Indonesian Journal of Clinical Pharmacy, March 2023
Vol. 12 Iss. 1, pp. 68–85
ISSN: 2252-6218, e-ISSN: 2337-5701
Available online at:
http://ijcp.or.id
DOI: 10.15416/ijcp.2023.12.1.68
Review Article

Heterologous Booster Profiles for Recipients of CoronaVac Inactivated Primary Vaccine: a Scoping Review

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Abstract
The administration of booster vaccines has been implemented in a number of countries. Unfortunately, there are limited studies of the immune response after booster to recipient with CoronaVac inactivated primary vaccine. This scoping review aims to determine heterologous booster profiles for recipients of the CoronaVac inactivated primary vaccine. This study obtained data from PubMed, Cochrane Library, Medrxiv, Google Scholar, and Grey literature. The inclusion criteria were SARS-CoV-2 article, heterologous boosters and CoronaVac vaccine published from 2020 to 2022, written in English, and in a form of an original research articles, project reports, articles with Randomized Control Trial (RCT) research designs, cohorts and articles with human research subjects. The keywords were SARS-CoV-2, COVID-19, heterologous boosters and CoronaVac. Profiles assessed were heterologous vaccine types, immune responses, intervals between the booster administration and the primary vaccine, and heterologous booster doses. The number of articles that met the inclusion criteria was 15 articles. Types of vaccines that could be used as heterologous boosters for recipients of CoronaVac inactivated primary vaccine were BNT162b2, AZD1222, mRNA-1273, and Ad26.COV2-S. The administration of heterologous booster vaccines for recipients of the CoronaVac inactivated primary vaccine was able to increase antibody levels against of the SARS-CoV-2 variants of Mild, Beta, Gamma, Delta and Omicron. The doses of booster vaccines (Ad26.COV2-S, BNT162b2, AZD1222, mRNA-1273 (Moderna) and CoronaVac) for the CoronaVac recipients respectively were 0.5 mL, 0.3 mL, 0.5mL, 100 µg and 0.5 mL. In conclusion, the heterologous boosters for the CoronaVac recipients could enhance immune responses against the SARS-CoV-2.

Keywords: CoronaVac, heterologous booster, scoping review

Profil Booster Heterolog pada Penerima Vaksin Primer Inaktif CoronaVac: *a Scoping Review*

Abstrak
Pemberian vaksin booster SARS-CoV-2 telah dilakukan di berbagai negara. Namun, studi mengenai respon imun pasca booster heterolog pada penerima vaksin primer inaktif CoronaVac masih terbatas. Tujuan studi ini adalah untuk mengetahui profil booster heterolog pada penerima vaksin CoronaVac. Penelitian ini merupakan scoping review dengan sumber data dari database elektronik PubMed, Cochrane Library, Medrxiv, Google Scholar, serta grey literature. Kriteria inklusi meliputi artikel tahun 2020–2022, berbahasa Inggris, bertema SARS-CoV-2, booster heterolog, dan vaksin CoronaVac, dengan desain penelitian RCT, kohort, atau laporan proyek pada subjek manusia. Strategi pencarian menggunakan kata kunci: SARS-CoV-2, COVID-19, heterologous booster, dan CoronaVac, dengan filter artikel asli dan tahun publikasi. Profil yang dikaji mencakup jenis vaksin booster heterolog, respon imun, interval antara pemberian booster dan vaksin primer, serta dosis booster. Sebanyak 15 artikel memenuhi kriteria inklusi. Vaksin yang digunakan sebagai booster heterolog meliputi BNT162b2, AZD1222, mRNA-1273, dan Ad26.COV2-S. Pemberian booster heterolog pada penerima vaksin CoronaVac meningkatkan kadar antibodi terhadap varian SARS-CoV-2, seperti Alpha (mild), Beta, Gamma, Delta, dan Omicron. Interval terbanyak pemberian booster adalah 6 bulan pasca dosis kedua CoronaVac. Dosis booster yang digunakan adalah: Ad26.COV2-S (0,5 mL), BNT162b2 (0,3 mL), AZD1222 (0,5 mL), mRNA-1273 (100 µg), dan CoronaVac (0,5 mL). Hasil menunjukkan bahwa booster heterolog meningkatkan respon imun pada penerima vaksin primer CoronaVac.

Keywords: *booster* heterolog, CoronaVac, *scoping review*

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Introduction

The COVID-19 pandemic in the world has not shown a decrease of cases. The latest data, reported from Worldometer, on March 19, 2024, indicated that 704,241,673 individuals of the world community were positively infected with COVID-19. In addition, 7,006,177 infected individuals died, and 675,140,313 individuals were recovered.[1] Based on the number of cases, globally Indonesia is on the 20th rank, and the United States is a country with the highest cases. Meanwhile in Asia, Indonesia is on the 8th rank after India, South Korea, Japan, Turkey, Vietnam, Taiwan and Iran.[1] Cases in Indonesia always increase, with 6,829,087 confirmed cases, with 162,062 deaths and with 6,647,104 recovered cases.[2] The fast increase of the cases is a result of the emergence of new variants of the SARS-CoV-2, namely Delta and Gamma which are able to spread quickly.[3]

Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) is a variant of the Human coronaviruses (HCoVs) that causes COVID-19. The HCoV has been identified since 1960 as a virus that can infect humans and animals.[4] The emergence of diseases caused by the corona virus began in 2003 in Guangdong, China, with a name of SARS-CoV. A decade later, the corona virus was again detected as a virus that causes an outbreak of respiratory disease in Saudi Arabia with a name of Middle East Respiratory Syndrome Coronavirus (MERS-CoV).[5] Until December 2019, a severe and very fast infectious pneumonia disease with a morphology resembling a corona virus named SARS-CoV-2 had emerged.[6] Various efforts to control the pandemic due to COVID-19 have been implemented, and one of them is by developing a COVID-19 vaccination. A clinical trial of the SARS-CoV-2 or CoronaVac vaccine candidates started on March 2020 (NCT04283461) with three clinical trial phases.[7] According to the World Health Organization (2020), there are three types of CoronaVac, namely traditional vaccines (inactivated or live-virus vaccines), licensed vaccines (recombinant protein vaccines and vectored vaccines) and vaccines that have not yet received a license (RNA and DNA vaccines). WHO recommends six vaccine candidates to the public that have entered the third phase of clinical trials, including AstraZeneca/Oxford University, Sinovac/Biotech, Sinopharm/ Beijing Institute of Biological Products, Moderna/NAID and Pfizer/Fosun Pharma.[8]

Indonesia is one of countries that promotes vaccines as early as possible with a letter of Presidential Decree No. 18/2020 on September 3, 2020 in which a team of COVID-19 vaccine development is established under supervision of the Coordinating Minister for Economic Affairs.[9] This is pursued by the Indonesian government to reduce the percentage of COVID-19 cases. Based on data from the Ministry of Health (2020) regarding perception and acceptance of Indonesians towards CoronaVac, it showed that 69% of them from the middle class and 58% from the low economic class had been vaccinated.[10] Due to the low achievement of vaccination targets by the government, strategies and regulations are promoted so that the achievement of herd immunity in the community can be maximally achieved.

