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REVIEW ARTICLE

Binding and neutralizing antibody levels and vaccine efficacy/effectiveness compared between heterologous and homologous primary series COVID-19 vaccination: A systematic review and meta-analysis

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Abstract

Background: The data on the immunogenicity and efficacy of heterologous primary series COVID-19 vaccination are still limited.

Objective: To investigate the immunogenicity and vaccine efficacy/effectiveness compared between heterologous and homologous primary series COVID-19 vaccination.

Methods: We conducted a multi-source search for randomized controlled trials, prospective cohort, and case-control studies that investigated the immunogenicity or vaccine efficacy/effectiveness (VE) of heterologous primary series vaccination. Six online databases were searched from inception to June 2022. The primary outcome was the levels of binding antibodies and neutralizing antibodies (NAbs), and the secondary outcomes were VE against COVID-19 infection, hospitalization, and death.

Results: Among the 28 included studies, 21 and 7 were included to investigate immunogenicity and VE outcome, respectively. Heterologous CoronaVac (CV)/ChAdOx1 (ChAd) induced higher anti-RBD IgG and NAbs against wild type and delta variants compared to homologous CV or ChAd. However, risk of documented infection of CV/ChAd was similar to homologous CV, but higher than homologous ChAd (odds ratio: 2.56, 95% CI: 1.02-6.37). Heterologous ChAd/BNT162b2 (BNT) elicited a higher anti-spike level than homologous ChAd or BNT, and induced a higher NAbs level against delta variants compared to homologous ChAd. The VE of ChAd/BNT and homologous ChAd or BNT against hospitalization were similar.

Conclusions: Heterologous CV/ChAd induced higher binding and neutralizing antibody levels than homologous CV or ChAd; and, ChAd/BNT induced higher binding and neutralizing antibody levels than homologous ChAd. However, CV/ChAd demonstrated increased risk of infection compared to homologous ChAd. Therefore, immunogenicity findings and real-world vaccine efficacy/effectiveness should be integrated in clinical practice.

Key words: Binding antibody, neutralizing antibody, vaccine efficacy/effectiveness, heterologous primary series, homologous primary series, COVID-19 vaccination, systematic review and meta-analysis

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic remains an ongoing global health threat with more than 617 million confirmed cases, and over 6.3 million deaths as of 3 October 2022.[1] Currently, eleven COVID-19 vaccines using four different platforms have been approved under the emergency use listing (EUL) by the World Health Organization (WHO), including messenger RNA (mRNA) either BNT162b2 (Pfizer) or mRNA-1273 (Moderna); viral vector (adenovirus), such as ChAdOx1 (AstraZeneca) or Ad26.COV2.S (Johnson & Johnson); inactivated virus, such as CoronaVac; and, protein subunit vaccine, such as Novavax.[2] Most COVID-19 vaccines require two doses of the same type of vaccine (homologous primary series) administered 3-12 weeks apart to induce adequate and persistent immunity.[3]

Heterologous primary series vaccination using a different prime-boost platform has been considered for several reasons, including the unpredictability of the vaccine supply, the fear of rare thrombotic events from ChAdOx1 vaccine,[4] and because this vaccination strategy tends to elicit a stronger and broader immune response. Messenger RNA (mRNA)-based vaccines induce a high level of neutralizing antibody, but Th1 and Th2 cell response depends on the SARS-CoV-2 mRNA design or the formulation of lipid nanoparticles.[5] The adenovirus-vectored vaccine influences a strong T cell response,[6] but mounting antibody response is affected by preexisting anti-vector antibody. Inactivated vaccines generally do not provide protection as strong as that conferred by live vaccines, but they can be beneficial in a multiple antigen-based vaccine context for single protein mutation.[7] The sequence of the priming and booster vaccine plays an important role in optimizing effective immunity. A decrease in the level of neutralization antibody over time increases the risk of and concerns about epidemic recurrence, especially relative to virus variants.[8]

Although the WHO supports heterologous vaccination with any EUL COVID-19 vaccine[9] to achieve high vaccination coverage in a timely manner, data specific to the immunogenicity and efficacy/effectiveness of specific vaccine combinations involving inactivated vaccine or those against circulating variants of concern remain limited. Accordingly, the aim of this systematic review and meta-analysis was to investigate the binding and neutralizing antibody levels and vaccine efficacy/effectiveness specific to infection, hospitalization, and death compared between heterologous and homologous primary series COVID-19 vaccination.

Methods

Protocol and registration

The protocol for this systematic review and meta-analysis was registered in PROSPERO, which is an international database for prospectively registered systematic reviews (reg. no. CRD42022350503).[10] This study also followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11] Ethical approval was not required due to the systematic review and meta-analysis design of our study.

Information sources and search strategy

The search was performed in electronic medical databases, including Medline (PubMed), Medline (Ovid), Embase (Ovid), and the Cochrane Central Register of Controlled Trials (Ovid), to identify publications from the database inception date to 29 June 2022. We also searched the preprint databases bioRxiv and medRxiv to identify newly published manuscripts since literature related to COVID-19 is rapidly and very currently produced. We framed the search according to population, intervention, comparison, and outcome of interest to identify relevant keywords to develop search terms that were then tailored to specifications of each accessed database. We also reviewed the reference lists from previous systematic reviews and all eligible studies to ensure that no related study would be overlooked.

Study selection

Search results from each database were imported into EndNote 20 to identify and remove duplicates. Title/abstract and full text were screened by four reviewers. Two authors were paired with two non-author reviewers (please see the acknowledgments subsection), and both paired teams (SK and JP; TB and WS) conducted independent reviews. Disagreements within and between review teams were resolved by consensus. If a consensus could not be reached, a third author (PL) helped with problem resolution.

The prespecified inclusion criteria during screening were, as follows: studies that included participants who received heterologous primary series COVID-19 vaccines and studies that assessed immunogenicity or COVID-19 vaccine efficacy/effectiveness (i.e., COVID-19-related infections either documented, asymptomatic, symptomatic, or severe infections, COVID-19-related hospitalization, and COVID-19-related death). Eligible studies included English language randomized controlled trials (RCTs), case-control studies, or prospective cohort studies (with intervention and comparator).

The exclusion criteria were, as follows: studies of population aged under 18 years; only unvaccinated COVID-19 vaccine population was used as the comparator; non-COVID-19 vaccine or placebo was used as the comparator; no comparator; non-human studies; other types of studies, such as reviews, systematic reviews, meta-analyses,

case reports, case series, protocol, commentaries, or editorials; and, studies that did not report sufficient information about the method or unit of immunogenicity measurement.

Data collection process

Four reviewers working in pairs (SK and JP; NJ and CP) appraised the selected studies independently and extracted the following data using Microsoft Excel 365 (Microsoft Corporation, Redmond, WA, USA): study characteristics (name of the first author, year of publication, type of article, study design, and setting), participant characteristics in the intervention and comparator groups (number of eligible participants, age, comorbidities), interventions and comparators (type of vaccine, number of doses, interval between dose, variant of COVID-19), and outcomes, including immunogenicity profile (level of binding and neutralizing antibody, type and method of antibody measured and unit of measurement at different time points), and vaccine efficacy or effectiveness (VE) (number of cases). Data presented only in graphical format were excluded due to the difficulty associated with estimating immunogenicity results from a scatter plot.

