Effectiveness of heterologous and homologous covid-19 vaccine regimens: living systematic review with network meta-analysis

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ABSTRACT

OBJECTIVE

To evaluate the effectiveness of heterologous and homologous covid-19 vaccine regimens with and without boosting in preventing covid-19 related infection, hospital admission, and death.

DESIGN

Living systematic review and network meta-analysis.

DATA SOURCES

World Health Organization covid-19 databases, including 38 sources of published studies and preprints.

STUDY SELECTION

Randomised controlled trials, cohort studies, and case-control studies.

METHODS

38 WHO covid-19 databases were searched on a weekly basis from 8 March 2022. Studies that assessed the effectiveness of heterologous and homologous covid-19 vaccine regimens with or without a booster were identified. Studies were eligible when they reported the number of documented, symptomatic, severe covid-19 infections, covid-19 related hospital admissions, or covid-19 related deaths among populations that were vaccinated and unvaccinated. The primary measure was vaccine effectiveness calculated as 1−odds ratio. Secondary measures were surface under the cumulative ranking curve (SUCRA) scores and the relative effects for pairwise comparisons. The risk of bias was evaluated by using the risk of bias in non-randomised studies of interventions (ROBINS-I) tool for all cohort and case-control studies. The Cochrane risk of bias tool (version 2; ROB-2) was used to assess randomised controlled trials.

RESULTS

The first round of the analysis comprised 53 studies. 24 combinations of covid-19 vaccine regimens were identified, of which a three dose mRNA regimen was found to be the most effective against asymptomatic and symptomatic covid-19 infections (vaccine effectiveness 96%, 95% credible interval 72% to 99%). Heterologous boosting using two dose adenovirus vector vaccines with one mRNA vaccine has a satisfactory vaccine effectiveness of 88% (59% to 97%). A homologous two dose mRNA regimen has a vaccine effectiveness of 99% (79% to 100%) in the prevention of severe covid-19 infections. Three dose mRNA is the most effective in reducing covid-19 related hospital admission (95%, 90% to 97%). The vaccine effectiveness against death in people who received three doses of mRNA vaccine remains uncertain owing to confounders. In the subgroup analyses, a three dose regimen is similarly effective in all age groups, even in the older population (≥65 years). A three dose mRNA regimen works comparably well in patients who are immunocompromised and those who are non-immunocompromised. Homologous and heterologous three dose regimens are effective in preventing infection by covid-19 variants (alpha, delta, and omicron).

CONCLUSION

An mRNA booster is recommended to supplement any primary vaccine course. Heterologous and homologous three dose regimens work comparably well in preventing covid-19 infections, even against different variants. The effectiveness of three dose vaccine regimens against covid-19 related death remains uncertain.

SYSTEMATIC REVIEW REGISTRATION

This review was not registered. The protocol is included in the supplementary document.

READERS' NOTE

This article is a living systematic review that will be updated to reflect emerging evidence. Updates may occur for up to two years from the date of original publication.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The efficacy and effectiveness of individual vaccine products for covid-19 and its variants of concern are well known

Research on the effectiveness of vaccine combinations, especially for particular populations such as older people and those who are immunocompromised, is lacking

WHAT THIS STUDY ADDS

This living systematic review and network meta-analysis investigated the effectiveness of different homologous and heterologous vaccine regimens with and without boosting against covid-19 infections and covid-19 related hospital admissions and deaths

An mRNA booster to any primary vaccination included in our study confers a high level of protection similar to a homologous three dose mRNA regimen; a third dose is needed to prevent infection caused by the omicron variant

Any homologous or heterologous three dose regimen induces higher immunity in people ≥65 than a two dose homologous regimen; a three dose mRNA regimen reduces the risk of asymptomatic or symptomatic covid-19 infections in the immunocompromised population

Introduction

The covid-19 pandemic caused by SARS-CoV-2 has led to more than 489 million confirmed cases and six million deaths worldwide according to the World Health Organization covid-19 weekly epidemiological update on 5 April 2022.[1] Vaccination remains an

important preventive measure against covid-19. Since the rollout of covid-19 vaccines in late 2020, global vaccine administration has accumulated up to 11 billion doses, with 13.08 million being administered daily.[2] WHO has authorised the emergency use of 10 vaccines developed by Janssen, Bharat Biotech, Pfizer-BioNTech, Oxford-AstraZeneca, Moderna, Sinopharm, Sinovac, Novavax, and Serum Institute of India.[3] Despite a rapid decline in the number of covid-19 symptomatic infections and deaths, several studies have raised concerns about waning vaccine induced immunity in vaccinated populations due to time and the emergence of covid-19 variants, which prompts the urgent need for a booster dose.[4-8] Furthermore, heterologous vaccine regimens could be an alternative strategy to homologous regimens when supplies are limited. Inconsistent covid-19 vaccine procurement and limited vaccine supply have resulted in certain vaccine types being unavailable in clinical settings.[9 10] Research that evaluates different vaccine regimens will aid decision making in public health policy and reduce vaccination hesitancy.

On 16 December 2021, WHO released interim guidance summarising the existing evidence on heterologous covid-19 vaccine schedules and gave recommendations for these schedules.[11] Although recent observational studies and systematic reviews have respectively assessed the clinical efficacy of covid-19 vaccines and provided a descriptive qualitative overview of various heterologous regimens, a quantitative comparison of different vaccine regimens against the original and new circulating variants of concern (such as omicron BA.1 and BA.2) is urgently needed.[12 13] Such a comparison is particularly important because randomised controlled trials that involve several vaccine types need to be multinational in scale and data are not readily available. Additionally, the effectiveness of a mixed combination of covid-19 vaccines remains uncertain. Quantitative systematic analyses of different vaccine regimens and a dynamic platform to monitor the effectiveness of various vaccine regimens in protecting against future variants of concern are urgently needed.

We compared the vaccine effectiveness of heterologous and homologous regimens with and without boosting in our living systematic review and network meta-analysis. Our study supplemented WHO's summary report by quantitatively evaluating different covid-19 vaccine regimens: heterologous prime boost, single dose, homologous two dose, heterologous and homologous third dose boosting, with the no-vaccine group as a reference. The advantage of a network meta-analysis compared with a conventional meta-analysis is the high comparability of direct and indirect evidence, which enables vaccine effectiveness to be compared across pairs of studies, resulting in a more comprehensive interpretation of the available evidence. With network meta-analysis, we were able to summarise the effectiveness of all available covid-19 vaccine regimens and determine the relative effects of various primary and boosting regimens as assessed in current clinical trials.

Overall, our study will serve as a monitoring platform for informing the public and health officials about the vaccine effectiveness of all WHO recommended vaccines and their homologous and heterologous regimen combinations against circulating SAR-CoV-2 (current and future variants of concern). This study is ongoing and will be updated through this living systematic review.