One of strategies to decrease the COVID-19 cases is to provide booster vaccinations. The administration of booster vaccines has been conducted in a number of countries. Several literature studies have been conducted to study immune responses to SARS-CoV-2 after administration of heterologous boosters to recipients of mRNA vaccines.[11-14] Some of literature studies focus on heterologous vaccine types for recipients of certain primary vaccines, not CoronaVac inactivated

vaccine type.[15-16]

As time goes by, heterologous booster vaccinations for recipients of the CoronaVac have been implemented in certain countries, including Indonesia. Antibody levels and ability to increase immune responses in the use of these boosters have been reported in forms of published articles in journals. A structured literature study (scoping review) regarding immune responses to the SARS-CoV-2 after the administration of heterologous boosters for the recipients of the CoronaVac has never been conducted. Until now there has been no systematic review that examines the heterologous booster profiles. By a scoping review, this study aims to determine types of vaccine used as heterologous boosters for of the CoronaVac recipients, to determine whether the administration of heterologous booster vaccines for the CoronaVac recipients is able to increase antibody levels against the SARS-CoV-2 variants, to determine intervals between the heterologous booster vaccines and the CoronaVac inactivated primary vaccine and to measure doses of heterologous booster vaccines for the CoronaVac recipients.

Methods

Article criteria

The inclusion criteria for articles in this scoping review were articles with themes of SARS-CoV-2, heterologous boosters and CoronaVac vaccine. Also, those were articles published between 2020 to 2022, articles in English, original research articles, project reports, articles with RCT research designs, Cohorts, and articles with human research subjects.

Data resources

Data resources of this study were obtained through electronic database using search engines such as PubMed, Cochrane Library, Medrxiv and Google Scholar. A search was also focused on Grey literature in a form of research reports.

Search strategies

The search strategy for this study used a combination of keywords of SARS-CoV-2, COVID-19, heterologous boosters and coronaVac. Then, the articles were filtered based on original articles and publication years of 2020, 2021 and 2022.

Selection process for the articles

The selection process consisted of some steps, and those were identification, screening, eligibility and determination of selected articles (included). The identification step began with articles displayed by each journal search engine based on the keywords entered. The number of articles obtained from the journal search engine was recorded.

The first screening for the articles was by looking at the title on the journal search engine. Appropriate titles were recorded with an Excel program. The second screening focused on the abstracts from the the obtained tittles in the excel program. Articles with appropriate abstracts were recorded in the Microsoft Excel program.

The eligibility step was performed on full texts of the selected journal articles. Articles containing measured parameters were logged. The selected articles were ready for scoping review (included). These articles were submitted to the Mendeley program to be processed in the next step.

The inclusion criteria for the articles were original articles in English containing the SARS-CoV-2 antibody parameters.

Data extraction

The data extraction method (data charting) from all the articles was done by the researchers themselves. The data extraction process was done manually on the texts of

the articles, and results of the data extraction were summarized in an Excel table.

Data items

In this section, it was possible to identify all parameters to be analyzed according to the purpose of this study. These parameter data were obtained from each article reviewed. The data items were the identity of the authors, the years of publication, the countries where the study was conducted, the study designs, the populations, the types of primary vaccines, the types of booster vaccines, the intervals between the boosters and the second primary vaccines, the intervals between observed parameters after the booster vaccines, parameter data and outcomes.

Results

Selection of evidence sources

The results of the selection of evidence sources are described in the following flow diagram (Diagram 1). Searching with data engines of PubMed, Cohrane Library, Medrxiv and Google Scholar found 13, 729, 42 and 784 articles, respectively. Totally, the number of the articles was 1568. The number of articles that met the title criteria was 88. The number of articles that passed the duplication step was 71. Then, 15 articles meet the inclusion criteria.

Characteristics of evidence sources

The characteristics of each article containing the author's name, year, and parameters relevant to the purpose of the scoping review are listed in the following table (Table 1).

Results from each source of evidence

The first article is study by Clemen et al. (2022). Its study was conducted at two study centers located in Sao Paulo and Salvador, Brazil, from August to September 2021. Its subjects were ≥ 18 years old, had received two doses of complete CoronaVac vaccine and were administered by vaccine boosters six months later. The heterologous boosters used were Ad26.COV2-S, Janssen (recombinant adenoviral vectored vaccine), BNT162b2, Pfizer–BioNTech, (mRNA vaccine), or AZD1222, AstraZeneca (recombinant adenoviral-vectored ChAdOx1 nCoV-19 vaccine). The three heterologous boosters were compared with the CoronaVac homologous booster. The doses of Ad26. COV2-S, BNT162b2, AZD1222 and CoronaVac vaccines respectively were 0.5, 0.3, 0.5 and 0.5 mL. Its parameters were anti-spike antibody (IgG) and neutralizing antibody titers which were observed on the 28th day after the boosters. The results of this study indicated that antibody levels had decreased on the sixth month after the second dose of CoronaVac vaccination. In older adults, neutralizing antibody titer was 8-22 times higher than the CoronaVac homologous boosters. The antibody produced by the heterologous boosters was higher than the homologous boosters.[17]

The second article is by Mok et al. (2022). The study was conducted at a community vaccination center at the Chinese University of Hong Kong Medical Centre, Prince of Wales Hospital and Kowloon Bay Vaccination Station, between 10th March and 31st August 2021. Its subjects were healthy adults aged 19-77 years old and had received two doses of CoronaVac 2-5 months before the booster administration. The heterologous booster used was mRNA, BNT162b2 and Pfizer. Its research parameters were observed one month after the booster. The parameters were levels of SARS-CoV-2 neutralizing antibody and spike binding antibody in plasma. The heterologous booster group with BNT162b2 vaccine had mean of sVNT against variants of Wild, Beta, Gamma and Delta of 96.83%, 92.29%, 92.51% and 95.33%, significantly higher than the CoronaVac homolog booster

group (Wild: 57.75%, Beta: 38.79%, Gamma: 32.22%, and Delta: 48.87%). The heterologous booster with BNT162b2 vaccine was better than the CoronaVac homologous booster vaccine.[18]