Endpoints

The primary outcomes were the levels of binding and neutralizing antibodies for various combinations of heterologous compared to homologous primary series vaccination. For binding antibody, we extracted the geometric mean concentration/titers (GMC/GMT) and standard deviation (SD). Data from studies that reported the antibody level as median and range or interquartile range (IQR) were converted to mean and standard deviation (SD) using the method proposed by Hozo, et al., 2005.[12] The unit used for anti-RBD was binding antibody units (BAU)/mL. Data reported as arbitrary units (AU)/mL were converted to BAU/mL by multiplying the reported data by 0.142.[13] The unit used for anti-spike antibody was international units (IU)/mL or enzyme-linked immunosorbent assay units (ELU)/mL based on data availability. Studies using the same units of measurement were combined. The time of measurement included 2-4 weeks and 10-12 weeks after the second dose of vaccine. We used the same measurement units and strategies for the measurement of neutralizing antibodies (NAbs). Geometric mean ratio (GMR) was excluded from quantitative analysis. The time of measurement of NAbs was 2-4 weeks and 16-20 weeks after the second dose of vaccine.

The secondary outcomes were vaccine efficacy or effectiveness against COVID-19 infection (documented, asymptomatic, symptomatic, and severe disease), COVID-19-related hospitalization, and mortality. We extracted the number of cases between the intervention (heterologous primary series) and comparator (homologous primary series) groups, and %VE, risk ratio, rate ratio, or odds ratio were converted to number of cases based on the formulae used in the included studies. We then used this information to estimate the odds ratio for the intervention to comparator comparison.

Summary measures

The included studies assessed the immunogenicity outcome using different methods and metrics. In the present study, we focused on the studies that reported anti-receptor binding domain (anti-RBD) IgG or anti-spike IgG and neutralizing antibody measured by plaque reduction neutralization assay (PRNT), pseudotyped virus neutralization test (pVNT), surrogate virus neutralization test (sVNT), or focus reduction neutralization test (FRNT) against wild type and variants of concern (VOC).

Risk of bias and quality assessment

Five reviewers (SK, JP, NJ, CP, and PL) independently assessed the included studies for risk of bias. Disagreements were resolved via discussion and consensus. For RCT studies, we used version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2),[14] which includes bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. The studies were graded as low risk, some concerns, or high risk of bias. Non-RCT studies were assessed for quality using the Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses,[15] which includes three components: selection, comparability, and outcome. A star scoring system was used. A maximum of 4, 2, and 3 stars could be assigned to the selection, comparability, and outcome components, respectively, for a total of 9 stars. A higher number of total stars indicates a higher quality study, and vice versa.

Data synthesis and statistical approach

For quantitative analysis, Microsoft Excel 365 was used for cleaning and preparing data. The meta-analysis was conducted using Stata statistical software Release 17 (StataCorp LLC, College Station, TX, USA). The geometric mean concentrations (GMC) of anti-RBD, IgG, or anti-spike IgG, and the geometric mean titer (GMT) of neutralizing antibody (i.e., PRNT, pVNT, sVNT, or fVNT) were extracted from eligible studies, and the geometric mean difference was used to compare the difference in immunogenicity. Forest plots were generated to show the point estimates of the mean difference and 95% confidence interval (95%CI) compared between heterologous and homologous primary series vaccinations.

The magnitude of between-study heterogeneity was evaluated using the I^2 statistical parameter (range from 0-100%). A fixed-effect model using the inverse-variance approach was employed when the I^2 statistic was less than 75%. When the I^2 statistic was 75% or greater, a random effects model using the restricted maximum-likelihood (REML) approach was used.[16] Our evaluation of the included clinical evidence revealed variation in immunogenicity response due to differences in study populations, so special populations, such as those having received solid organ transplantation, were not included in the pooled estimate.

Due to the inappropriateness of pooling VE across different VOCs, eligible studies that reported VE against COVID-19 infection were classified by clinical outcomes and assessed descriptively. The effect of heterologous versus homologous primary series was calculated using the formula 1-odds ratio (OR). When comparing with a homologous regimen, the odd ratios of heterologous regimens smaller than 1 indicated reduced risk, and greater than 1 indicated increased risk of the outcome of interest.

Results

Study characteristics

Among the 21,339 identified studies, 7,973 duplicates were removed, which left 13,366 studies for screening. We excluded 13,123 studies by title and abstract screening, which left 237 studies for full-text review (**Figure 1**). Of those, 43 studies fulfilled the inclusion and exclusion criteria.[17-59] Of those 43 studies, 32 were peer-reviewed publications and 11 were preprint studies. The total sample size was 1,038,028 participants from 13 countries. Five studies were RCTs, and 38 studies were observational studies (37 prospective cohort, and one test negative case-control study). The median age of the study population was 42.5 years and 32% were male. Of the 43 included studies, 26 were conducted in general population (23 studies in patients aged > 18 years, and 3 studies in patients aged 50 years or older), 14 studies collected data from healthcare workers, and 3 studies investigated vaccine immunogenicity among patients (2 studies in hemodialysis patients, and one study in organ transplantation patients). Of the 43 studies, 15 were excluded for the following reasons: no timepoint of interest (n = 2), no vaccine pairwise of interest (n = 5), use of different units of measurement (n = 3), insufficient data for analysis (n = 2), insufficient studies for analysis (n = 2), and organ transplantation patients (n = 1). Among the 28 studies included for quantitative analysis,[17,20,22-27,29-30,35-37,39-41,43-51,55-57] 21 studies (17 non-RCTs and 4 RCTs) were included to analyze the immunogenicity outcome, and 7 non-RCT studies were included to analyze the effect of heterologous prime-boost regimens against documented infection