Methods

This living systematic review and network meta-analysis followed the preferred reporting items for a systematic review and meta-analysis of network meta-analysis (PRISMA-NMA). Supplementary table 9 presents the PRISMA-NMA checklist.

Search strategy and selection criteria

We searched 38 WHO covid-19 databases for published studies and preprint databases on a weekly basis from 8 March 2022. No language restrictions were applied to the search. Supplementary table 1 gives the full search strategy. We followed prespecified inclusion criteria during study screening (supplementary protocol 2.1): studies that assessed the efficacy or effectiveness of covid-19 vaccines in humans; studies that investigated documented, symptomatic, severe covid-19 infections, covid-19 related hospital admissions, or covid-19 related deaths; commentaries, editorials, and correspondence were included if sufficient data were provided in a supplementary file. Populations of all ages and both sexes were included in this analysis. Age was stratified into three groups: young (<18 years), adult (18-64 years), and older (≥65 years). Exclusion criteria were applied in the network meta-analysis: one arm studies were excluded; studies that did not report vaccine efficacy or effectiveness were excluded.

WYA and PPHC independently performed a study search and screened titles and abstracts of all retrieved studies in EndNote 20. Retrieved studies were further assessed for eligibility using full text screening by the same reviewers. All disagreements were resolved by consensus between WYA and PPHC. Duplicated results were removed upon reference importation in EndNote 20 by WYA. Any remaining duplicates were eliminated manually.

Data synthesis

For every eligible study identified from full text screening, WYA and PPHC independently extracted information on the study characteristics: author and year, participant eligibility, age of participants, the proportion of male participants, distribution of baseline characteristics, vaccine priority groups, ethnicity, country of study, SARS-CoV-2 variants of concern investigated, an overall sample size of the study, trial registry for randomised controlled trials, study design, research aim, intervention group (treatment 1), comparator group (treatment 2), dose interval, follow-up period, clinical outcome assessed, and outcome measures (supplementary table 2). WYA and PPHC also extracted the respective number

of events in the intervention and comparator groups and reported vaccine efficacy or effectiveness. When the number of events was not provided, the figure was derived using the reported odds ratio, risk ratio, incidence rate ratio, or hazard ratio, given that the total number of participants in each intervention and comparator group was known. For studies that recorded the number of events at two or more time points, data were extracted for the period when the vaccine was the most effective.

We estimated the overall effectiveness of each vaccine regimen (1−odds ratio). We created league tables that present relative effects in pairwise comparisons with 95% credible intervals. To rank the vaccination regimens with different combinations of vaccines, we determined the surface under the cumulative ranking curve (SUCRA) scores. To combine randomised and non-randomised evidence in the network meta-analysis, we estimated treatment effects using a three level bayesian hierarchical modelling approach with random effects (supplementary protocol 2.4.2).[14 15] We assumed that all studies shared a common heterogeneity variance. Vague priors were used for heterogeneity variance and treatment effect estimates. The number of iterations, burn-in, and adaptation used in the Markov chain Monte Carlo method is described in the protocol. JAGS was used to implement the bayesian hierarchical model.[16] BUGS codes were provided on GitHub (https://github.com/wyauac/NMA-of-heterologous-and-homologous-vaccine-effectiveness).

Network meta-analysis was performed twice, each with nodes defined in two different ways—vaccine product based and platform based—providing two perspectives on vaccine effectiveness. For the vaccine product based network, a node was made of vaccines of the same brand with the same number of doses. For the platform based network, vaccines of the same platform but different brands were grouped into the same nodes, given the number of doses was the same. Inconsistency in the networks was evaluated using the guideline developed by Daly and colleagues.[17] Finally, we performed subgroup analyses by reanalysing studies that investigated the variable of interest (age, ethnicity, immunocompromised or not, or covid-19 variant) with all other factors controlled. Sensitivity analysis was done by restricting the analysis to low risk of bias studies.

For quality assessment of non-randomised trials, the risk of bias within individual studies was evaluated using the ROBINS-I tool (risk of bias in non-randomised studies of interventions), which was recommended by Cochrane reviews.[18] The ROB-2 tool (Cochrane risk of bias version 2) was used to assess randomised controlled trials.[19] We assessed the quality of the evidence by applying the GRADE method (grading of recommendations assessment, development, and evaluation) and gave a rating to each estimate obtained in our network meta-analysis.[20] Publication bias in our analysis was assessed through a comparison adjusted funnel plot. Each data point in the funnel represented a pair of comparisons of treatments instead of a single study.[21] The plot was drawn with the function netmeta::funnel.

Patient and public involvement

Many discussions with the public, such as the media, doctors, and patients, on their queries on the need for a booster vaccine dose have inspired this review. However, there is no direct patient and public involvement because our analysis does not require their involvement. We spoke to patients with covid-19 about the study, and we asked several public members to read our article after submission.

Results

Study characteristics

Study selection followed PRISMA-NMA guidelines (fig 1). We identified 12 962 studies from 38 databases and removed 5559 duplicates, retaining 7403 studies for full text screening. We excluded 6923 studies by title, abstract, and subheading screening, of which 3007 (43.4%) were non-vaccine studies, and 1398 (20.2%) were studies of viruses other than SARS-CoV-2, 800 (11.6%) were reviews, and 502 (7.3%) investigated non-human subjects. The remaining 1216 studies (17.6%) were descriptive literature with no supplementary data. During the full text screening and data extraction, we excluded 404 studies. Twenty seven (6.7%) were protocols, seven (1.7%) were vaccine safety studies, and 370 (91.6%) only examined immunogenicity and reactogenicity in people who were vaccinated. Of the remaining 76 studies, we were able to extract data from 53,[22-74] which gave us a sample size of 100 190 476 participants from 15 countries. Supplementary table 2 presents a summary of the study characteristics. Eight studies included participants older than 65[27 31 43 47 48 55 68 69] and seven studies enrolled participants younger than 18.[45 53 57 60 61 68 73] Seven studies included high risk populations (defined as having more than one chronic condition),[27 40 41 43 47 48 69] of which two studies included patients who were immunocompromised in a subset of the high risk populations.[48 69] Of the 53 included studies, 19 investigated the protectiveness of vaccines against covid-19 variants of concern or variants of interest, including alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and omicron (B.1.1.529).[22 26 30 32 34 37-39 41 42 44 47-49 57 61 63 68 70]