The third article is a study by Caglayan et al. (2021) from Turkey (19). It was a prospective cohort study conducted between 4th March and 10th September 2021 on health workers at Dokuz Eylul University Hospital, Turkey. The characteristics of its subjects were health workers who had received two doses of CoronaVac vaccine. The exclusion criteria were health workers who were diagnosed with COVID-19 any time before the study period. Its parameter was anti-RBD IgG antibody. There was an increase in antibody levels in the group receiving the BNT162b2 heterologous booster by 104.8 times (17609.4 vs. 168 AU/ml). The homologous booster group with CoronaVac vaccine experienced an antibody increase of only 8.7 times (1237.9 vs. 141.4 AU/ml). The heterologous booster with the mRNA BNT162b2 vaccine had a higher antibody than the CoronaVac homolog booster.[19]

The fourth article is a study by Khong et al. (2020) (20). Its research design was a prospective cohort study. The study was conducted between November 2021 and December 2021 at Hong Kong West Cluster Hospitals (The Hospital Authority, Hong Kong). Its participants were native healthy individuals who had received the second dose of CoronaVac vaccine and received 1 booster dose of IM BNT162b2 (0.3 mL). The interval between the booster and the primary vaccine was 6 months. Its research parameter was vMN geometric mean titer (GMT) against variants of Wild, Beta, Delta and Omicron. The GMT antibody level of the BNT162b2 heterologous booster group was 207 (95% CI, 22.7–1893) compared to the CoronaVac homologous booster group (34.3, 95% CI, 16.3–72.1). A single dose of heterologous booster of mRNA vaccine could increase protection against SARS-CoV-2 variants of Wild, Beta, Delta and Omicron, although responses to the Omicron variant (OV) were less strong compared to other variants.[20]

The fifth study is by Nantanee et al. (2022). This study was conducted at Chulalongkorn University Health Center, Faculty of Medicine, Chulalongkorn University, Bangkok Thailand. Its research design was a prospective cohort study. Its participants were enrolled during August 2021. Its inclusion criteria were recipients of two complete dose of CoronaVac vaccine aged 18 - 59 years, and the interval between the booster and the second vaccine was at least 60 days (2 months). Its exclusion criteria were recipients of immunosuppressants or blood products within 3 months before the booster administration. The heterologous booster used was IM AZD1222 (0.5 mL). Its research parameters were spike receptor binding domain (S-RBD) IgG and functional neutralizing antibody (NAb) against SARS-CoV-2 variants of Wild and Delta using the surrogate virus neutralization test (sVNT). The heterologous booster vaccine with ID AZD1222 in adults who had received the second dose of CoronaVac increased IgG RBD anti-S306 RBD >506 BAU/ml and indicated high levels of functional neutralizing antibody >80% against variants of Wild and Delta.[21]

The six study is Zuo et al. (2022) reported that heterologous booster using mRNA vaccine on complete-dose inactivated vaccine recipients could increase specific antibody levels and responses of B and T cell and enhance protection against SARS-CoV-2 variants including Omicron. The study included 183 samples of 124 healthy volunteers (54.3% women, mean age of 34 years old) in Sweden (n = 75), Germany (n = 18) and Iran (n = 31) in 2021. Its inclusion criteria were participants >18 years old

who had received inactivated vaccines. Its parameter was the level of specific antibody to the receptor binding domain (RBD) of the spike protein of variants of Wild, Beta, Delta and Omicron. The primary vaccine used was CoronaVac, while the booster vaccines used were BNT162b2 and mRNA-1273. The heterologous booster with mRNA vaccine significantly increased the levels of specific antibodies binding to RBD domain of Wild (6 times) and to VOC including Delta (8 times) and Omicron (14 times) .[22]

Then, the seven study is by Jara from Chile. A study found that the use of heterologous boosters after receiving CoronaVac could reduce the severity and mortality of COVID-19. Its research design was a prospective national cohort. The population involved was 11.2 million people, aged 16 years old. The primary vaccine used was CoronaVac. The heterologous boosters used were AZD1222 and BNT162b2 vaccines. This study was conducted in Chile, from February 2 to November 10, 2021. The effectiveness of the vaccines against COVID-19 symptoms was 78.8% (95% CI, 76.8–80.6) for the CoronaVac booster, 96.5 % (95% CI, 96.2–96.7) for the BNT162b2 booster, and 93.2% (95% CI, 92.9–93.6) for the AZD1222 booster. The effectiveness of the vaccines on hospitalizations, ICU admissions and COVID-19-related deaths was 86.3%, 92.2% and 86.7% for the CoronaVac, 96.1%, 96.2% and 96-8% for the BNT162b2 booster, and 97.7%, 98.9%, and 98.1% for the AZD1222 booster.[23]

The eight study is by Li et al. (2022). The safety and immunogenicity of the heterologous booster of Convidecia vaccine after the administration of two doses of the CoronaVac primary vaccine were reported by Li et al. (2022). The study began between 25 and 26 May 2021, with 300 registered participants. Its research design was a randomized, controlled, observer-blinded trial. Its subjects were healthy people aged 18-59 years old who had received the second CoronaVac vaccine. Observations of the parameters were conducted on the 14th day and the 28th day after booster vaccination. Heterologous immunization with Convidecia induced higher live virus neutralizing antibodies than homogeneous immunization with CoronaVac (197.4[167.7, 232.4] vs. 33.6[28.3, 39.8] and 54.4[37. 9, 78.0] vs. 12.8 [9.3, 17.5]).[24]

The nine study is by Yorsaeng et al. (2022) at Thailand. Other cohort studies indicated that heterologous boosters to inactivated vaccines could increase antibodies. Participants who had previously received two doses of CoronaVac were immunized with AZD1222 as the third dose between June 11 and July 23, 2021. Participants who had received the heterologous booster of AZD1222 had higher levels of IgG-specific RBD, total immunoglobulin and IgA anti-S1 IgA than the recipients of two doses of the vaccine ($p < 0.001$). There was a higher neutralizing activity against Mild and all variants of concern. This study demonstrated the high immunogenicity of the AZD1222 booster in individuals receiving two doses of inactivated vaccines.[25]

The ten study is by Kuloglu et al. (2022) at Turkey. Individuals who had two doses vaccines were as participants. Studies conducted at three centers (Koc University Hospital, Cerrahpasa Hospital of Istanbul University and Istanbul Medical School Hospital) in Istanbul showed that neutralizing antibody levels were higher in the BNT162b2 heterologous booster than the CoronaVac homologous booster. This increase of titers was observed after three months of the BNT162b2 booster. Observations of the parameters were conducted one to three months after the booster.[26]

The 11th study is by Assawakosri et al. (2022). This study took place in Thailand.