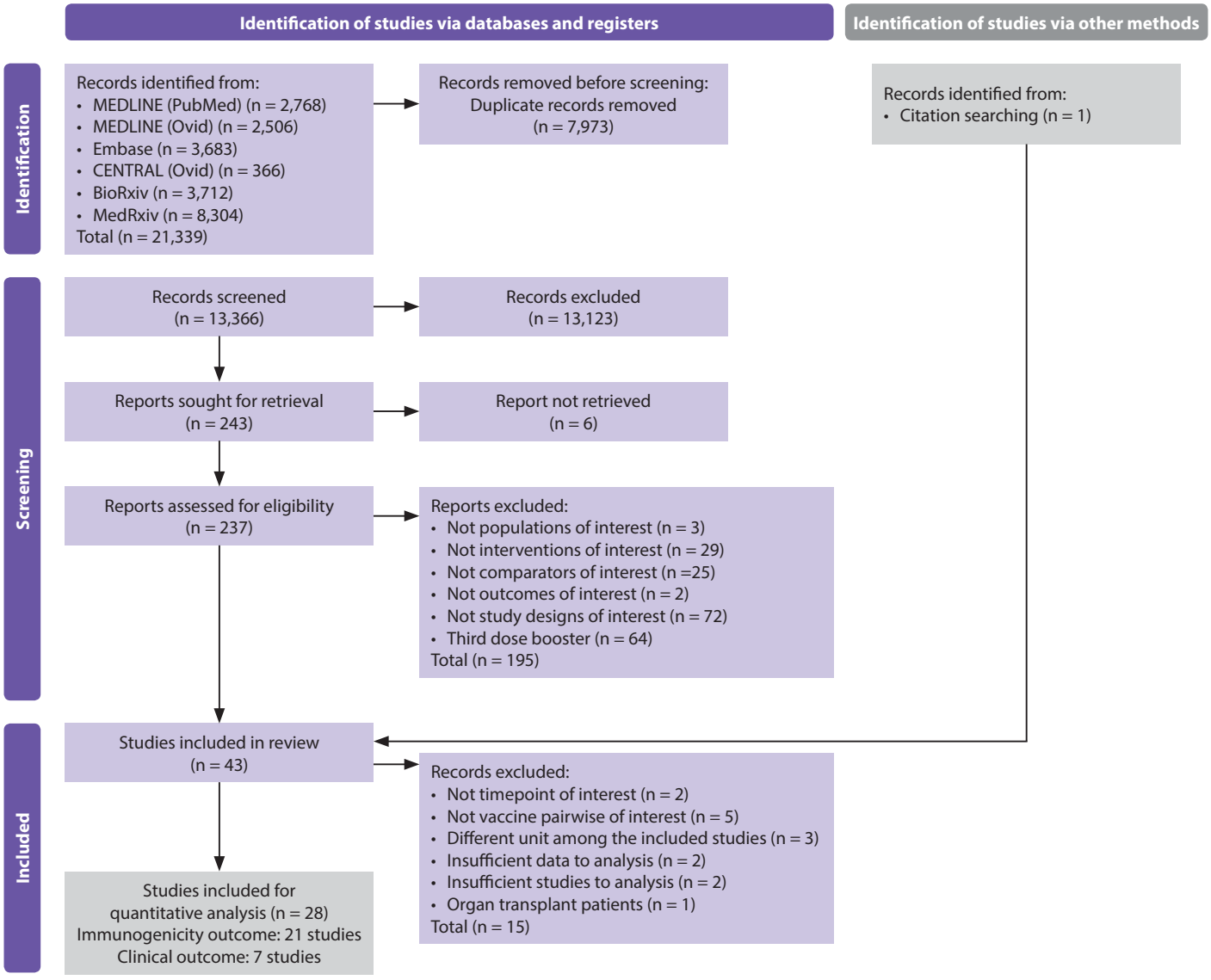


Figure 1. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the study search, screening, and inclusion protocol.

(6 studies), against symptomatic infection (2 studies), against hospitalization (2 studies), and against asymptomatic infection (1 study).

Among the 21 studies included in the meta-analysis of the immunogenicity outcome, we identified six different heterologous prime-boost regimens. Among those studies, the median age of participants was 42 years and 39% were male. The levels of binding and neutralizing antibodies were compared between heterologous prime-boost regimens and homologous prime-boost regimens. Specifically, CoronaVac (CV)/ChAdOx1 (ChAd) or ChAd/CV versus (*vs.*) CV/CV or ChAd/ChAd; CV/BNT162b2 (BNT) or BNT/CV *vs.* CV/CV or BNT/BNT; ChAd/BNT or BNT/ChAd *vs.* ChAd/ChAd or BNT/BNT; and ChAd/mRNA-1273 (Mdn) or Mdn/ChAd *vs.* ChAd/ChAd or Mdn/Mdn. As shown in **Figures 2-4**, the median age of participants among all vaccine regimens ranged from 33 to 58 years, and the proportion of male participants ranged from 26% to 48%. Among participants who received heterologous BNT/ChAd compared to homologous ChAd or homologous BNT and who were measured for the immunogenicity outcome of anti-spike IgG (**Figure 2C, 2D**) were older (58 years) and had a higher proportion of male participants (54-57%) compared to the other studies. Similarly, among participants who received heterologous ChAd/BNT compared to homologous ChAd and who were measured for the outcome of neutralizing antibodies were older (52 years) compared to the other studies.

Binding antibody

Four studies[23,36,55,56] that measured anti-RBD IgG of heterologous CV/ChAd compared with homologous CV (median age 42 years, 44% male), and three studies[36,55,56] that measured anti-RBD IgG of heterologous CV/ChAd compared with homologous ChAd (median age 44 years, 40% male) reported a significantly higher level of anti-RBD IgG compared to homologous primary series of CV or ChAd with a geometric mean (GM) difference of 505 BAU/mL and 430 BAU/mL, respectively (**Figure 2A-B**). Two studies[23,55] found no significant difference in anti-RBD IgG between heterologous ChAd/CV and homologous CV (median age 43 years, 46% male) (**Figure 2C**). Two studies[39,57] reported no significant difference in anti-RBD IgG between heterologous CV/BNT and homologous BNT (median age 33 years, 34% male) (**Figure 2D**).

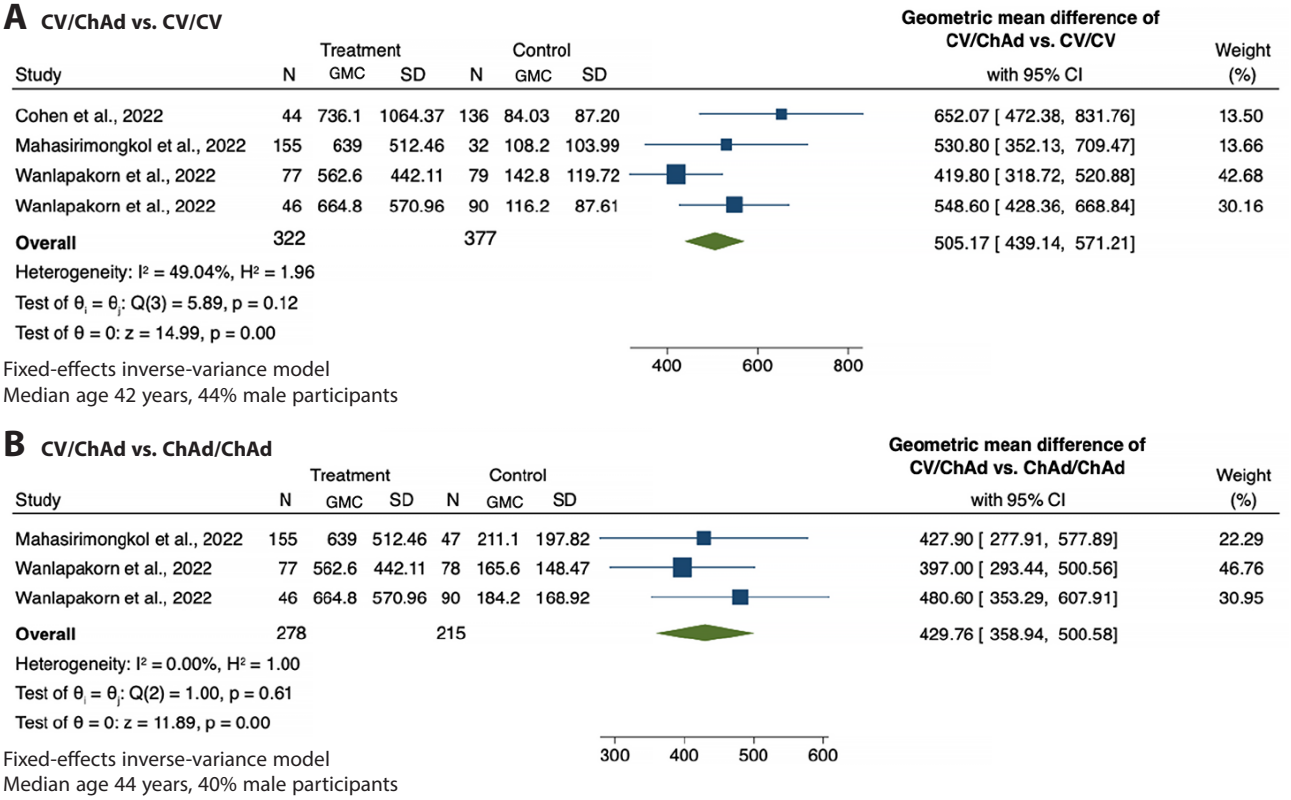


Figure 2. Forest plots of binding antibody (anti-RBD IgG) levels from 4 comparisons between heterologous primary series with CoronaVac (CV) and ChAdOx1(ChAd) or BNT (BNT162b2) and different homologous primary series regimens (A-D).