Risk of bias

We evaluated the risk of bias by following instructions in ROB-2 for randomised controlled trials and ROBINS-I for non-randomised studies.[18 19] Of the 37 non-randomised studies, 16 were rated to have a moderate risk of bias, mainly because they did not control for confounders such as comorbidities and other baseline characteristics.[22 32-35 37 38 44 46 50 56 60 61 65 68 74] Nine studies from the same pool were also prone to high selection bias for having an imbalanced proportion of participants of different ages and sexes.[22 32-35 37 50 56 61] Three non-randomised studies relied on surveillance

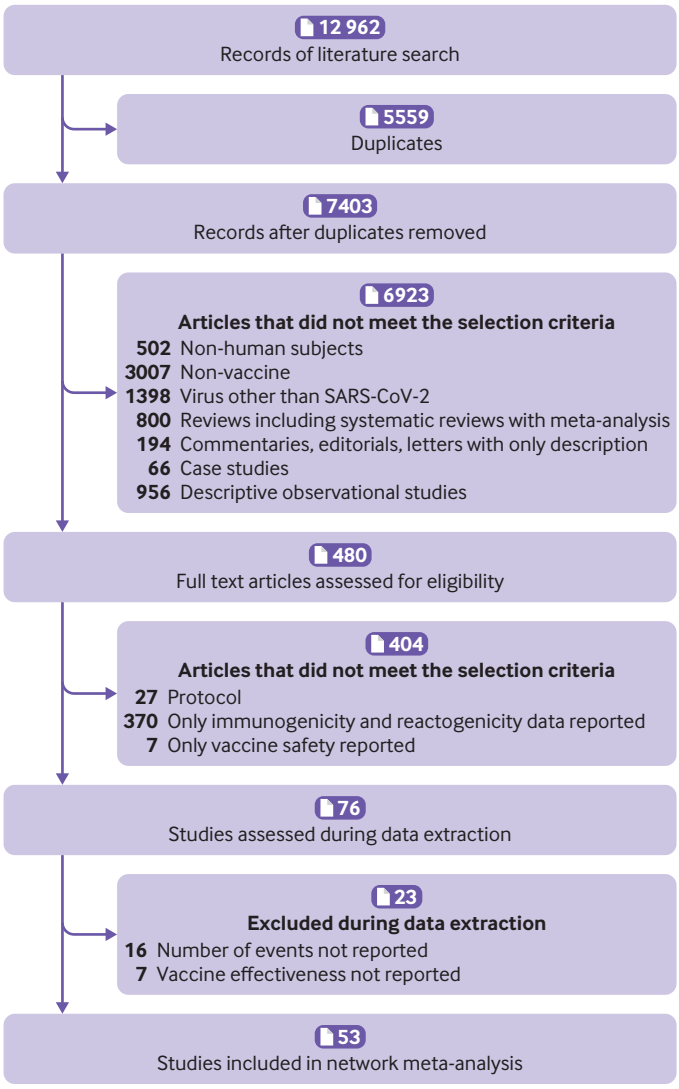

Fig 1 | Flowchart of study selection

data, which were subject to incomplete information, and so received a moderate risk of bias score in the domain of bias due to missing data.[38 46 68] Finally, one study was rated as having a severe bias in selecting the reported result because the authors reported the overall vaccine effectiveness for mRNA vaccines instead of the specific vaccine products investigated in the study.[44] All randomised controlled trials were considered low risk of bias except for three studies in which participants were unblinded after the second dose.[40 43 47] Supplementary figure 2 and supplementary table 4 show the results of ROB-2 and ROBINS-I.

Combinations of vaccine regimens in networks

There were two network analyses in this study: vaccine product based and platform based. In the vaccine product based network, we identified 24 covid-19 vaccine combinations from the 53 included studies and coded them by the number of doses used and the acronym of the vaccines (supplementary table 3). For example, 1AZ1BNT represented a heterologous prime boost regimen using ChAdOx1 (Oxford-AstraZeneca) as the first dose and BNT162b2 (Pfizer-BioNTech) as the second dose. In the platform based network, we identified 13 vaccine regimens where vaccine products of the same platform were grouped into the same node in the second network. Network diagrams for all five outcomes were drawn to depict the relation between all regimens. Most studies compared mRNA vaccines in the vaccine based and platform based networks, as indicated by the thickest lines (supplementary fig 1A-J). There was no disconnection between nodes.

Effect of vaccine regimens against documented covid-19 infections

Thirty five studies contributed to the investigation of vaccine effectiveness against documented covid-19 infections, of which 11 were randomised controlled trials. Supplementary tables 5 and 6 present the results of relative treatment effects for all pairwise comparisons of vaccine regimens. The odds ratios of all regimens analysed are smaller than 1 compared with the no-vaccine group, indicating that any vaccine regimen can confer protection against covid-19 infections, either asymptomatic or symptomatic. For three dose regimens in the vaccine product based network, two dose BNT162b2 with one mRNA-1273 (Moderna) booster is the most effective regimen (odds ratio 0.022, 95% credible interval 0 to 2.914), followed by three dose BNT162b2 (0.036, 0 to 3.033). However, the actual estimate for three dose homologous BNT162b2 is uncertain due to selection bias in one study that assessed BNT162b2 regimens.[32] A two dose CoronaVac (Sinovac) with one dose BNT162b2 regimen is also highly effective (0.046, 0.004 to 0.567). Among the two dose regimens, heterologous primary vaccination with ChAdOx1 and BNT162b2 is more effective than two dose BNT162b2 or two dose mRNA-1273, with an average odds ratio difference of 0.04 (supplementary table 5A).

In the platform based network, three dose mRNA and two dose inactivated vaccine with one dose mRNA regimens are comparably effective (0.046, 0.009 to 0.275 for homologous mRNA; 0.047, 0.003 to 0.675 for heterologous inactivated). Two dose adenovirus with one dose mRNA is slightly less effective but prevents covid-19 better than any homologous two dose regimens (0.066, 0.007 to 0.541 for heterologous adenovirus; supplementary table 6A). One dose regimens (mRNA or adenovirus vector or protein based) are less protective than two dose regimens (mRNA or adenovirus vector or inactivated or protein based). Table 1 shows the SUCRA scores.

Effect of vaccine regimens against symptomatic covid-19 infections

We were able to pool results from 23 studies that evaluated the vaccine effectiveness against symptomatic covid-19 infections, of which three studies assessed the effect of homologous boosters with BNT162b2, mRNA-1273, or ChAdOx1.[25 26 32] The odds ratios between a homologous booster dose and the no-vaccine group are 0.175 (95% credible interval

Table 1 | Ranking of vaccine regimens

Rank and SUCRA	Vaccine regimen							
	Three dose mRNA	Two dose adenovirus with one dose mRNA	Two dose mRNA	Two dose adenovirus	One dose adenovirus	One dose mRNA	Two dose inactivated	No vaccine
Rank	1	2	3	4	5	6	7	8
SUCRA	0.864	0.780	0.680	0.468	0.341	0.282	0.261	0.047

Descending order of SUCRA (surface under the cumulative ranking curve) scores for eight vaccine regimens in the prevention of any covid-19 infections, asymptomatic and symptomatic; the higher the score, the higher the vaccine effectiveness. Vaccine regimens from high risk of bias studies were not ranked. Unranked vaccine regimens are not shown.

