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 to 31 July 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 second iteration of the analysis comprised 63 studies. 25 combinations of covid-19 vaccine regimens were identified, of which three doses of mRNA vaccine were found to be 93% (95% credible interval 70% to 98%) effective against asymptomatic or symptomatic covid-19 infections for non-delta or non-omicron related infections. Heterologous boosting using two dose adenovirus vector vaccines with one dose mRNA vaccine showed a vaccine effectiveness of 94% (72% to 99%) against non-delta or non-omicron related asymptomatic or symptomatic infections. Three doses of mRNA vaccine were found to be the most effective in reducing non-delta or non-omicron related hospital admission (96%, 82% to 99%). The vaccine effectiveness against death in people who received three doses of mRNA vaccine remains uncertain owing to confounders. The estimate for a four dose mRNA vaccine regimen was of low certainty, as only one study on the effectiveness of four doses could be included in this update. More evidence on four dose regimens will be needed to accurately assess the effectiveness of a fourth vaccine dose. For people with delta or omicron related infection, a two dose regimen of an adenovirus vector vaccine with one dose of mRNA booster was 77% (42% to 91%) effective against asymptomatic or symptomatic covid-19 infections, and a three dose regimen of a mRNA vaccine was 93% (76% to 98%) effective against covid-19 related hospital admission.

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. This version is update 1 of the original article published on 31 May 2022 (*BMJ*

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

True estimates for vaccine effectiveness against the delta and omicron variants were analysed with current included studies and showed that a three dose regimen effectively prevents covid-19 for all SARS-CoV-2 strains

2022;377:e069989), and previous versions can be found as data supplements (https://www.bmj.com/content/377/bmj-2022-069989/related). When citing this paper please consider adding the version number and date of access for clarity.

Introduction

The covid-19 pandemic caused by SARS-CoV-2 has led to more than 605 million confirmed cases and 6.4 million deaths worldwide according to the World Health Organization covid-19 weekly epidemiological update on 14 September 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 12 billion doses, with 6.85 million being administered daily.[2] WHO has authorised the emergency use of 11 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.

Recent systematic reviews with meta-regression assessed vaccine effectiveness over time.[11 12] The earlier study found vaccine effectiveness against SARS-CoV-2 infection decreased from one to six months after full vaccination by 21% (95% confidence interval 13.9% to 29.8%) for all ages.[11] The other study suggested a 29% (18% to 41%) decline in vaccine effectiveness against symptomatic infections one to four months after a booster during the omicron period.[12] The WHO strategic advisory group of experts (SAGE) also reviewed the evidence of the immunogenicity or effectiveness of a second booster (the fourth or fifth dose) descriptively and made relevant recommendations on the use of additional booster doses.[13] The WHO report summarised recent evidence on mRNA and adenovirus vector vaccines, but mentioned that the evidence for booster doses using inactivated virus and protein based vaccines is limited.[13] The report also noted that limited data on heterologous boosting are available. In accordance with another of its documents, WHO recommends prioritisation of booster doses for elderly people, health workers, and immunocompromised patients.[14] In our second update of this systemic review, we mainly reviewed new evidence on the third dose and on vaccines that were not evaluated in the first publication. With the new evidence we also aimed to evaluate the vaccine effectiveness of different vaccine regimens among elderly people and those who were immunocompromised.

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 unvaccinated 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 SARS-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 preprints on a weekly basis from 8 March 2022 to 31 July 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 (18-65 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).[15 16] 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.[17] 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.[18] 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.[19] The ROB-2 tool (Cochrane risk of bias version 2) was used to assess randomised controlled trials.[20] 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.[21] 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.[22] 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 15 427 studies from 38 databases and removed 6261 duplicates, retaining 9166 studies for full text screening. We excluded 8554 studies by title, abstract, and subheading screening, of which 3697 (43.2%) were non-vaccine studies, 2046 (23.9%) were studies of viruses other than SARS-CoV-2, 834 (9.7%) were reviews, and 612 (7.2%) investigated non-human subjects. The remaining 1365 studies (16%) were descriptive literature with no supplementary data. During the full text screening and data extraction, we excluded 506 studies. Thirty six (7.1%) were protocols, 32 (6.3%) were vaccine safety studies, and 438 (86.6%) only examined immunogenicity and reactogenicity in people who were vaccinated. Of the remaining 106 studies, we were able to extract data from 63, including 10 new studies added to this update,[23-85] which gave us a sample size of 193 955 736 participants from 20 countries. Supplementary table 2 presents a summary of the study characteristics, with the newly included studies highlighted.[76-85] Fifteen studies included participants older than 65 years,[28 32 44 48 49 56 69 70 76 77 79-81 83 84] and eight studies enrolled participants younger than 18