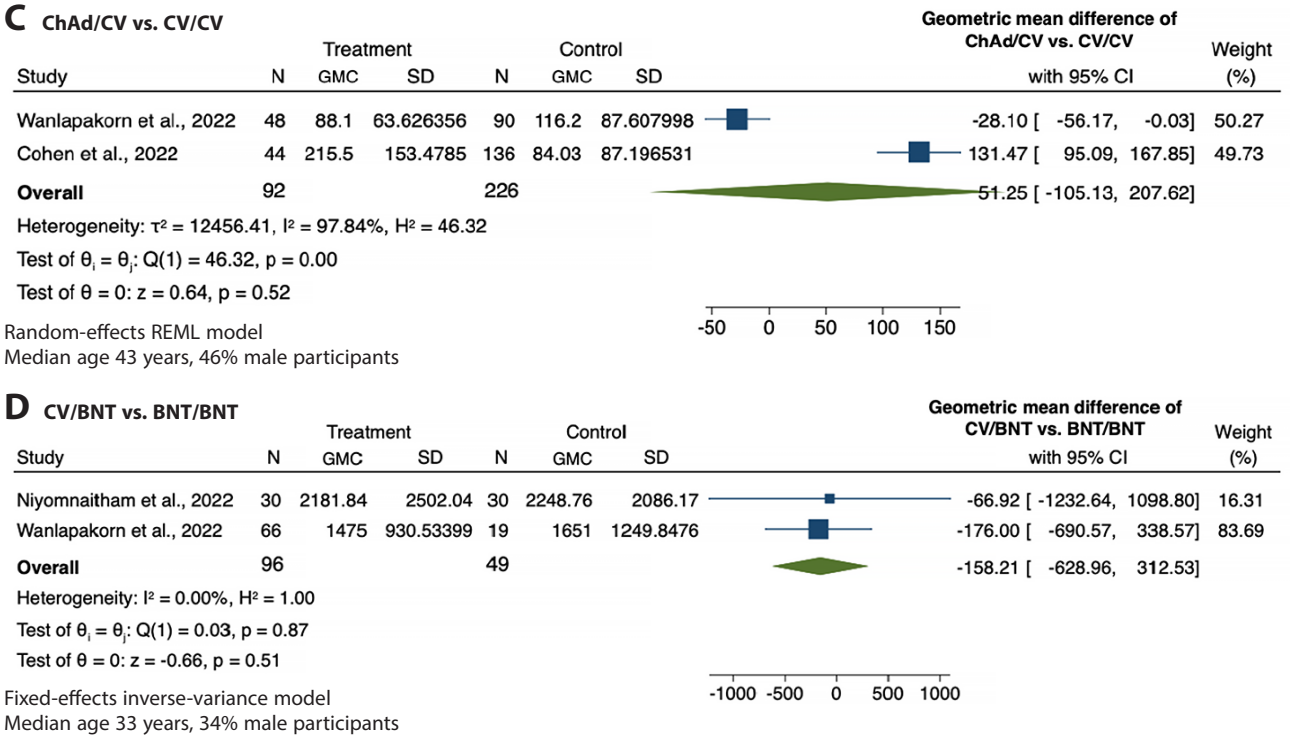


Figure 2. (Continued)

Three and five studies reported a difference in anti-RBD IgG between heterologous ChAd/BNT and homologous ChAd (median age 37 years, 26% male)[17,24,26] or homologous BNT (median age 37 years, 33% male), respectively.[17,24-26,39] The results showed that anti-RBD IgG induced by heterologous ChAd/BNT tended to be higher than that induced by homologous ChAd (**Figure 3A**) or homologous BNT (**Figure 3B**) with a geometric mean difference of 3,973 BAU/mL and 2,175 BAU/mL, respectively. Two studies reported a difference in anti-spike IgG between heterologous BNT/ChAd and homologous ChAd (median age 58 years, 57% male)[35,47] or homologous BNT (median age 58 years, 54% male).[35,47] The results showed that anti-spike IgG induced by heterologous BNT/ChAd was significantly higher than that induced by homologous ChAd (**Figure 3C**), but lower than that induced by homologous BNT (**Figure 3D**).

The studies that measured anti-spike IgG showed slightly different results. The ChAd/BNT regimen induced significantly higher anti-spike IgG than homologous ChAd, and lower anti-spike IgG than homologous BNT, but that difference was not statistically significant. A similar trend was observed when priming with ChAd and boosting with Mdn. At 10-12 weeks after the second dose, there was no significant difference in anti-RBD IgG level between the ChAd/BNT and ChAd/ChAd or BNT/BNT regimens.

Neutralizing antibodies (NAbs) against wild type and VOCs

Two studies that evaluated the NAbs of CV/ChAd via sVNT found a significantly higher NAb level against wild type, alpha, and delta variants[55,56] compared to homologous CV (median age 42 years, 44% male). When compared with homologous ChAd (median age 44 years, 40% male), a similar observation was found for wild type and delta variant[55,56] (**Figure 4A**). Using pVNT, ChAd/BNT induced a similar NAb level against wild type, but a significantly higher NAb level against delta variants[22,30] compared to homologous ChAd regimen (median age 52 years, 48% male) (**Figure 4B**).

Comparison of vaccine efficacy/effectiveness (VE)

Six non-RCT studies[27,40,43-45,49] evaluated VE against documented infection for different combinations of heterologous primary series (**Table 1**). Compared to unvaccinated individuals, the CV/ChAd, CV/CV, and ChAd/ChAd regimens had VE of 77%, 80%, and 91%, respectively, against delta variants. When compared with homologous regimens, CV/ChAd had a similar risk of infection as that of homologous CV, but a higher risk against documented infection compared to homologous ChAd (OR: 2.56, 95%CI: 1.02-6.37). Priming with Ad26.COV2.S (JJ) vaccine and boosting with BNT or Mdn had a higher risk than homologous BNT against mixed variant. Compared to homologous ChAd or BNT or Mdn, heterologous priming with ChAd and boosting with BNT or Mdn showed conflicting results (lower risk, no difference, or higher risk of infection).