0.021 to 1.388), 0.104 (0.016 to 0.733), and 0.147 (0.017 to 1.240) for three dose mRNA-1273, three dose BNT162b2, and three dose ChAdOx1, respectively (supplementary table 5B). Three dose mRNA-1273 and three dose ChAdOx1 are more effective than the two dose homologous regimen of mRNA-1273 and ChAdOx1 with reference to the no-vaccine group. In the platform based network, three dose mRNA is shown to be the most effective among all regimens (0.019, 0.002 to 0.136; supplementary table 6B). The one dose protein based regimen appeared to be highly effective (0.094, 0.001 to 10.134). Still, the studies that investigated this regimen were found to be confounded by unblinding and unexplained censoring of data.[40 47] Therefore, certainty in the estimate for a one dose protein based vaccine regimen is low.

Effect of vaccine regimens against severe covid-19 infections

We analysed 12 studies for vaccine effectiveness against severe covid-19 infections. With reference to the no-vaccine group, all one dose regimens are less effective than two dose and three dose regimens, of which one dose Ad26.cov2.S (Janssen) and one dose CoronaVac had no association with a reduction of severe covid-19 infections (odds ratio>1; supplementary table 5C). Three dose BNT162b2 was more effective compared with any vaccine regimens (odds ratio<1 in all comparisons; supplementary table 5C).

Effect of vaccine regimens against covid-19 related hospital admission

Seventeen studies were evaluated for vaccine effectiveness against covid-19 related hospital admissions. Individuals receiving three dose BNT162b2 or three dose mRNA-1273 are the least likely to be admitted to hospital because of covid-19 (odds ratio 0.054, 95% credible interval 0.010 to 0.294 for three dose BNT162b2; and 0.018, 0.001 to 0.291 for three dose mRNA-1273; supplementary table 5D). Results showed that heterologous primary vaccination of ChAdOx1 with BNT162b2 is not as effective as two dose homologous BNT162b2, mRNA-1273, or ChAdOx1 regimens (0.515, 0.091 to 3.291 for heterologous primary ChAdOx1 with BNT162b2; supplementary table 5D). However, the estimates for two dose BNT162b2 and mRNA-1273 could be biased by confounders in the studies that assessed them; therefore, the true estimates of odds ratios for the two dose homologous mRNA vaccine regimens might be higher. Studies that reported covid-19 hospital admissions are mainly observational, which also adds uncertainty to the estimates.

Effect of vaccine regimens against covid-19 related deaths

Eight studies were evaluated for vaccine effectiveness against covid-19 related deaths. Estimates for the prevention of deaths are highly uncertain because observational studies were the only evidence available in this analysis. None of the randomised controlled trials reported deaths. Results could be confounded by age and disease conditions, leading to highly uncertain estimates.

Subgroup analyses

Owing to high uncertainty in the estimates of vaccine effectiveness and limited data availability for severe covid-19, hospital admissions, and deaths, we only performed subgroup analyses on studies that investigated non-severe SARS-CoV-2 infections, asymptomatic and symptomatic. We were able to stratify studies by age, being immunocompromised or not, and covid-19 variants. Sex and ethnicity were not investigated because of limited data.

We found that three dose regimens conferred protection to all age groups (young, adult, and older). However, the young group appeared to have slightly better immunity than the adult group (odds ratio difference 0.02) and the older group (odds ratio difference 0.07) after receiving a three dose regimen (supplementary table 8A). On average, the vaccine effectiveness of any regimen was lowest in the older group. A two dose CoronaVac regimen was found to have no association with covid-19 infections in the older group (odds ratio 1.13, 95% credible interval 0.22 to 16.92; supplementary table 8A). Supplementary table 8B shows comparisons of vaccine effectiveness in patients who are immunocompromised. A three dose mRNA regimen worked comparably well in the non-immunocompromised and immunocompromised groups. However, the effect of two dose mRNA vaccines is weaker in those who are immunocompromised than in those who are non-immunocompromised (supplementary table 8B).

For the covid-19 variant subgroups, sufficient data were only available to analyse alpha, delta, and omicron variants. Vaccine regimens with two or more doses were found to be effective against the alpha variant. The effectiveness of three dose vaccine regimens within variants is comparable; however, effectiveness between variants differs considerably.

Table 2 | Odds ratios (95% credible intervals) and vaccine effectiveness of vaccine regimens by platform with only low risk of bias studies

Outcome and vaccine regimen	Odds ratio (95% credible interval)	Vaccine effectiveness (%)	GRADE
Documented covid-19 infections			
Three dose mRNA	0.04 (0.01 to 0.28)	96 (72 to 99)	High
Two dose adenovirus with one dose mRNA	0.12 (0.03 to 0.41)	88 (59 to 97)	High
Two dose mRNA	0.23 (0.12 to 0.42)	77 (58 to 88)	Moderate
Two dose adenovirus	0.26 (0.11 to 0.58)	74 (42 to 89)	High
One dose adenovirus	0.39 (0.18 to 0.84)	61 (16 to 82)	Moderate
One dose mRNA	0.41 (0.18 to 0.95)	59 (5 to 82)	High
Two dose inactivated	0.43 (0.09 to 2.02)	57 (−102 to 91)	High
Symptomatic covid-19 infections			
Three dose mRNA	0.02 (0.01 to 0.08)	98 (92 to 99)	High
Two dose mRNA	0.09 (0.03 to 0.28)	91 (72 to 97)	High
Two dose inactivated	0.28 (0.08 to 1.06)	72 (−6 to 92)	Moderate
One dose mRNA	0.45 (0.14 to 1.38)	55 (−38 to 86)	High
One dose inactivated	0.52 (0.07 to 3.83)	48 (−283 to 93)	Moderate
One dose adenovirus	0.57 (0.17 to 1.89)	43 (−89 to 83)	High
Severe covid-19 infections			
Two dose mRNA	0.01 (0 to 0.21)	99 (79 to 100)	High
Two dose adenovirus	0.04 (0 to 0.77)	96 (23 to 100)	High
One dose mRNA	0.04 (0 to 0.89)	96 (11 to 100)	High
two dose inactivated	0.12 (0.02 to 0.67)	88 (33 to 98)	Moderate
One dose adenovirus	0.38 (0.07 to 2)	62 (−100 to 93)	High
Covid-19 related hospital admission			
Three dose mRNA	0.05 (0.03 to 0.1)	95 (90 to 97)	Moderate
Two dose mRNA	0.19 (0.13 to 0.28)	81 (72 to 87)	Moderate
Two dose adenovirus	0.19 (0.06 to 0.62)	81 (38 to 94)	Moderate
One dose adenovirus	0.2 (0.07 to 0.58)	80 (42 to 93)	Moderate

No-vaccine group was used as a reference.
GRADE=grading of recommendations assessment, development, and evaluation.