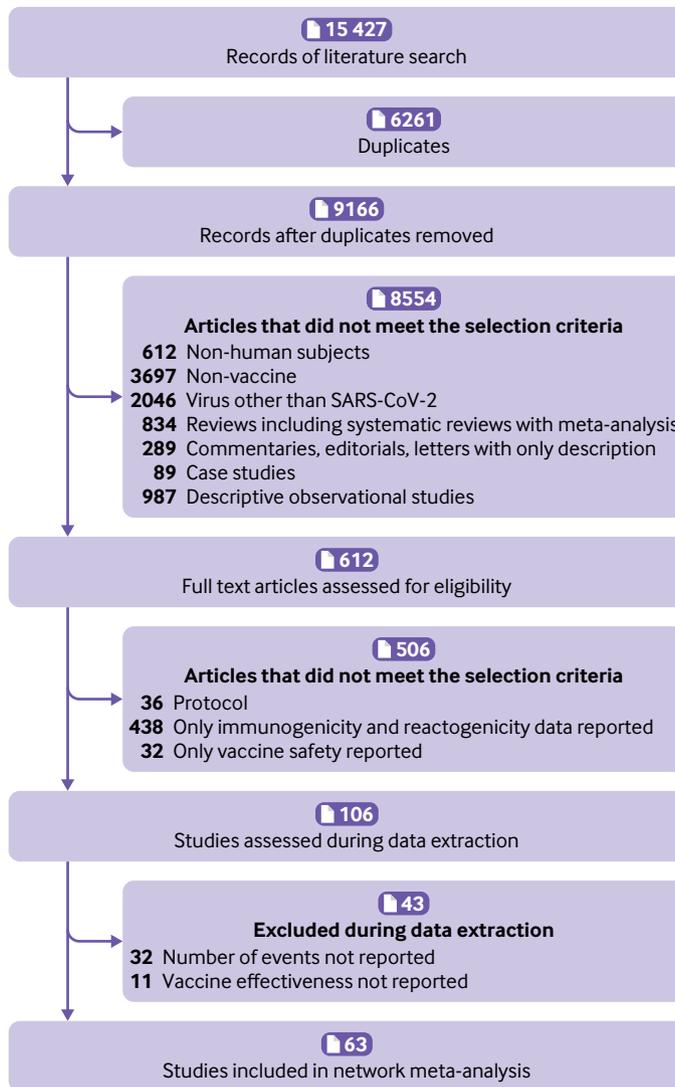|		
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Fig 1 | Flowchart of study selection

years.[46 54 58 61 62 69 74 78] Sixteen studies included high risk populations (defined as having more than one chronic condition),[28 41 42 44 48 49 70 76-84] of which five studies included patients who were immunocompromised in a subset of the high risk populations.[49 70 77 80 84] Of the 63 included studies, 29 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 (any lineage).[23 27 31 33 35 38 39 40 42 43 45 48-50 58 62 64 69 71 76-85]

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.[19 20] Of the 47 non-randomised studies, 21 were rated to have a moderate risk of bias, mainly because they did not control for confounders such as comorbidities and other baseline characteristics.[23 33-36 38 39 45 47 51 57 61 62 66 69 75 77 78 81 82 83] 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.[23 33-36 38 51 57 62] Five non-randomised studies relied on surveillance data, which were subject to incomplete information, and so received a moderate to severe risk of bias score in the domain of bias due to missing data.[39 47 69 82 83] Finally, two studies were rated as having a severe bias in selecting the reported result. In one study, the authors reported the overall vaccine effectiveness for mRNA vaccines instead of the specific vaccine products investigated in the study.[45] In the other study, the authors selectively reported the data for symptomatic infection.[83] All randomised controlled trials were considered low risk of bias except for three studies in which participants were unblinded after the second dose.[41 44 48] Supplementary figure 2 and supplementary table 4 show the results of ROB-2 and ROBINS-I, respectively.