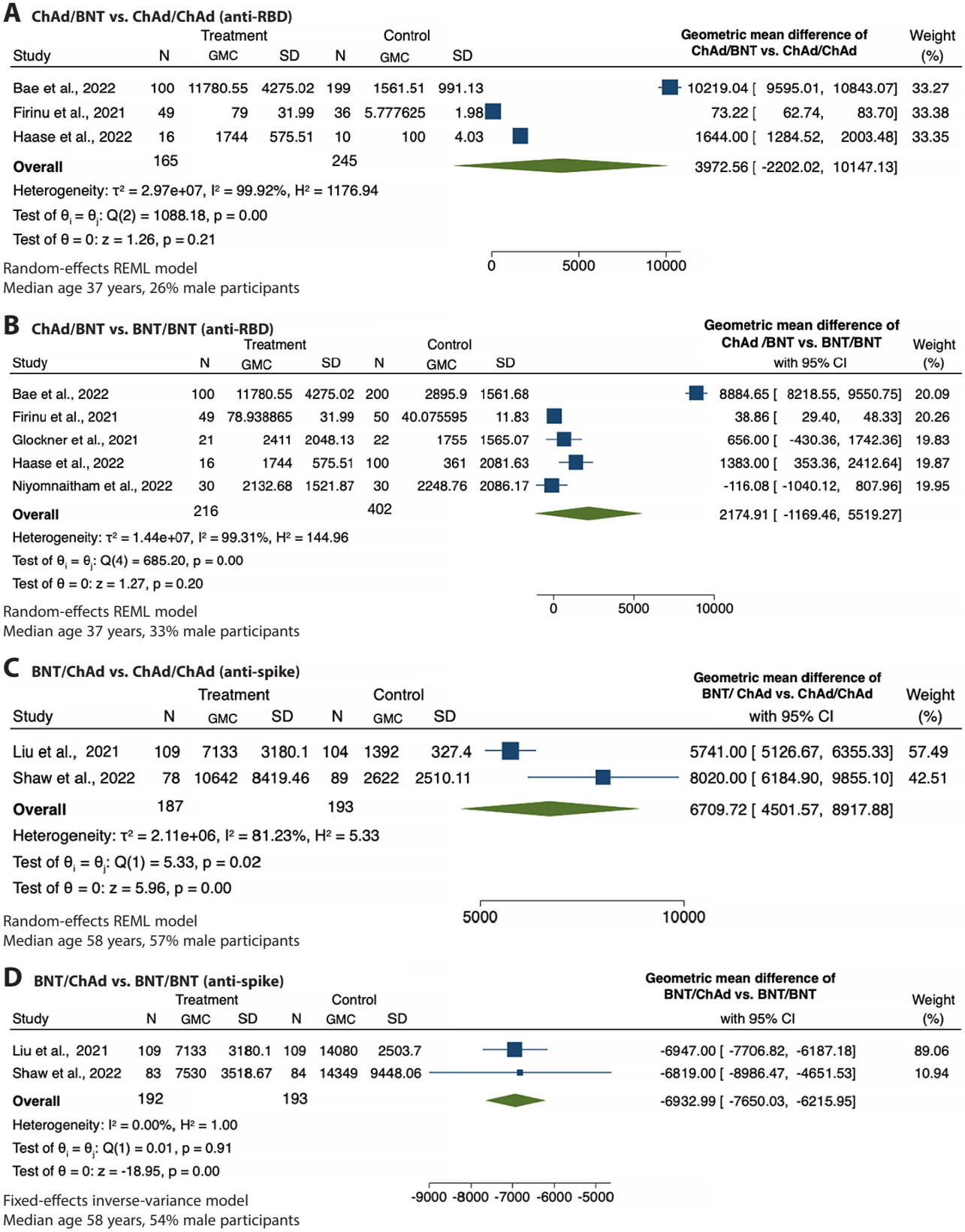
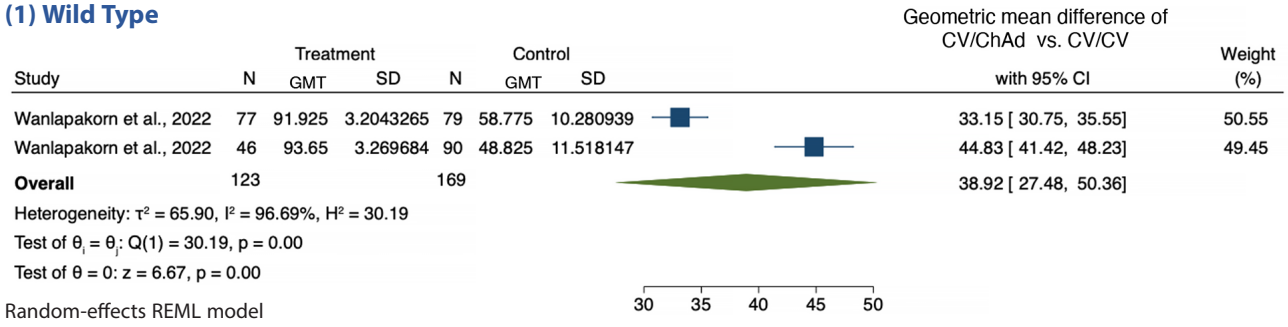


Figure 3. Forest plots of binding antibody (anti-RBD IgG and anti-spike) levels from 4 comparisons between heterologous primary series with BNT (BNT162b2) and ChAdOx1(ChAd) and different homologous primary series regimens (A-D).