The three dose regimens are less effective in preventing delta and omicron infections (supplementary table 8C). All one dose and two dose regimens appear to be ineffective against omicron. The estimates in the variant subgroups could be underestimated owing to a surge in confirmed infections during the outbreak of omicron; therefore, we have low certainty on the true vaccine effectiveness against this variant. We reanalysed the vaccine effectiveness in a sensitivity analysis without all high risk of bias studies. Table 2 shows the results.

Inconsistency assessment of network

We assessed inconsistency in the vaccine product based and platform based networks by comparing residual deviance between the inconsistency and consistency model. The deviance contribution plot shows some points below the line of equality (supplementary fig 3A, B). Further assessment of inconsistency was done using the node splitting model (supplementary table 7).

Publication bias

Publication bias was examined by using the comparison adjusted funnel plot. We hypothesised that published studies tend to report better results than unpublished studies. A comparison adjusted funnel plot coupled with Egger's test was used to detect a small study effect (supplementary fig 4). Although a few estimates were lying away from the centre, Egger's test P value indicated that statistical significance was not reached (P=0.08).

Discussion

Since the launch of covid-19 vaccines in 2020, research efforts have been made to investigate different combinations of covid-19 vaccines as alternatives to homologous regimens. This review has provided a comprehensive analysis of the effectiveness of WHO approved vaccines and compared all available vaccine regimens. We assessed vaccines of different brands and platforms. Comparisons by platforms are more informative and translatable into practice because vaccines from different manufacturers have been shown to have similar efficacy in phase trials.[27 40 41 45 47 55 63 71 73] Our findings will serve as a reference for clinicians, public health policy makers, and researchers for vaccine related purposes, such as making recommendations to patients and public health decision making.

Principal findings

We compared the vaccine effectiveness in preventing five outcomes: covid-19 related documented infections, symptomatic infections, severe infections, and covid-19 related hospital admissions and deaths. We have higher certainty in the evidence relating to covid-19 infections than for covid-19 related hospital admissions and deaths owing to a high risk of bias and imprecision. We have low certainty in the true estimates for vaccine effectiveness against the omicron variant because the relevant studies were conducted during the omicron outbreak. However, we are confident that a three dose regimen will effectively prevent covid-19 variants. The results have consistently shown a considerable reduction in covid-19 infections across different variants, despite the studies conducted during the peak of infections.

Three dose mRNA vaccines (three dose BNT162b2 or mRNA-1273) appear to be the most effective in preventing non-severe covid-19 infections. A heterologous regimen with an mRNA booster in recipients of two dose adenovirus vector vaccines also has 80% protection against covid-19. Among all two dose regimens, mRNA vaccines remain the gold standard for prevention against all covid-19 related outcomes, although we have moderate certainty in the actual effectiveness against hospital admission caused by covid-19. Our results imply that mRNA vaccines will continue to be the preferred vaccine type, either as primary vaccines or booster doses. When comparing vaccine effectiveness between age groups, we found people younger than 18 have a lower chance of covid-19 infection after receiving vaccines of any platform. This finding agrees with a recent immunogenicity study in children and adolescents.[75] We also found that a heterologous or a homologous third dose booster can confer an equal level of protection in all age groups, even in the older

group (≥65). If several boosters are administered to any age group, a heterologous or homologous regimen will not make much difference in immunity improvement. Importantly, we discovered that any homologous or heterologous three dose regimen induces a considerably higher level of immunity in older people than a two dose homologous regimen, which is comparable to that seen in all other age groups.

Vaccine effectiveness in patients who are immunocompromised

In the vaccine effectiveness comparison between immunocompromised and non-immunocompromised groups, we found that all vaccine regimens have lower effectiveness in people who are immunosuppressed or immunodeficient, with a decrease of 2% vaccine effectiveness. Similarly, a review paper has shown weaker vaccine induced immunity among people who are immunocompromised, such as lower seroconversion rates.[76] Our review suggests that a third booster dose, as part of a heterologous or homologous regimen, will greatly improve protection in these patients compared with a two dose primary vaccination. This finding orthogonally agrees with a randomised trial that studied SARS-CoV-2 antibody seroconversion in people who were immunocompromised and received a heterologous or homologous booster after primary mRNA vaccination. Therefore, the number of doses of vaccines seems to be the key to improving immunity rather than the combinations of vaccine types.[77]

Vaccine effectiveness against covid-19 variants

Rapidly evolving viral strains continually pose challenges to the elimination of covid-19. Recent immunogenicity research has reported waning vaccine effectiveness against delta and omicron variants.[78] Our estimates showed that the two dose and one dose regimens were ineffective against the omicron variant. These estimates are in line with the findings on omicron variant neutralisation after a homologous two dose mRNA regimen.[79] However, our study shows that homologous and heterologous three dose regimens successfully reduce covid-19 infections caused by the omicron variant. One study has shown that people receiving an mRNA booster after two doses of CoronaVac have a 1.4-fold increase in neutralisation activity against omicron.[80] Therefore, boosting vaccination will effectively control the spread of covid-19 variants. The latest study of the fourth dose of BNT162b2 reported that effectiveness against confirmed infection and severe covid-19 improves from receiving a third dose to a fourth dose in people aged 60 or older.[81] This finding implies that ongoing vaccine campaigns will be needed to prevent covid-19 infections in the long term. According to our results, mRNA vaccines appear to be the preferred choice for any additional dose.

Although we could not pool the results from 23 studies, all studies suggested that people who received a third dose mRNA or heterologous boosting regimen are less likely to get infected by SARS-CoV-2 than those receiving only a primary homologous regimen. When considering the safety of heterologous and booster vaccines, one study that assessed the safety and reactogenicity of heterologous primary vaccination with mRNA, adenovirus vector, and protein based vaccines showed no safety concerns.[82] Another study that examined the safety of booster doses in adults also showed fewer local and systemic reactions after a homologous mRNA booster than after a two dose homologous regimen.[83]

Limitations of study

Our study did not evaluate the optimum time interval for prime boost or boosting regimens owing to limited information about the dynamics of vaccine effectiveness across a period in a few studies. However, we anticipate more longitudinal research on the varying infection rates among people who are vaccinated and those who are not vaccinated. This type of study that combines timely measurement of antibody titres will provide more evidence on how the impact of vaccination changes over time and the protection period of a series of vaccinations.