Table 1 Characteristics of Evidence Sources

Study Author	Study Design	Population	Primary Series	Booster	Interval for 2nd vaccines	Follow up	Parameter
Clemen et al. (2022) Brazil	A phase 4, non-inferiority, single blind, randomised study	adults (≥18 years) in São Paulo or Salvador	CoronaVac	Ad26.COV2-S (Janssen), BNT162b2 (Pfizer–BioNTech), AZD1222 (AstraZeneca), CoronaVac	6 month	28 days	Anti-spike IgG antibodies, Neutralising antibody titres , Local and systemic reactogenicity profiles, Adverse events
Mok et al. (2022) China	RCT	Adults (19-77 years) in Hong Kong SAR, China	CoronaVac	CoronaVac, BNT162b2	2-5 month	1 month	Humoral immunogenicity, adverse reactions
Çağlayan et al. (2021) Turkey	Prospective cohort study	Healthcare workers in a university hospital in Turkey	CoronaVac	CoronaVac, BNT162b2	6 month	2 month	Anti RBD IgG
Khong et al. (2022) China	Prospective cohort study	23 SARS-CoV-2 naïve healthy	CoronaVac	BNT162b2	6 month		The neutralizing
Nantanee et al. (2022), Thailand	Prospective cohort study	Adult (18-59 years)	CoronaVac	ChAdOx1 nCoV-19 vaccine(AZD1222,Oxford/ AstraZeneca)	2 month	0,14,28,90 day	Surrogate virus neutralization test(sVNT), anti-S-RBD IgG
Zuo et al. (2022) Sweden, Germany, Iran		≥ 18 years	CoronaVac	BNT162b2	4-16 month		Anti-S-RBD

Table 1 Characteristics of Evidence Sources

Study Author	Study Design	Population	Primary Series	Booster	Interval for 2nd vaccines	Follow up	Parameter
Jara et al. (2022) Chile	A prospective observational national-level cohort	11•2 million participants (≥16 years) affiliated with the Fondo Nacional de Salud (FONASA)	CoronaVac	CoronaVac, AZD1222, BNT162b2	14 day	14 day	
Li et al. (2022)			CoronaVac	Convidecia, CoronaVac	3-6 month	28 days	GMTs of neutralizing antibody against SARS-CoV-2
Yorsaeng et al. (2022) Thailand	Cohort	younger (mean age 40 years	CoronaVac	AZD1222	1-2 month	14-35 day	Spike RBD-specific IgG, anti-S1 IgA
Kuloglu et al. (2022) Turkey	Cohort	Individuals who had two doses	CoronaVac	BNT162b2	5 month	1-3 month	neutralizing antibody titers (Geometric Mean Titer [GMT]
Assawakosri et al. (2022) Thailand	Cohort	A total of 224 individuals who completed the two-dose CoronaVac for six months were included	CoronaVac	BBIBP AZD1222 BNT162B2 and mRNA-1273	6 month	14-28 day	Total RBD (Ig), anti-RBD IgG, FRNT50 against delta and omicron variants, and T cell response were highest in the mRNA-1273 group followed by the BNT162b2, AZD1222 and BBIBP groups
Perez-Then et al. (2022) Dominican Republic	Cohort	101 non-hospitalized adult participants	CoronaVac	BNT162b2	1 month	7-28 day	

Table 1 Characteristics of Evidence Sources

Study Author	Study Design	Population	Primary Series	Booster	Interval for 2nd vaccines	Follow up	Parameter
Kanokudom et al. (2021) Thailand	Cohort	Participants were healthy volunteers (age: 18 years)	CoronaVac	BBIBP AZD122 BNT162b2	3-4 month	14-28 day	Ig anti-receptor binding domain (RBD
Sinto et al. (2021) Indonesia	Cohort	Hospital staff in Jakarta, Indonesia	CoronaVac	mRNA-1273 (Moderna)	6 month	28 day	Anti-Spike IgG
Angkasekwinai et al. (2022) Thailand	Cohort	healthy adults	CoronaVac	BBIBP-CorV (Sinopharm Biotech), ChAdOx1, 30µg-BNT162b2 and 15µg-BNT162b2 (Pfizer-50 BioNTech)	2-3 month	2, 16-20 weeks	Anti-SARS-CoV-2 RBD IgG Neutralizing antibody responses

This study examined 224 people who had received two doses of CoronaVac with an interval of 6 months before the boosters.. This study assessed genicity reaction and immunogenicity after heterologous boosters with inactivated vaccine (BBIBP), viral vector vaccine (AZD1222), and mRNA vaccine (both BNT162B2 and mRNA-1273). This study also determined immunogenicity 3 and 6 months after the boosters. The results of this study were total RBD immunoglobulin (Ig), anti-RBD IgG, focus reduction neutralization (FRNT50) against Delta and Omicron, and the highest T cell response was in the mRNA-1273 followed by BNT162b2, AZD1222 and BBIBP.[27]

The 12th study is by Perez-Then et al. (2022). This study conducted in the Dominican Republic. The participants were 101 nonhospitalized adult. The primary vaccination used was CoronaVac inactivated vaccine with a heterologous booster of BNT162b2. This study showed that the heterologous booster induced increased levels of virus-specific antibodies and strong neutralizing activity against the virus and Delta variant, resembling the titers obtained after two doses of the mRNA vaccine. While Omicron neutralization was not detected in participants who had received two doses of CoronaVac vaccine. The BNT162b2 Booster contributed 1.4 times of increase in neutralizing activity against Omicron, compared with two doses of mRNA vaccine.[28]

The 13th study is by Kanokudom et al. (2021) from Thailand. Participants were healthy volunteers 18 years old. This study showed that booster administration with viral vector (AZD1222 0.5 mL) or mRNA (BNT162b2 0.3 mL) in individuals with a history of two doses of the inactivated vaccine (CoronaVac) increased immunogenicity.[29] Completion of two doses inactivated vaccine might increased immunogenicity.

The 14th study is by Sinto et al. (2021), from Indonesia. This article reported a cohort study on hospital staff in Pasar Minggu hospitals and St Carolus hospital in Jakarta, Indonesia. Its inclusion criteria were staff who had received two doses of the CoronaVac primary vaccine six months before (median 190 days) and age > 18 years old. Anti-Spike IgG titers were measured in paired serum samples taken before and 28 days after the 100µg mRNA-1273 booster (Moderna). This study found that the heterologous booster with mRNA-1273 (Moderna) after the two doses of CoronaVac vaccine was highly immunogenic and safe.[30] The 15th study reviewed in this scoping review study was an article by Angkasekwinai et al. (2022). This is a cohort study on healthy adult. The primary vaccine given was CoronaVac. The heterologous booster given was the mRNA BNT162b2 vaccine. The interval between the booster and the primary vaccine was 3-4 months. Observations for antibodies were 14 days after the booster. The heterologous booster with BNT162b2 had the most immunogenic protective antibodies against variants of Delta, Beta and Omicron, and responses of T cell. Half-dose of BNT162b2 booster administration was as immunogenic as the standard dose, but with less reactogenicity. This suggested that a small amount of antigen might be sufficient to enhance the immune response to SARS-CoV-2. Homologous boosters with BBIBP-CorV and ChAdOx1 were effective booster vaccines.[31]

Synthesis of the results

Based on the article data of this scoping review, there are result of profile heterologous booster vaccines used after the administration of two doses of CoronaVac inactivated primary vaccine.