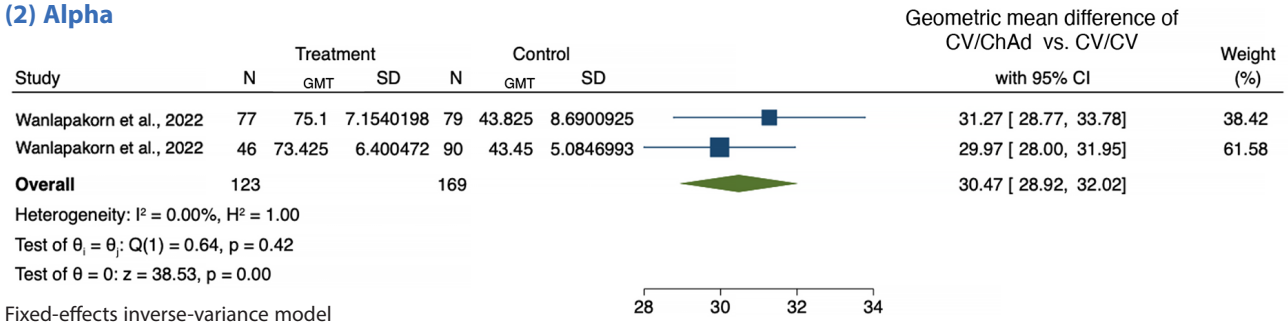
4A Surrogate NT

a. CV/ChAd vs. CV/CV

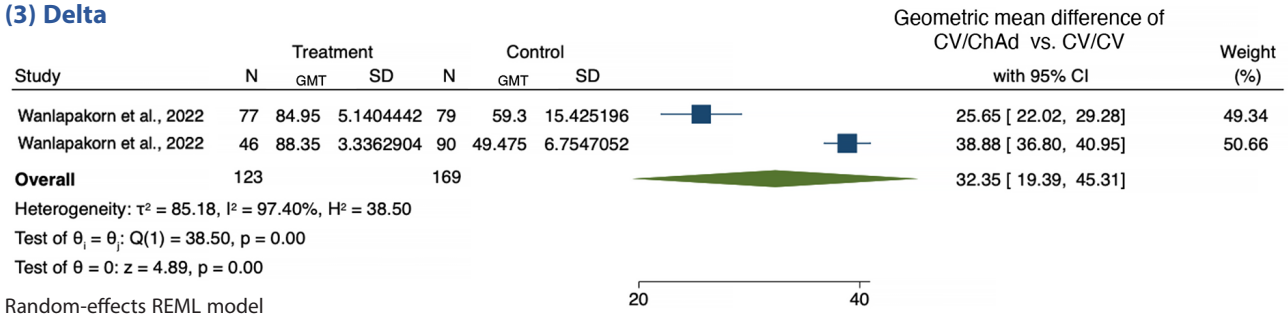
(1) Wild Type



(2) Alpha



(3) Delta



Median age 42 years, 44% male participants

b. CV/ChAd vs. ChAd/ChAd

(1) Wild Type

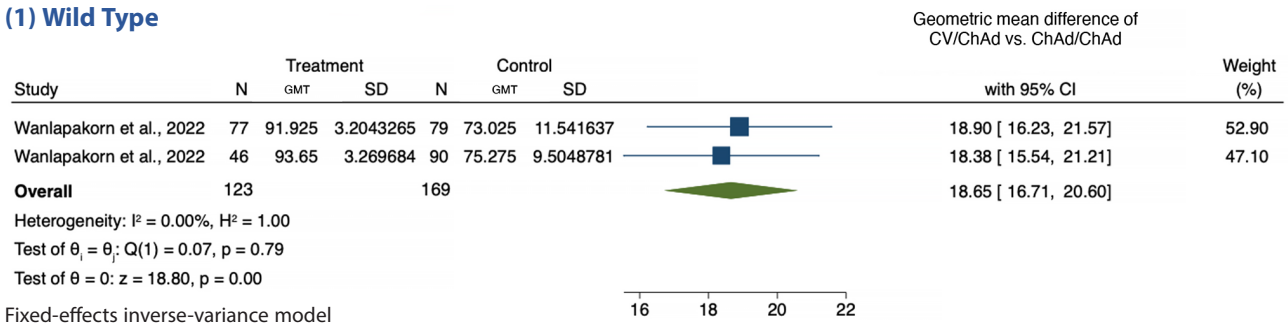
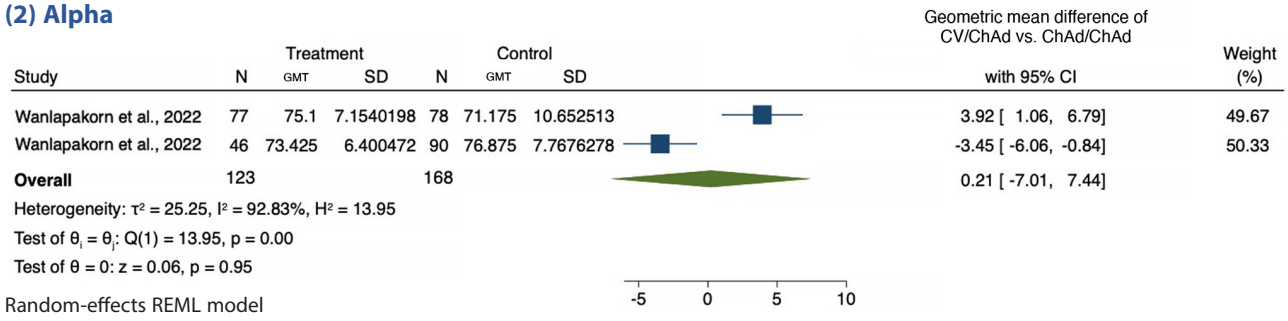
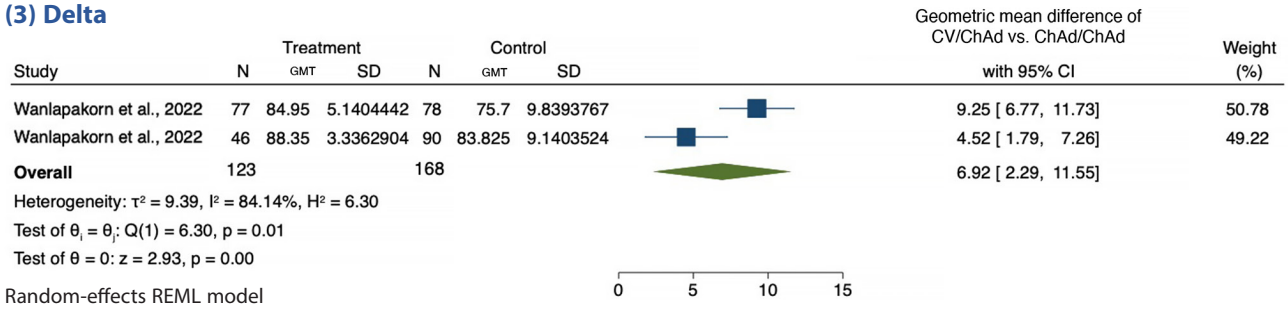


Figure 4. Forest plots of the geometric mean difference in neutralizing antibody levels (geometric mean titer, 95%CI) using surrogate neutralizing titer (NT) (4A) or pseudovirus NT (4B) at 2-4 weeks post second dose.

(2) Alpha



(3) Delta

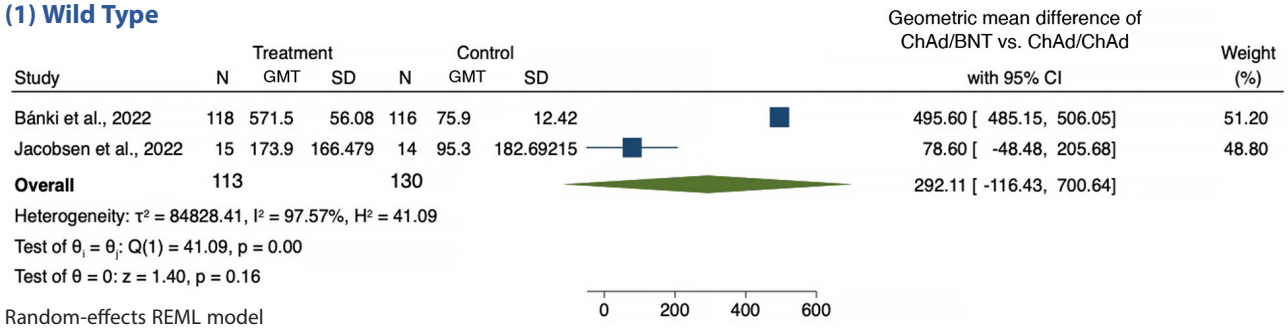


Median age 44 years, 40% male participants

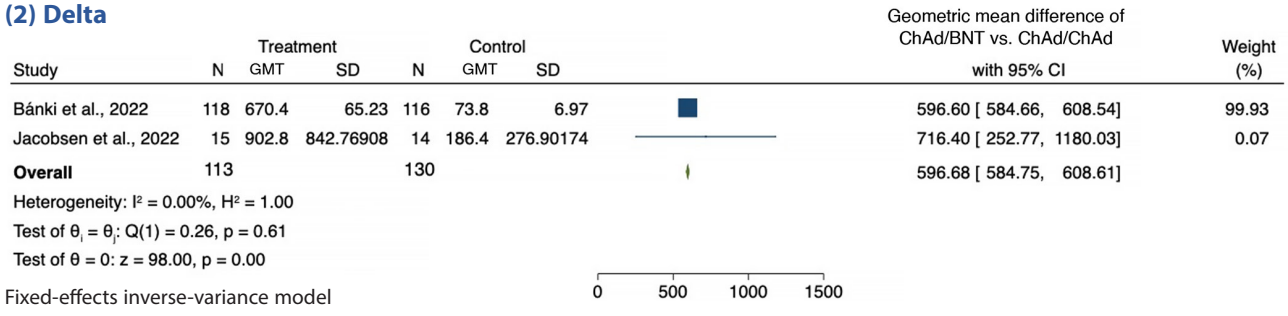
4B Pseudovirus NT

a. CV/ChAd vs. CV/CV

(1) Wild Type



(2) Delta



Median age 52 years, 48% male participants

Figure 4. (Continued)

Table 1. Effect of heterologous primary series COVID-19 vaccination from non-randomized controlled trial studies, and classified by clinical outcome.

