-vaccination [68].

5. Conclusion

The use of inactivated COVID-19 vaccines as a primary series is very safe and can be used as a primary vaccine because its effectiveness against the severity of COVID-19 is relatively long. This contributes to reducing the burden of COVID-19 on healthcare systems and the health of healthcare personnel during early epidemics/pandemics. However, the immune response and efficacy wane rapidly together with the emergence of immune escape VOCs, which contribute to the high number of cases but a relatively low mortality rate. Heterologous booster regimens have been recommended over the inactivated primary series, as they provide greater immune responses and better efficacy/effectiveness than homologous boosters with the inactivated COVID-19 vaccine. The recommended boosting interval is 12 months between doses in the healthy population.

6. Expert opinion

Inactivated vaccines manufactured from China (Coronavac/Sinovac and BBIBP-CorV/Sinopharm had been delivered to low- and middle-income countries during the early pandemics of COVID-19 in 2021. About 1 billion doses had been distributed globally. However, with the appearance of Delta wave and waning of the immunity of two doses of after 3 months, WHO and many local governments have recommended and launched the booster-dose program especially with heterologous platform vaccine. Homologous and heterologous booster COVID-19 vaccines have been used as the third dose in those who received an inactivated COVID-19 primary series of vaccinations. The heterologous

regimens include boosting with vector-based (Ad26.COV2-S, ChAdOx1 nCoV-19), mRNA-based (BNT162b2, mRNA-1273), and subunit and recombinant protein COVID-19 vaccines. There were no safety concerns. The inactivated vaccine appeared to have good priming effects which were able to raise the immune responses up after one dose of heterologous boost especially in preventing severity of disease even during the Omicron (BA.01). Both Chinese vaccines kill the SARS-COV-2 virus, so the immune response generated against many viral proteins might lead to relatively durable T cell responses after boosting with vector or mRNA-based COVID-19 vaccine. The advantage of inactivated vaccine is mainly on safety. But it has less effects in elderly population. As the immunity after inactivated vaccine waned over time after 3 months. The production process required high biosafety-level facility and the longer time for production as compare to the mRNA platform. So the use of these products after the pandemics was not considered. As the data especially on vaccine efficacy and effectiveness of other similar inactivated COVID-19 vaccine produced from other manufacturers were limited. So the data were presented only in the form of table (Table 1).

Many efforts have been made to develop new concept of inactivated vaccine by inactivating recombinant vector virus using a recombinant vector inactivated platform, the NDV-HXP-S COVID-19 (Wuhan-Hu-1 strain) vaccine, is now approved for booster administration for emergency situation. The new generation for the Omicron variant is underway. A new approach using different routes of administration such as the intranasal administration of the NDV-HXP-S bivalent (VoC strains) COVID-19 vaccine is now in phase 1/2 development.

Another approach, which is difficult and takes time to develop, but finally the subunit vaccines were licensed for use as both primary series and booster-dose eg.Novavax vaccine. The other, the Bimeravax vaccine, was just approved by EMA earlier this year. Bimervax is a recombinant protein consisting of part of the SARS-CoV -2 spike protein from the Alpha and Beta virus variants and is adjuvanted.

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Declaration of interest

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I confirm all authors should have (1) substantially contributed to the conception and design of the review article and interpreting the relevant literature, and (2) been involved in writing the review article or revised it for intellectual content.

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