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 25 covid-19 vaccine combinations from the 63 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

In the second iteration, 37 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. In the second iteration, we were able to include two studies rated low risk of bias.[76 80] In the vaccine product based network, heterologous regimens were significantly effective (odds ratio 0.044, 95% credible interval 0.005 to 0.428 for two doses of CoronaVac with one dose of BNT162b2; 0.07, 0.008 to 0.583 for one dose of ChAdOx1 with one dose of BNT162b2; supplementary table 5A). However, only one study contributed to the estimation for two doses of CoronaVac with one dose of BNT162b2.[36] Further evidence is needed to obtain a more precise estimate for this regimen. Among two dose regimens showing significant effectiveness, two doses of either BNT162b2 or mRNA-1273 conferred similar protection to two doses of Novavax's NVX-CoV2373 (odds ratios for two doses: 0.11, 95% credible interval 0.041 to 0.293 for

Table 1 | Ranking of vaccine regimens

Rank and SUCRA	Three dose mRNA	Two dose regimen				One dose regimen			
		Adenovirus vector+one dose mRNA	mRNA	Inactivated	Adenovirus vector	mRNA	Inactivated	Adenovirus vector	Unvaccinated
Rank	1	2	3	4	5	6	7	8	9
SUCRA	0.903	0.774	0.687	0.417	0.403	0.353	0.345	0.330	0.049

SUCRA=surface under the cumulative ranking curve.
Descending order of SUCRA 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.

BNT162b2; 0.124, 0.04 to 0.343 for mRNA-1273; and 0.116, 0.02 to 0.598 for NVX-CoV2373). However, as only one randomised controlled trial assessed the effectiveness of two doses of NVX-CoV2373 before the outbreak of the delta variant, we are less certain about the actual estimate for this regimen.[41]

In the platform based network, the risk of any documented covid-19 infection after vaccination was greatly reduced after at least three doses. The odds ratio for three doses of mRNA vaccine was 0.076 (95% credible interval 0.016 to 0.310) and for two doses of inactivated vaccine with one dose of mRNA vaccine was 0.045 (0.005 to 0.399). The effectiveness of two doses of adenovirus vaccine with one dose of mRNA vaccine was comparable to three doses of mRNA vaccine (odds ratio 0.071, 0.008 to 0.582; supplementary table 6A). The odds ratio for a regimen comprising four doses of mRNA vaccine was 0.058 (0.005 to 0.595), although this estimate was contributed from only one study conducted during the omicron outbreak in January 2022, resulting in a lower estimation

for the regimen.[80] Table 1 shows the SUCRA scores. Vaccine effectiveness was found to be non-significant for one dose of adenovirus vaccine and two doses of inactivated virus vaccine (supplementary table 6A). This could be attributed to different study periods; thus we analysed vaccine effectiveness before the delta or omicron outbreaks. Vaccine effectiveness for two doses of inactivated virus vaccine was 58% (32% to 77%) and for one dose of adenovirus vector vaccine was 51% (22% to 71%) before the outbreak (table 2). Limited studies were available for the analysis of effectiveness of these regimens after the delta or omicron outbreaks.

Effect of vaccine regimens against symptomatic covid-19 infections

We were able to pool results from 29 studies that evaluated vaccine effectiveness against symptomatic covid-19 infections, of which six studies assessed the effect of homologous boosters with BNT162b2, mRNA-1273, or ChAdOx1.[26 27 33 76 77 80] The odds ratios between a homologous booster dose group

Table 2 | Odds ratios (95% credible intervals) and vaccine effectiveness of vaccine regimens by platform for non-delta or non-omicron related infections and delta or omicron related infections