No.	Author (year)	Country	Study design	Population group	Age group	VOCs	Vaccine regimen	Intervention arm (Number of cases/ total population)	Comparator arm (Number of cases/ total population)	Time point*	%VE [95%CI]	OR [95%CI]
1. Documented COVID-19 infections												
1	Sritipsukho (2022)[49]	Thailand	Test negative case control	General population#	≥ 18 years	Delta	CV/ChAd vs. unvaccinated	9/40	544/974	3	77% [51% to 89%]	0.23 [0.11 to 0.49]
							CV/CV vs. unvaccinated	166/821	544/974		80% [75% to 84%]	0.20 [0.16 to 0.25]
							ChAd/ChAd vs. unvaccinated	15/147	544/974		91% [84% to 95%]	0.09 [0.05 to 0.16]
							CV/ChAd vs. CV/CV	9/40	166/821		--	1.15 [0.54 to 2.45]
							CV/ChAd vs. ChAd/ChAd	9/40	15/147		--	2.56 [1.02 to 6.37]
2	Hermosilla (2022)^[27]	Spain	Prospective cohort	General population	> 18 years	NA	ChAd/BNT vs. ChAd/ChAd	464/14,325	694/14,325	NA	--	0.66 [0.58 to 0.74]
3	Norddahl (2022)^[40]	Iceland	Prospective cohort	General population	> 18 years	Mixed	J&J/BNT vs. BNT/BNT	696/16,633	1,589/42,900	NA	--	1.14 [1.04 to 1.24]
							J&J/Mdn vs. BNT/BNT	1,272/17,714	1,589/42,900		--	2.01 [1.86 to 2.17]
4	Poukka (2022)[43]	Finland	Prospective cohort	HCW	> 16 years	Mixed	ChAd/Mdn or BNT vs. unvaccinated	38/30,548	3,874/43,449	2	98.70% [98.20% to 99.10%]	0.013 [0.009 to 0.018]
							Mdn or BNT/Mdn or BNT vs. unvaccinated	162/315,413	3,874/43,449		99.50% [99.40% to 99.60%]	0.005 [0.004 to 0.006]
							ChAd/ChAd vs. unvaccinated	5/14,760	3,874/43,449		99.70% [99.20% to 99.90%]	0.003 [0.001 to 0.008]
							ChAd/Mdn or BNT vs. ChAd/ChAd	38/30,548	5/14,760		--	3.68 [1.45 to 9.34]
							Mdn or BNT/Mdn or BNT vs. ChAd/ChAd	162/315,413	5/14,760		--	1.52 [0.62 to 3.69]
5	Pozzetto (2021)^[44]	France	Prospective cohort	General population	> 18 years	Wild Type	ChAd/BNT vs. BNT/BNT	10/2,512	81/10,609	2	--	0.52 [0.27 to 1.003]
6	Saade (2022)^[45]	France	Prospective cohort	HCW	> 18 years	Mixed	BNT/Mdn vs. ChAd/ChAd	1/44	0/50	28	--	3.48 [0.14 to 87.71]
							ChAd/Mdn or BNT or ChAd vs. ChAd/ChAd	45/2,219	0/50		--	2.11 [0.13 to 34.79]
							BNT/Mdn vs. Mdn/Mdn	1/44	42/1,931		--	1.05 [0.14 to 7.78]
							ChAd/Mdn or BNT or ChAd vs. Mdn/Mdn	45/2,219	42/1,931		--	0.93 [0.61 to 1.42]
							BNT/Mdn vs. BNT/BNT	1/44	70/2,426		--	0.78 [0.11 to 5.77]
							ChAd/Mdn or BNT or ChAd vs. BNT/BNT	45/2,219	70/2,426		--	0.70 [0.48 to 1.02]

Table 1. (Continued)

No.	Author (year)	Country	Study design	Population group	Age group	VOCs	Vaccine regimen	Intervention arm (Number of cases/ total population)	Comparator arm (Number of cases/ total population)	Time point*	%VE [95%CI]	OR [95%CI]
2. Symptomatic infections												
1	Nordström (2021)[41]	Sweden	Prospective cohort	General population	> 18 years	Delta	ChAd/BNT vs. Unvaccinated	170/94,569	259/60,190	9-12	58% [49% to 66%]	0.42 [0.34 to 0.51]
							ChAd/Mdn vs. Unvaccinated	446/430,100	47/10,984		76% [58% to 86%]	0.24 [0.14 to 0.42]
							ChAd/ChAd vs. Unvaccinated	446/430,100	323/109,542		65% [59% to 70%]	0.35 [0.30 to 0.41]
							ChAd/BNT vs. ChAd/ChAd	170/94,569	446/430,100		--	1.74 [1.45 to 2.07]
							ChAd/Mdn vs. ChAd/ChAd	446/430,100	446/430,100		--	1.00 [0.62 to 1.62]
2	Sritipsukho (2022)[49]	Thailand	Test negative case control	General population#	> 18 years	Delta	CV/ChAd vs. Unvaccinated	9/40	501/974	3	73% [42% to 87%]	0.27 [0.13 to 0.58]
							CV/CV vs. Unvaccinated	155/821	501/974		78% [73% to 82%]	0.22 [0.18 to 0.27]
							ChAd/ChAd vs. Unvaccinated	15/147	501/974		89% [81% to 94%]	0.11 [0.06 to 0.19]
							CV/ChAd vs. CV/CV	9/40	155/821		--	1.25 [0.58 to 2.67]
							CV/ChAd vs. ChAd/ChAd	9/40	15/147		--	2.56 [1.02 to 6.37]

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Table 1. (Continued)

No.	Author (year)	Country	Study design	Population group	Age group	VOCs	Vaccine regimen	Intervention arm (Number of cases/ total population)	Comparator arm (Number of cases/ total population)	Time point*	%VE [95%CI]	OR [95%CI]
3. COVID-19-related hospitalization												
1	Poukka (2022)[43]	Finland	Prospective cohort	HCW	> 16 years	Mixed	ChAd/Mdn or BNT vs. unvaccinated	5/30,548	220/43,449	13	97% [92% to 99%]	0.03 [0.01 to 0.08]
							Mdn or BNT/Mdn or BNT vs. unvaccinated	5/315,413	220/43,449		99.7% [99.20% to 99.90%]	0.003 [0.001 to 0.008]
							ChAd/ChAd vs. unvaccinated	5/14,760	220/43,449		93% [84% to 97%]	0.07 [0.03 to 0.16]
							ChAd/Mdn or BNT vs. ChAd/ChAd	5/30,548	5/14,760		--	0.48 [0.14 to 1.67]
							Mdn or BNT/Mdn or BNT vs. ChAd/ChAd	5/315,413	5/14,760		--	0.05 [0.01 to 0.16]
2	Nordström (2021)[41]	Sweden	Prospective cohort	General population	> 18 years	Delta	ChAd/BNT vs. unvaccinated	1/94,569	16/180,716	9-12	88% [10% to 98%]	0.12 [0.02 to 0.90]
							ChAd/Mdn vs. unvaccinated	0/16,402	16/180,716		67% [-457% to 98%]	0.33 [0.02 to 5.57]
							ChAd/ChAd vs. unvaccinated	2/430,100	16/180,716		95% [77% to 99%]	0.05 [0.01 to 0.23]
							ChAd/BNT vs. ChAd/ChAd	1/94,569	2/430,100		--	2.27 [0.21 to 25.08]
							ChAd/Mdn vs. ChAd/ChAd	0/16,402	2/430,100		--	5.24 [0.25 to 109.25]
4. Asymptomatic infections												
1	Sritipsukho (2022)[49]	Thailand	Test negative case control	General population#	> 18 years	Delta	CV/ChAd vs. unvaccinated	0/40	36/974	3	67% [-447 to 98%]	0.33 [0.02 to 5.47]
							CV/CV vs. unvaccinated	11/821	36/974		63% [27% to 81%]	0.37 [0.19 to 0.73]
							ChAd/ChAd vs. unvaccinated	0/147	36/974		91% [-48% to 99%]	0.09 [0.01 to 1.48]
							CV/ChAd vs. CV/CV	0/40	11/821		--	0.87 [0.05 to 15.03]
							CV/ChAd vs. ChAd/ChAd	0/40	0/147		--	3.64 [0.07 to 186.40]

#30% of participants Having persons with COVID–19 at home
*Timepoint of outcome measured (weeks after the second dose)
^No unvaccinated group
Abbreviation: VOCs, Variant of concerns; OR, Odd ratio; VE, Vaccine effectiveness; 95%CI, 95% Confidence interval;

Table 2. Effect of each heterologous prime-boost regimen intervention on binding antibodies, neutralizing antibodies, and vaccine efficacy/effectiveness compared to that of comparator.