Conclusions

A three dose mRNA regimen seems to be the most effective in preventing covid-19 infections. An mRNA booster can induce a similar level of protection against covid-19 infections to homologous primary vaccination. A third dose vaccine is needed to prevent covid-19 variant infections. Heterologous and homologous three dose regimens work equally well in preventing any covid-19 infections, even variants. We will update the results when newly published studies or preprints become available. For example, we will add other vaccine types and multiple dose regimens to the analysis as more vaccines are approved by the WHO emergency use listing. More research on multiple doses of the primary vaccination is expected. We will also examine the efficacies of vaccine regimens against new variants for the general population and other subgroups, such as sex, ethnicity, and other high risk populations.

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Contributors: PPHC conceived and supervised the study. WYA and PPHC initiated and designed the study plan. WYA and PPHC performed the search, independently screened search results and extracted data from eligible studies. WYA and PPHC exchanged data extraction results and resolved disagreement through discussion. WYA performed the statistical analysis. WYA and PPHC wrote the manuscript. We confirm that both authors had full access to all data in the study and final responsibility for publishing it. WYA and PPHC accessed and verified the data. WYA and PPHC are study guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not required.

Data sharing: Raw data in this systematic review with meta-analysis are extracted from published and preprint studies available on the internet. Our processed data for network meta-analysis and R codes on GitHub (https://github.com/wyauac/NMA-of-heterologous-and-homologous-vaccine-effectiveness).

The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We will disseminate the results to clinicians, patients, governmental organisations, and agencies through social media and press releases.

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1 WHO Team ER. *Weekly epidemiological update on COVID-19 - 5 April 2022. Emergency Situational Updates*. World Health Organization, 2022.
2 Hannah Ritchie EM. *Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald, Diana Beltekian and Max Roser. Coronavirus Pandemic (COVID-19)*. Our World in Data, 2020.
3 Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process: World Health Organization.
4 Mohammed I, Nauman A, Paul P, et al. The efficacy and effectiveness of the COVID-19 vaccines in reducing infection, severity, hospitalization, and mortality: a systematic review. *Hum Vaccin Immunother* 2022;18:2027160. doi:10.1080/21645515.2022.2027160
5 Yue L, Xie T, Yang T, et al. A third booster dose may be necessary to mitigate neutralizing antibody fading after inoculation with two doses of an inactivated SARS-CoV-2 vaccine. *J Med Virol* 2022;94:35-8. doi:10.1002/jmv.27334
6 Tré-Hardy M, Cupaiolo R, Wilmet A, et al. Immunogenicity of mRNA-1273 COVID vaccine after 6 months surveillance in health care workers; a third dose is necessary. *J Infect* 2021;83:559-64. doi:10.1016/j.jinf.2021.08.031
7 Li Y, Fang X, Pei R, et al. Immunogenicity and safety of the homogenous booster shot of a recombinant fusion protein vaccine (V-01) against COVID-19 in healthy adult participants primed with a two-dose regimen.*medRxiv* 2021:2021.11.04.21265780. doi:10.1101/2021.11.04.21265780
8 Sablerolles RSG, Rietdijk WJR, Goorhuis A, et al. Immunogenicity and reactogenicity of booster vaccinations after Ad26.COV2.S priming.*medRxiv* 2021:2021.10.18.21264979. doi:10.1101/2021.10.18.21264979
9 Chiu N-C, Chi H, Tu Y-K, et al. To mix or not to mix? A rapid systematic review of heterologous prime-boost covid-19 vaccination. *Expert Rev Vaccines* 2021;20:1211-20. doi:10.1080/14760584.2021.1971522
10 Atmar RL, Lyke KE, Deming ME, et al. Heterologous SARS-CoV-2 booster vaccinations – preliminary report.*medRxiv* 2021. doi:10.1101/2021.10.10.21264827
11 World Health Organization. Interim recommendations for heterologous COVID-19 vaccine schedules. 2021.
12 Rotshild V, Hirsh-Raccah B, Miskin I, Muszkat M, Matok I. Comparing the clinical efficacy of COVID-19 vaccines: a systematic review and network meta-analysis. *Sci Rep* 2021;11:22777. doi:10.1038/s41598-021-02321-z
13 Hu Y, Wang Y, Shao T, et al. Reactogenicity and Immunogenicity of heterologous ChAdOx1-nCoV19 and BNT162b2 vaccination: a systematic review and meta-analysis of the heterologous COVID-19 vaccination outcomes.*Available atSSRN* 39229512021. doi:10.2139/ssrn.3922951.
14 Prevost TC, Abrams KR, Jones DR. Hierarchical models in generalized synthesis of evidence: an example based on studies of breast cancer screening. *Stat Med* 2000;19:3359-76. doi:10.1002/1097-0258(20001230)19:24‹3359::AID-SIM710›3.0.CO;2-N
15 Schmitz S, Adams R, Walsh C. Incorporating data from various trial designs into a mixed treatment comparison model. *Stat Med* 2013;32:2935-49. doi:10.1002/sim.5764
16 JAGS. A program for analysis of Bayesian graphical models using Gibbs sampling. 2003.
17 Daly C, Downing BC, Welton NJ. A Practical Guide to Inconsistency Checks in Bayesian Network Meta-Analysis.
18 Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919. doi:10.1136/bmj.i4919
19 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi:10.1136/bmj.l4898
20 Puhan MA, Schünemann HJ, Murad MH, et al, GRADE Working Group. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:g5630. doi:10.1136/bmj.g5630
21 Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;9:e99682. doi:10.1371/journal.pone.0099682
22 Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. *N Engl J Med* 2021;385:187-9. doi:10.1056/NEJMc2104974
23 Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. *JAMA* 2021;326:35-45. doi:10.1001/jama.2021.8565
24 Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. *N Engl J Med* 2021;385:2241-51. doi:10.1056/NEJMoa2109522
25 Andrews N, Stowe J, Kirsebom F, et al. Effectiveness of BNT162b2 (Comirnaty, Pfizer-BioNTech) COVID-19 booster vaccine against covid-19 related symptoms in England: test negative case-control study.*medRxiv* 2021:2021.11.15.21266341. doi:10.1101/2021.11.15.21266341
26 Andrews N, Stowe J, Kirsebom F, et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. *N Engl J Med* 2022;386:1532-46. doi:10.1056/NEJMoa2119451
27 Baden LR, El Sahly HM, Essink B, et al, COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021;384:403-16. doi:10.1056/NEJMoa2035389
28 Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* 2021;398:2093-100. doi:10.1016/S0140-6736(21)02249-2
29 Björk J, Inghammar M, Moghaddassi M, Rasmussen M, Malmqvist U, Kahn F. High level of protection against COVID-19 after two doses of BNT162b2 vaccine in the working age population - first results from a cohort study in Southern Sweden. *Infect Dis (Lond)* 2022;54:128-33. doi:10.1080/23744235.2021.1982144
30 Bruxvoort KJ, Sy LS, Qian L, et al. Effectiveness of mRNA-1273 against delta, mu, and other emerging variants of SARS-CoV-2: test negative case-control study. *BMJ* 2021;375:e068848. doi:10.1136/bmj-2021-068848
31 Bruxvoort KJ, Sy LS, Qian L, et al. Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study. *Lancet Reg Health Am* 2022;6:100134. doi:10.1016/j.lana.2021.100134
32 Butt AA, Talisa VB, Yan P, Shaikh OS, Omer SB, Mayr FB. Vaccine Effectiveness of Three vs. Two Doses of SARS-CoV-2 mRNA Vaccines in a High Risk National Population. *Clin Infect Dis* 2022;ciac178. doi:10.1093/cid/ciac178
33 Carazo S, Talbot D, Boulianne N, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2 in healthcare workers extending 16 weeks post-vaccination: a test-negative design from Quebec, Canada.*medRxiv* 2021:2021.07.19.21260445. doi:10.1101/2021.07.19.21260445
34 Cerqueira-Silva T, Andrews JR, Boaventura VS, et al. Effectiveness of CoronaVac, ChAdOx1, BNT162b2 and Ad26.COV2.S among individuals with prior SARS-CoV-2 infection in Brazil.*medRxiv* 2021. doi:10.1101/2021.12.21.21268058
35 Cerqueira-Silva T, Katikireddi SV, de Araujo Oliveira V, et al. Vaccine effectiveness of heterologous CoronaVac plus BNT162b2 in Brazil. *Nat Med* 2022;28:838-43. doi:10.1038/s41591-022-01701-w
36 Cerqueira-Silva T, Oliveira VA, Boaventura VS, et al. Influence of age on the effectiveness and duration of protection of Vaxzevria and CoronaVac vaccines: A population-based study. *Lancet Reg Health Am* 2022;6:100154. doi:10.1016/j.lana.2021.100154
37 Chin ET, Leidner D, Zhang Y, et al. Effectiveness of COVID-19 vaccines among incarcerated people in California state prisons: a retrospective cohort study.*medRxiv* 202110.1101/2021.08.16.21262149 [published Online First: 20210818]
38 Collie S, Champion J, Moultrie H, Bekker LG, Gray G. Effectiveness of BNT162b2 vaccine against omicron variant in South Africa. *N Engl J Med* 2022;386:494-6. doi:10.1056/NEJMc2119270