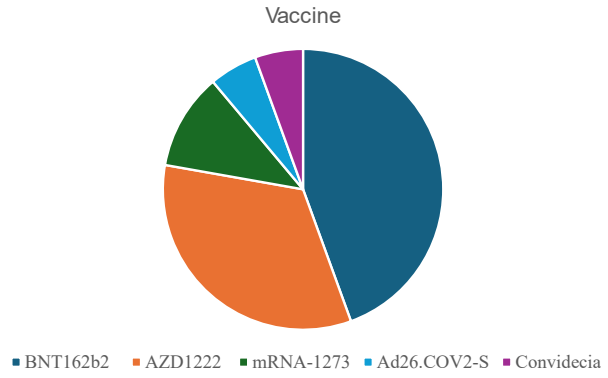

Figure 1. Types of Vaccine Used as Heterologous Boosters for The CoronaVac Recipients

Determine types of vaccine used as heterologous boosters for of the CoronaVac recipients

Types of vaccines used as heterologous boosters for recipients of the CoronaVac inactivated primary vaccine are BNT162b2, Pfizer–BioNTech[17–20,23,26,28,31], AZD1222, AstraZeneca (recombinant adenoviral-vectored ChAdOx1 nCoV-19 vaccine)[17,21,23,25,27,29], mRNA-1273[22,30], Ad26.COV2-S, Janssen (recombinant adenoviral vectored vaccine)[17], and Convidecia[32] (Figure 1).

Determine whether the administration of heterologous booster vaccines for the CoronaVac recipients is able to increase antibody levels against the SARS-CoV-2 variants

The heterologous boosters were able to provide protection against the SARS-CoV-2 variant of Wild and beta are BNT162b2, AZD1222, and mRNA-1273. The heterologous boosters were able to provide protection against SARS-CoV-2 variant of Gamma are BNT162b2 and AZD1222. The heterologous boosters were able to provide protection against SARS-CoV-2 variant of Delta and Omicron are BNT162b2, AZD1222, mRNA-1273, and BBIBP (Table 2).

A heterologous booster with BNT162b2

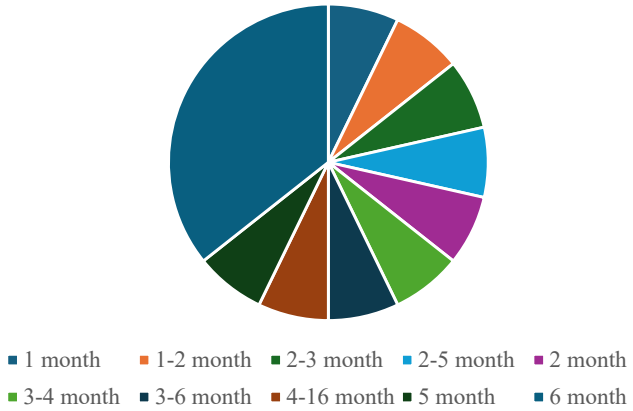

Figure 3. Intervals Between the Heterologous Booster Vaccines and the CoronaVac Inactivated Primary Vaccine

Table 2. Heterologous Booster Vaccines For The Coronavac Recipients Is Able To Increase Antibody Levels Against The SARS-CoV-2 Variants

Vaccine	Anti-spike antibody (IgG)	Againts variants of wild	Againts variants of beta	Againts variants of gamma	Againts variants of delta	Againts variants of omicron
BNT162b2	+ -27	+ (18,20,22)	+ (18,20,22,31)	+ (18,22)	+ (18,20,22,27,31)	+ -28
AZD1222	+ -27	+ (16, 20)	+ -20	+ -20	+ (20,22)	+ (20,22)
mRNA-1273	+ -27	+ -17	+ -17		+ (17,23)	+ (17,22)
BBIBP	+ -27				+ -23	+ -22

vaccine was better than the CoronaVac homologous booster vaccine.[18,19,27] The BNT162b2 vaccine had a mean sVNT against variants of Wild, Beta, Gamma and Delta with 96.83%, 92.29%, 92.51% and 95.33%, respectively, significantly higher than the CoronaVac homologous booster group (Wild: 57.75%, Beta: 38.79%, Gamma: 32.22% and Delta 48.87%).[18] CoronaVac Neutralizing antibody levels were higher in the BNT162b2 heterologous booster than un the CoronaVac homologous booster.[26] A heterologous booster with BNT162b2 was better than CoronaVac homologous booster vaccine A heterologous booster with mRNA-1273 (Moderna) after two doses of CoronaVac vaccine was highly immunogenic and safe.[30]

Heterologous booster vaccine with ID AZD1222 in adults who had received the second dose of CoronaVac had a high level of functional neutralizing antibody >80%.[21] A heterologous booster vaccine with Convidecia induced higher live virus neutralizing antibodies than homogeneous

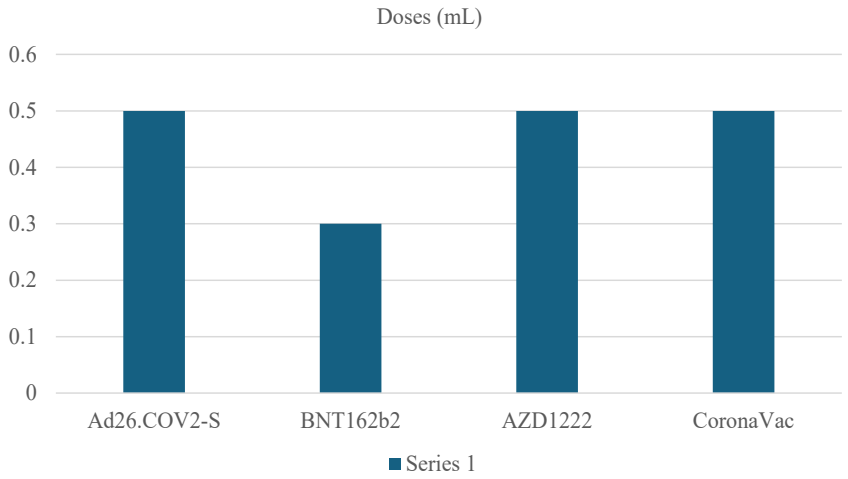

Figure 4. Doses of Heterologous Booster Vaccines for the Coronavac Recipients

immunization with CoronaVac.[32]

Determine intervals between the heterologous booster vaccines and the CoronaVac inactivated primary vaccine

Intervals of heterologous booster vaccine administration and the CoronaVac inactivated primary vaccine are 1 months in Dominican Republic[28], 2 months in Thailand[21], 2-5 months in China[18], 6 months in Indonesia, Chile, Thailand, China, Turkey, and Brazil[17,19,20,27,30], 4-16 months in Sweden, Germany, and Iran[22], 3-6 months in China[24], 3-4 months in Thailand[29], 1-2 months in Thailand[25], 5 months inTurkey[26], and 2-3 months inThailand[31] (Figure 3).