Intervention	Comparator	Binding Abs	NAbs	Vaccine effectiveness			
				Documented	Symptomatic	Hospitalization	Asymptomatic
CV/ChAd vs.	CV/CV	↑	↑	↔	↔	-	↔
	ChAd/ChAd	↑	↑	↓	↓	-	↔
ChAd/CV vs.	CV/CV	↔	-	-	-	-	-
CV/BNT vs.	BNT/BNT	↔	-	-	-	-	-
ChAd/BNT vs.	ChAd/ChAd	↔ ↑	↔ Wild ↑ Delta	Conflicting ↑ / ↔ / ↓	↑	↔	-
	BNT/BNT	↔ ↓	-	↔	-	-	-

homologous prime-boost regimen(s)
*Except alpha strain
Symbols for interpreting binding Abs:
↑ The intervention vaccine significantly increased the level of binding antibodies.
↔ No differences in binding antibody levels
↓ The intervention vaccine significantly decreased the level of binding antibodies.

Symbols for interpreting VE:
↑ The intervention vaccine significantly increased VE
↔ No differences in VE
↓ The intervention vaccine significantly decreased VE

Two non-RCT studies[41,49] that evaluated VE against symptomatic infection (**Table 1**) reported that CV/ChAd had similar risk to that of homologous CV, but higher risk against symptomatic infection by the delta variant compared to homologous ChAd (OR: 2.56, 95%CI: 1.02-6.37). Two studies[41,43] that investigated VE against hospitalization using heterologous priming with ChAd and boosting with BNT or Mdn found a similar risk to that of homologous ChAd (**Table 1**). One non-RCT study[49] that evaluated VE against asymptomatic infection found a similar risk between CV/ChAd and homologous CV or ChAd vaccine (**Table 1**).

Discussion

The global supply of COVID-19 vaccines remains limited. This systematic review and meta-analysis reports current findings specific to the immunogenicity and efficacy/effectiveness of different heterologous prime-boost regimens. These data and findings are important because they enhance and support vaccine program flexibility during vaccine supply shortages and delays. Our findings show that heterologous priming with CV and boosting with ChAd induced higher binding and neutralizing antibody level compared to homologous CV and homologous ChAd. However, switching sequence by priming with ChAd and boosting with CV did not induce a level of binding Abs as high as that induced by CV/ChAd. Priming with CV and boosting with BNT induced binding antibody similar to that of homologous BNT. ChAd/BNT induced a higher level of binding antibody and neutralizing antibody against delta variant than homologous ChAd. There is growing evidence linking humoral immune response and vaccine efficacy against symptomatic infection for both binding and neutralizing antibody.[8,60-62] Heterologous prime-boost vaccination with different antigens provides diverse antigen delivery. Since CoronaVac is derived from inactivated whole cell virus of SARS-CoV2, the host immune system will respond to several parts of the virus, including the spike protein, the envelope protein (E), the matrix protein (M), and the nucleocapsid protein (N).[63] Anti-N response from inactivated vaccine was found to be correlated with the level of anti-spike and anti-RBD antibody.[64,65] The finding that CV/ChAd enhanced a higher antibody level compared to homologous ChAd may be due to preexisting anti-vector antibody that reduced the potency of the booster dose, especially when given after a short interval (< 84 days or 12 weeks). Although a longer interval provided a better response, the probability of infection would also increase while waiting for the second dose.[66] Not surprisingly, boosting with mRNA vaccine with CV priming induced antibody as high as that induced by homologous BNT. Therefore, CoronaVac appears to be a good priming vaccine for both vector-based and mRNA vaccines. Our finding that ChAd/BNT induced a better neutralizing antibody response against VOCs is similar to that reported from a previous systematic review.[67] Consistent with the findings of 2 previously published systematic reviews, switching the sequence of the heterologous regimen with BNT/ChAd was found to be less immunogenic than homologous BNT.[67,68]

We evaluated the vaccine efficacy of heterologous vaccination compared to homologous vaccination relative to the prevention of four outcomes: COVID-19-related documented infection, symptomatic infection, asymptomatic infection, and hospitalization. Compared with unvaccinated individuals, all vaccine regimens (either heterologous or homologous primary vaccination) provided VE against documented infection ranging from 77% to 99.9%, against symptomatic infection ranging from 58% to 89%, against asymptomatic infection ranging from 63% to 91%, and against hospitalization ranging from 88% to 99.7%. When compared with homologous vaccine regimen, the risk of documented or symptomatic infection from CV/ChAd was similar to that of homologous CV, but higher than that of homologous ChAd, which is in contrast to the binding and neutralizing antibody response. It should be noted that protective

immunity is also mediated by cellular immunity, which plays an important role in protection against severe disease and infection by viral variants that escape from the recognition of NAbs.[69] However, there is limited data specific to the persistence of T cell response to heterologous CV/ChAd. Heterologous ChAd/BNT was found to influence a better antibody response, but showed an inconsistent result for risk of infection compared to the homologous ChAd or homologous BNT regimens. However, VE against hospitalization was similar among these three regimens. This is likely due to the fact that the antibody level required for protection against severe infection is much lower than that required for protection against infection.[8] It may also be a function of cellular-mediated immunity (CMI), which was not evaluated or described in this study.

Limitations

This study has some mentionable limitations. First, the combination of heterologous prime-boost regimen, and the type and unit of measurement of immunogenicity varied markedly among the included studies. Direct comparisons for some regimens were, therefore, unachievable. Second, we did not review the cellular immunity and reactogenicity of the evaluated heterologous regimens. Lastly, subgroup analysis to assess for differences in the immunogenicity outcome among age groups or between genders could not be performed due to the limited number of studies included for each vaccine regimen.

Conclusions

Heterologous CV/ChAd induced higher binding and neutralizing antibody levels than homologous CV or ChAd; and, ChAd/BNT induced higher binding and neutralizing antibody levels than homologous ChAd. However, CV/ChAd demonstrated reduced VE against infection compared to homologous ChAd. Therefore, immunogenicity findings and real-world vaccine efficacy/effectiveness should be integrated in clinical practice.

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Authors' contributions

- Study conception and design, data interpretation, and critical review of the manuscript: NA, JP, PL, SK, CP, NC, VS, KC.
- Manuscript development, critical review, and data acquisition and analysis: JP.
- Manuscript development, critical review, data acquisition and analysis, and supervision of the study: NA.
- All authors agree to be individually and collectively accountable for all aspects of this study.
- Finally, all authors have read and approved the final version of the manuscript to be submitted for journal publication.

Conflict of interest declaration

All authors hereby declare no personal or professional conflicts of interest relating to any aspect of this study.

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