39 Desai D, Khan AR, Soneja M, et al. Effectiveness of an inactivated virus-based SARS-CoV-2 vaccine, BBV152, in India: a test-negative, case-control study. *Lancet Infect Dis* 2022;22:349-56. doi:10.1016/S1473-3099(21)00674-5
40 Dunkle LM, Kotloff KL, Gay CL, et al, 2019nCoV-301 Study Group. Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. *N Engl J Med* 2022;386:531-43. doi:10.1056/NEJMoa2116185
41 Ella R, Reddy S, Blackwelder W, et al, COVAXIN Study Group. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. *Lancet* 2021;398:2173-84. doi:10.1016/S0140-6736(21)02000-6
42 Emary KRW, Golubchik T, Aley PK, et al, COVID-19 Genomics UK consortium, AMPHEUS Project, Oxford COVID-19 Vaccine Trial Group. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *Lancet* 2021;397:1351-62. doi:10.1016/S0140-6736(21)00628-0
43 Falsey AR, Sobieszczyk ME, Hirsch I, et al, AstraZeneca AZD1222 Clinical Study Group. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. *N Engl J Med* 2021;385:2348-60. doi:10.1056/NEJMoa2105290
44 Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance - VISION Network, 10 States, August 2021-January 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:255-63. doi:10.15585/mmwr.mm7107e2
45 Frenck RWJr, Klein NP, Kitchin N, et al, C4591001 Clinical Trial Group. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med* 2021;385:239-50. doi:10.1056/NEJMoa2107456
46 Glatman-Freedman A, Bromberg M, Dichtiar R, Hershkovitz Y, Keinan-Boker L. The BNT162b2 vaccine effectiveness against new COVID-19 cases and complications of breakthrough cases: a nation-wide retrospective longitudinal multiple cohort analysis using individualised data. *EBioMedicine* 2021;72:103574. doi:10.1016/j.ebiom.2021.103574
47 Heath PT, Galiza EP, Baxter DN, et al, 2019nCoV-302 Study Group. Safety and efficacy of NVX-CoV2373 covid-19 vaccine. *N Engl J Med* 2021;385:1172-83. doi:10.1056/NEJMoa2107659
48 Lauring AS, Tenforde MW, Chappell JD, et al. *Clinical Severity and mRNA Vaccine Effectiveness for Omicron, Delta, and Alpha SARS-CoV-2 Variants in the United States: A Prospective Observational Study.* Cold Spring Harbor Laboratory, 2022.
49 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of covid-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021;385:585-94. doi:10.1056/NEJMoa2108891
50 Martínez-Baz I, Trobajo-Sanmartín C, Miqueleiz A, et al, Working Group for the Study of COVID-19 in Navarre, Investigators, other members of the Working Group for the Study of COVID-19 in Navarre. Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021. *Euro Surveill* 2021;26:2100894. doi:10.2807/1560-7917.ES.2021.26.39.2100894
51 Nordström P, Ballin M, Nordström A. Effectiveness of heterologous ChAdOx1 nCoV-19 and mRNA prime-boost vaccination against symptomatic Covid-19 infection in Sweden: A nationwide cohort study. *Lancet Reg Health Eur* 2021;11:100249. doi:10.1016/j.lanepe.2021.100249
52 Nordström P, Ballin M, Nordström A. *Effectiveness of Covid-19 vaccination against risk of symptomatic infection, hospitalization, and death up to 9 months: a Swedish total-population cohort study.* Hospitalization, and Death Up to, 2021:9.
53 Olson SM, Newhams MM, Halasa NB, et al, Overcoming Covid-19 Investigators. Effectiveness of BNT162b2 vaccine against critical Covid-19 in adolescents. *N Engl J Med* 2022;386:713-23. doi:10.1056/NEJMoa2117995
54 Palacios R, Batista AP, Albuquerque CSN, et al. Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: the PROFISCOV study. 2021.
55 Polack FP, Thomas SJ, Kitchin N, et al, C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383:2603-15. doi:10.1056/NEJMoa2034577
56 Poukka E, Baum U, Palmu AA, et al. Cohort study of Covid-19 vaccine effectiveness among healthcare workers in Finland, December 2020-October 2021. *medRxiv* 2021.
57 Powell AA, Kirsebom F, Stowe J, et al. *Adolescent vaccination with BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccine and effectiveness against COVID-19: national test-negative case-control study.* Cold Spring Harbor Laboratory, 2021.
58 Pozzetto B, Legros V, Djebali S, et al, Covid-Ser study group. Immunogenicity and efficacy of heterologous ChAdOx1-BNT162b2 vaccination. *Nature* 2021;600:701-6. doi:10.1038/s41586-021-04120-y
59 Prieto-Alhambra D, Hermosilla E, Coma E, et al. Comparative effectiveness and safety of homologous two-dose ChAdOx1 versus heterologous vaccination with ChAdOx1 and BNT162b2: a cohort analysis. *Nat Commun* 2022;13:1639. doi:10.1038/s41467-022-29301-9.
60 Prunas O, Weinberger DM, Pitzer VE, et al. *Waning Effectiveness of the BNT162b2 Vaccine Against Infection in Adolescents.* Cold Spring Harbor Laboratory, 2022. doi:10.1101/2022.01.04.22268776.
61 Reis BY, Barda N, Leshchinsky M, et al. Effectiveness of bnt162b2 vaccine against delta variant in adolescents. *N Engl J Med* 2021;385:2101-3. doi:10.1056/NEJMc2114290
62 Sadoff J, Gray G, Vandebosch A, et al, ENSEMBLE Study Group. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med* 2021;384:2187-201. doi:10.1056/NEJMoa2101544
63 Sadoff J, Gray G, Vandebosch A, et al, ENSEMBLE Study Group. Final analysis of efficacy and safety of single-dose Ad26.COV2.S. *N Engl J Med* 2022;386:847-60. doi:10.1056/NEJMoa2117608
64 Shrotri M, Krutikov M, Palmer T, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study. *Lancet Infect Dis* 2021;21:1529-38. doi:10.1016/S1473-3099(21)00289-9
65 Skowronski DM, Setayeshgar S, Zou M, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2, including P.1 and B.1.1.7 variants: a test-negative design in adults 70 years and older in British Columbia, Canada. *medRxiv* 2021:2021.06.07.21258332. doi:10.1101/2021.06.07.21258332
66 Skowronski DM, Setayeshgar S, Zou M, et al. Comparative single-dose mRNA and ChAdOx1 vaccine effectiveness against SARS-CoV-2, including early variants of concern: a test-negative design, British Columbia, Canada.*medRxiv* 2021. doi:10.1101/2021.09.20.21263875.
67 Tanriover MD, Doğanay HL, Akova M, et al, CoronaVac Study Group. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* 2021;398:213-22. doi:10.1016/S0140-6736(21)01429-X
68 Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet* 2021;398:1407-16. doi:10.1016/S0140-6736(21)02183-8
69 Tartof SY, Slezak JM, Puzniak L, et al. Effectiveness of a third dose of BNT162b2 mRNA COVID-19 vaccine in a large US health system: a retrospective cohort study. *Lancet Reg Health Am* 2022;100198:100198. doi:10.1016/j.lana.2022.100198
70 Thompson MG, Natarajan K, Irving SA, et al. Effectiveness of a third dose of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance - VISION Network, 10 States, August 2021-January 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:139-45. doi:10.15585/mmwr.mm7104e3
71 Voysey M, Clemens SAC, Madhi SA, et al, Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397:99-111. doi:10.1016/S0140-6736(20)32661-1
72 Voysey M, Costa Clemens SA, Madhi SA, et al, Oxford COVID Vaccine Trial Group. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* 2021;397:881-91. doi:10.1016/S0140-6736(21)00432-3
73 Walter EB, Talaat KR, Sabharwal C, et al, C4591007 Clinical Trial Group. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. *N Engl J Med* 2022;386:35-46. doi:10.1056/NEJMoa2116298
74 Wickert DP, Almand EA, Baldovich KJ, et al. Estimates of single dose and full dose BNT162b2 vaccine effectiveness among USAF Academy cadets, 1 Mar - 1 May 2021. *medRxiv* 2021:2021.07.28.21261138. doi:10.1101/2021.07.28.21261138
75 Lau Y-L, Duque JR, Wang X, et al. Immunogenicity and reactogenicity of SARS-CoV-2 mRNA and inactivated vaccines in healthy adolescents: *Research Square* Platform LLC, 2022. doi:10.21203/rs.3.rs-1327020/v1.
76 Lee ARYB, Wong SY, Chai LYA, et al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. *BMJ* 2022;376:e068632. doi:10.1136/bmj-2021-068632