Measure doses of heterologous booster vaccines for the CoronaVac recipients

Doses of heterologous booster vaccines for the CoronaVac recipients are 0.5, 0.3, 0.5 and 0.5 mL for Ad26.COV2-S, BNT162b2, AZD1222 and CoronaVac[17,21,34–37]. One of the articles stated that the dose of Moderna vaccine given as a heterologous booster was a high dose of 100 μg[25] (Figure 4).

Discussion

The CoronaVac inactivated vaccine has been used as a primary vaccine in several countries, including Indonesia. Since 2021, Indonesia has administered the third vaccine using a heterologous vaccine scheme. Based on the scoping review data, countries that use the CoronaVac vaccine as a primary vaccine are China, Turkey, Brazil, Thailand, Chile, the Dominican Republic and Indonesia. The 7 countries have continued their COVID-19 vaccination program by using the heterologous vaccine scheme. The types of heterologous vaccines are BNT162b2, Pfizer–BioNTech (mRNA vaccine), AZD1222, AstraZeneca (recombinant adenoviral-vectored ChAdOx1 nCoV-19 vaccine), mRNA-1273, Ad26.COV2-S, Janssen and Convidecia. The results of this scoping review indicate other countries that have used heterologous vaccines. One of systematic reviews that was conducted in 2021 stated that Spain, England and Germany had performed heterologous boosters (not CoronaVac) by using ChAd/BNT.[15] Countries that use heterologous vaccines (not CoronaVac) with ChAd/BNT and ChAdOx1-S/mRNA-1273 in the use of primary vaccines of ChAdOx1-S/ChAdOx1-S, BNT162b2/BNT162b2, and mRNA-1273/mRNA-1273 are Sweden, Germany, Denmark, Spain and the UK.[16]

The heterologous booster vaccine program is considered to be able to increase immunity against the SARS-CoV-2 variants. The data of this study showed that there was an increase in antibody activity after the administration of the heterologous booster vaccines. The group that received the BNT162b2 booster vaccine experienced an increase in Anti-spike antibody (IgG) several times to hundreds of times (104.8 times). There was a significant increase in Anti-S-RBD-antibodies after BNT162b2 booster compared with other heterologous boosters of ChAdOx1 nCoV-19: 22.558 U/mL (IQR, 15.956–25.000) vs. 5.159 U/mL (IQR, 3.647.75–.,196.75). Neutralizing antibody levels were higher in the BNT162b2 heterologous booster than in the CoronaVac homologous booster. The BNT162b2 booster resulted in 1.4 times of increase in neutralizing activity against Omicron, compared to the two doses of mRNA vaccine. The results of this scoping review support systematic review data concluding that ChAdOx1-S heterologous booster and mRNA vaccine can enhance the immune response against SARS-CoV-2.[16] The ability to induce an immune response against variants of concern also supports a systematic review of the ability of heterologous booster vaccines against variants of concern (B.1.1.7,

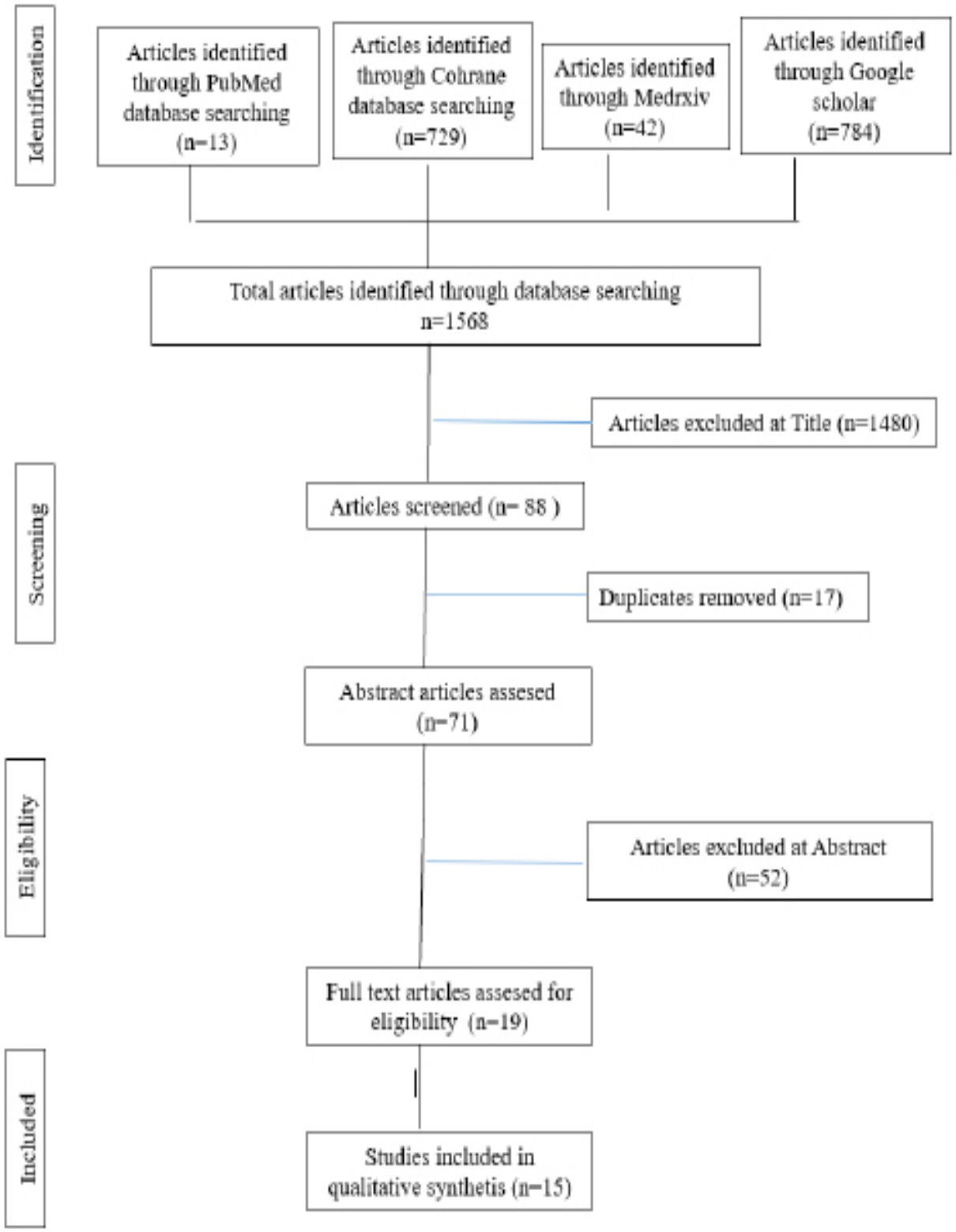

Diagram 1 –Selection of evidence sourc

B.1.351, and B.1.617).[15]

A heterologous booster with viral vector (AZD1222) in individuals with a history of two doses of inactivated vaccine (CoronaVac) can enhance immunogenicity. There is an increase in IgG RBD anti-S306 RBD >506 BAU/ml in adults. There were total RBD immunoglobulin (Ig), anti-RBD IgG, focus reduction neutralization against variants of Delta and Omicron, and the highest response of T cell in the mRNA-1273 group.The heterologous booster vaccine with Convidecia induces higher levels of live virus neutralizing antibodies than homogeneous immunization with CoronaVac.

Booster vaccine program in Indonesia uses a heterologous vaccine scheme, namely mRNA-1273 (Moderna), BNT162b2 pfizer and AZD1222 AstraZeneca. One of the articles in this scoping review explained that there was an increase in antibody levels after the third booster using Moderna. Based on this scoping review, the use of the three types of booster vaccines in Indonesia is expected to provide protection against the SARS-CoV-2 variants of Wild, Beta, Gamma, Delta and Omicron. It should be noted that the ability of each heterologous vaccine is different against the Omicron variant.

Another interesting finding is the doses of heterologous booster. The doses of Ad26.COV2-S, BNT162b2, AZD1222, and CoronaVac respectively are 0.5, 0.3, 0.5, dan 0.5 mL.[17,20,21,29]. One of articles stated that the dose of Moderna vaccine as a heterologous booster was a high dose of 100 µg.[30] The dose of BNT162b2 vaccine used should be 0.3 mL. The heterologous booster vaccine is given at most six months after the second dose of vaccine.

Completion of two doses inactivated vaccine might increased immunogenicity. There are more studies that support the finding that booster administration with mRNA (BNT162b2 0.3 mL) in individuals with a history of two doses of the inactivated vaccine (CoronaVac) potentially increase immunogenicity.[38].

The limitation of this scoping review process is the minimal data on the doses of the heterologous boosters and the primary vaccines.

Conclusions

The types of vaccines that can be used as heterologous boosters for the recipients of the CoronaVac inactivated primary vaccine are BNT162b2, AZD1222, mRNA-1273 and Ad26.COV2-S. The administration of heterologous booster vaccines for the recipients of the CoronaVac inactivated primary vaccine is able to increase antibody levels against SARS-CoV-2 variants of Mild, Beta, Gamma, Delta and Omicron. The interval between the administration of the heterologous booster vaccine and the CoronaVac inactivated primary vaccine is 6 months since the administration of the second dose of CoronaVac. Doses of the boosters (Ad26.COV2-S, BNT162b2, AZD1222, mRNA-1273 (Moderna) and CoronaVac) in the use of the CoronaVac respectively are 0.5 mL, 0.3 mL, 0.5mL, 100 µg, and 0.5 mL.

Acknowledgements

The authors thank to UPPM FK UII for the funding support.

Funding

The research was funded by UPPM FK UII.

Conflict of interest

There is no conflict of interest in this article.

References

1. Worldometers.info. Worldometers.info. [cited 2022 Feb 9]. COVID-19 Coronavirus Pandemic. Available from: https://www.worldometers.info/coronavirus/#countries
2. Covid19.go.id. Covid19.go.id. 2022 [cited 2022 Feb 9]. Data Sebaran Perkembangan Covid-19. Available from: https://covid19.go.id/
3. Muhamad SV. Pandemi Covid-19 Sebagai Persoalan Serius Banyak Negara di Dunia. Info Singkat. 2021;8(13).
4. Dong Y, Mo X HY. Epidemiological Characteristics of 2143 Pediatric Patients with 2019 Coronavirus Disease in China. American Academy of Pediatrics. 2020.
5. Shereen MA, Khan S, Kazmi A, Bashir N SR. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;24:91–8.
6. Li Q, Guan X WP. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;
7. Krammer F. SARS-CoV-2 Vaccines in Development: Review. Nature. 2020;586.
8. Who.int. who.int. 2022 [cited 2022 Feb 9]. Draft Lanscape of Covid-19 Candidate Vaccines. Available from: https://www.who.int/ publications/m/item/draftlandscape-of-covid-19-candidatevaccines
9. Indonesia KKR. Survei Penerimaan Vaksin Covid-19 di Indonesia. Jakarta Indonesia; 2020.
10. The Ministry of Health, NITAG, UNICEF, WHO. COVID-19 Vaccine Acceptance Survey in Indonesia. 2020.
11. Marchese AM, Rousculp M, Macbeth J, Beyhaghi H, Seet BT, Toback S. The Novavax Heterologous Coronavirus Disease 2019 Booster Demonstrates Lower Reactogenicity Than Messenger RNA: A Targeted Review. J Infect Dis. 2023 Nov 22;
12. espers V, Leroy R, Hulstaert F, Wyndham Thomas C, Van Montfort T, Van Damme UAntwerpen P, et al. RAPID REVIEW OF THE EVIDENCE ON A COVID-19 BOOSTER DOSE AFTER A PRIMARY VACCINATION SCHEDULE REPORT FOR THE TASK FORCE VACCINATION (VERSION WITH SUMMARY IN DUTCH). 2021.
13. Napuri NI, Curcio D, Swerdlow DL, Srivastava A. Immune Response to COVID-19 and mRNA Vaccination in Immunocompromised Individuals: A Narrative Review. Vol. 11, Infectious Diseases and Therapy. Adis; 2022. p. 1391–414.
14. Deng J, Ma Y, Liu Q, Du M, Liu M, Liu J. Comparison of the Effectiveness and Safety of Heterologous Booster Doses with Homologous Booster Doses for SARS-CoV-2 Vaccines: A Systematic Review and Meta-Analysis. Vol. 19, International Journal of Environmental Research and Public Health. MDPI; 2022.
15. Chiu NC, Chi H, Tu YK, Huang YN, Tai YL, Weng SL, et al. To mix or not to mix? A rapid systematic review of heterologous prime–boost covid-19 vaccination. Expert Rev Vaccines. 2021;20(10):1211–20.
16. Ho TC, Chen YMA, Chan HP, Chang CC, Chuang KP, Lee CH, et al. The effects of heterologous immunization with prime-boost covid-19 vaccination against sars-cov-2. Vaccines (Basel). 2021;9(10):1–14.
17. Clemens SAC, Weckx L, Clemens R, Mendes AVA, Souza AR, Silveira MB V, et al. Heterologous versus homologous COVID-19 booster vaccination in

previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. Lancet. 2022;(January):19–21.
18. Mok CKP, Chen C, Yiu K, Chan TO, Lai KC, Ling KC, et al. A Randomized Clinical Trial Using CoronaVac or BNT162b2 Vaccine as a Third Dose in Adults Vaccinated with Two Doses of CoronaVac. Am J Respir Crit Care Med. 2022;205(7):844–7.
19. Çağlayan D, Süner AF, Şiyve N, Güzel I, Irmak Ç, Işik E, et al. An analysis of antibody response following the second dose of CoronaVac and humoral response after booster dose with BNT162b2 or CoronaVac among healthcare workers in Turkey. J Med Virol. 2022;94(5):2212–21.
20. Khong KW, Liu D, Leung KY, Lu L, Lam HY, Chen L, et al. Antibody Response of Combination of BNT162b2 and CoronaVac Platforms of COVID-19 Vaccines against Omicron Variant. Vaccines (Basel). 2022;10(2):1–10.
21. Nantanee R, Aikphaibul P, Jaru-Ampornpan P, Sodsai P, Himananto O, Theerawit T, et al. Immunogenicity and reactogenicity after booster dose with AZD1222 via intradermal route among adult who had received CoronaVac. Vaccine. 2022;40(24):3320–9.
22. Zuo F, Abolhassani H, Du L, Piralla A, Bertoglio F, de Campos-Mata L, et al. Heterologous immunization with inactivated vaccine followed by mRNA-booster elicits strong immunity against SARS-CoV-2 Omicron variant. Nat Commun. 2022;13(1):1–8.
23. Jara A, Undurraga EA, Zubizarreta JR, Gonzalez C, Pizarro A, Acevedo J, et al. Effectiveness of Homologous and Heterologous Booster Shots for an Inactivated SARS-CoV-2 Vaccine: A Large-Scale Observational Study. SSRN Electronic Journal. 2022;(February).
24. Li J, Hou L, Guo X, Jin P, Wu S, Zhu J, et al. Heterologous AD5-nCOV plus CoronaVac versus homologous CoronaVac vaccination: a randomized phase 4 trial. Nat Med. 2022;28(2):401–9.
25. Yorsaeng R, Suntronwong N, Phowatthanasathian H, Assawakosri S. Immunogenicity of a third dose viral-vectored COVID-19 vaccine after receiving two-dose inactivated vaccines in healthy adults. Vaccine. 2022;40(January):524–30.
26. Kuloğlu ZE, El R, Guney-Esken G, Tok Y, Talay ZG, Barlas T, et al. Effect of BTN162b2 and CoronaVac boosters on humoral and cellular immunity of individuals previously fully vaccinated with CoronaVac against SARS-CoV-2: A longitudinal study. Allergy: European Journal of Allergy and Clinical Immunology. 2022;(April).
27. Assawakosri S, Kanokudom S, Suntronwong N, Auphimai C, Nilyanimit P, Vichaiwattana P, et al. Neutralizing Activities against the Omicron Variant after a Heterologous Booster in Healthy Adults Receiving Two Doses of CoronaVac Vaccination. J Infect Dis. 2022;
28. Pérez-Then E, Lucas C, Monteiro VS, Miric M, Brache V, Cochon L, et al. Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination. Nat Med. 2022;28(3):481–5.
29. Kanokudom S, Assawakosri S, Suntronwong N, Auphimai C, Nilyanimit P, Vichaiwattana P, et al. Safety and Immunogenicity of the Third Booster Dose with Inactivated, Viral Vector, and mRNA COVID-19 Vaccines

in Fully Immunized Healthy Adults with Inactivated Vaccine. Vaccines (Basel). 2022;10(1):1–13.
30. Sinto R, Utomo D, Suwarti, Nelwan EJ, Surendra H, Natasha C, et al. Serum anti-Spike antibody titers before and after heterologous booster with mRNA-1273 SARS-CoV-2 vaccine following two doses of inactivated whole-virus CoronaVac vaccine. medRxiv. 2021;(02 1):2021.12.24.21268360.
31. Angkasekwinai N, Sewatanon J, Niyomnaitham S, Phumiamorn S, Sukapirom K, Sapsutthipas S, et al. Comparison of safety and immunogenicity of CoronaVac and ChAdOx1 against the SARS-CoV-2 circulating variants of concern (Alpha, Delta, Beta) in Thai healthcare workers. Vaccines (Basel). 2022;10:100153.
32. Li J, Hou L, Guo X, Jin P, Wu S, Zhu J, et al. Heterologous prime-boost immunization with CoronaVac and Convidecia Jingxin. Beijing, China; 2021.
33. Yorsaeng R, Suntronwong N, Phowatthanasathian H, Assawakosri S, Kanokudom S, Thongmee T, et al. Immunogenicity of a third dose viral-vectored COVID-19 vaccine after receiving two-dose inactivated vaccines in healthy adults. Vaccine. 2022;40(3):524–30.
34. Costa Clemens SA, Weckx L, Clemens R, Almeida Mendes AV, Ramos Souza A, Silveira MB V, et al. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. The Lancet. 2022;399:521–9.
35. Khong KW, Liu D, Leung KY, Lu L, Lam HY, Chen L, et al. Antibody Response of Combination of BNT162b2 and CoronaVac Platforms of COVID-19 Vaccines against Omicron Variant. Vaccines (Basel). 2022;10(2):1–10.
36. Nantanee R, Aikphaibul P, Jaru-Ampornpan P, Sodsai P, Himananto O, Theerawit T, et al. Immunogenicity and reactogenicity after booster dose with AZD1222 via intradermal route among adult who had received CoronaVac. Bangkok; 2021.
37. Kanokudom S, Assawakosri S, Suntronwong N, Auphimai C, Nilyanimit P, Vichaiwattana P, et al. Safety and Immunogenicity of the Third Booster Dose with Inactivated, Viral Vector, and mRNA COVID-19 Vaccines in Fully Immunized Healthy Adults with Inactivated Vaccine. Vaccines (Basel). 2022;10(1):1–13.
38. Campos GRF, Almeida NBF, Filgueiras PS, Corsini CA, Gomes SVC, de Miranda DAP, et al. Booster dose of BNT162b2 after two doses of CoronaVac improves neutralization of SARS-CoV-2 Omicron variant. Communications Medicine. 2022 Jun 29;2(1).