77 Bonelli M, Mrak D, Tobudic S, et al. Additional heterologous versus homologous booster vaccination in immunosuppressed patients without SARS-CoV-2 antibody seroconversion after primary mRNA vaccination: a randomised controlled trial. *Ann Rheum Dis* 2022;81:687-94. doi:10.1136/annrheumdis-2021-221558
78 Gardner BJ, Kilpatrick AM. *Estimates of reduced vaccine effectiveness against hospitalization, infection, transmission and symptomatic disease of a new SARS-CoV-2 variant, Omicron (B.1.1.529), using neutralizing antibody titers.* Cold Spring Harbor Laboratory, 2021. doi :10.1101/2021.12.10.21267594.
79 Pajon R, Doria-Rose NA, Shen X, et al. SARS-CoV-2 omicron variant neutralization after mRNA-1273 booster vaccination. *N Engl J Med* 2022;386:1088-91. doi:10.1056/NEJMc2119912
80 Pérez-Then E, Lucas C, Monteiro VS, et al. *Immunogenicity of heterologous BNT162b2 booster in fully vaccinated individuals with CoronaVac against SARS-CoV-2 variants Delta and Omicron: the Dominican Republic Experience.* Cold Spring Harbor Laboratory, 2021.
81 Bar-On YM, Goldberg Y, Mandel M, et al. Protection by a fourth dose of BNT162b2 against omicron in Israel. *N Engl J Med* 2022. doi:10.1056/NEJMoa2201570
82 Stuart ASV, Shaw RH, Liu X, et al, Com-COV2 Study Group. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. *Lancet* 2022;399:36-49. doi:10.1016/S0140-6736(21)02718-5
83 Hause AM, Baggs J, Marquez P, et al. Safety monitoring of COVID-19 vaccine booster doses among adults - United States, September 22, 2021-February 6, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:249-54. doi:10.15585/mmwr.mm7107e1

Web appendix: Supplementary materials