Vaccine regimens	Odds ratio (95% CrI)	Vaccine effectiveness (%) (95% CI)	GRADE
Non-delta or non-omicron related infections			
Asymptomatic or symptomatic covid-19 infections:			
Two dose adenovirus vector+one dose mRNA	0.06 (0.01 to 0.28)	94 (72 to 99)	Moderate
Three dose mRNA	0.07 (0.02 to 0.3)	93 (70 to 98)	Moderate
Two dose mRNA	0.12 (0.04 to 0.39)	88 (61 to 96)	Moderate
Two dose adenovirus vector	0.3 (0.19 to 0.46)	70 (54 to 81)	Moderate
Two dose inactivated	0.42 (0.23 to 0.68)	58 (32 to 77)	Low
One dose adenovirus vector	0.49 (0.29 to 0.78)	51 (22 to 71)	Low
Covid-19 related hospital admissions:			
Three dose mRNA	0.04 (0.01 to 0.18)	96 (82 to 99)	Moderate
Two dose adenovirus vector+one dose mRNA	0.06 (0.02 to 0.21)	94 (79 to 98)	Moderate
Two dose mRNA	0.11 (0.03 to 0.45)	89 (55 to 97)	Moderate
Two dose adenovirus vector	0.21 (0.07 to 0.62)	79 (38 to 93)	Moderate
One dose adenovirus vector	0.31 (0.15 to 0.66)	69 (34 to 85)	Low
Two dose inactivated	0.32 (0.12 to 0.82)	68 (18 to 88)	Low
Delta or omicron related infections			
Asymptomatic or symptomatic covid-19 infections:			
Two dose adenovirus vector+one dose mRNA	0.23 (0.09 to 0.58)	77 (42 to 91)	Moderate
Three dose adenovirus vector	0.24 (0.07 to 0.79)	76 (21 to 93)	Moderate
Two dose inactivated+one dose mRNA	0.29 (0.11 to 0.78)	71 (22 to 89)	Low
Two dose adenovirus vector	0.4 (0.18 to 0.9)	60 (10 to 82)	Low
Covid-19 related hospital admissions:			
Three dose mRNA	0.07 (0.02 to 0.24)	93 (76 to 98)	Moderate
Two dose adenovirus vector+one dose mRNA	0.08 (0.01 to 0.7)	92 (30 to 99)	Moderate
Two dose mRNA	0.12 (0.04 to 0.32)	88 (68 to 96)	Low
Two dose adenovirus vector	0.27 (0.08 to 0.87)	73 (13 to 92)	Low

CrI=credible interval; CI=confidence interval.
Unvaccinated group was used as reference.
GRADE=grading of recommendations assessment, development, and evaluation.

and the unvaccinated group were 0.235 (95% credible interval 0.083 to 0.681), for three doses of mRNA-1273, 0.155 (0.062 to 0.420) for three doses of BNT162b2, and 0.205 (0.067 to 0.655) for three doses of ChAdOx1 (supplementary table 5B). The estimation of effectiveness for the homologous three dose regimens in the second iteration were shown to be lower than the estimation in the first iteration because the 10 newly included studies all assessed vaccine effectiveness against either the delta or the omicron variant.[76-85] Only one case-control study reported the effectiveness of three doses of CoronaVac and the authors mainly examined vaccine effectiveness against omicron (B1.1.529) in countries with high coverage of inactivated covid-19 vaccines.[83] In the platform based network, four doses of mRNA vaccine were shown to be the most effective among all regimens compared in this study (odds ratio 0.061, 0.009 to 0.408; supplementary table 6B). This estimate was, however, contributed by only one study.[80] The second effective regimen was three doses of mRNA vaccines (odds ratio 0.115, 0.053 to 0.260).

Effect of vaccine regimens against severe covid-19 infections
We analysed 15 studies for vaccine effectiveness against severe covid-19 infections. With reference to the unvaccinated group, all one dose regimens were less effective than two dose and three dose regimens (supplementary table 5C). Three doses of BNT162b2 maintained a high level of protection compared with any one dose or two dose vaccine regimens (odds ratio 0.146, 0.021 to 0.978; supplementary table 5C). Up to the second iteration, only one randomised study reported the effectiveness of two doses of BBV152 (Covaxin), and one retrospective study reported the effectiveness of BBIBP-CorV.[42 85] More real world evidence will be needed to obtain accurate estimates for these two vaccines. In the platform based network, three doses of a mRNA vaccine was the most significantly effective regimen in this study (odds ratio 0.147, 0.024 to 0.844).

Effect of vaccine regimens against covid-19 related hospital admission
Twenty three studies were evaluated for vaccine effectiveness against covid-19 related hospital admissions. Individuals receiving four doses of BNT162b2, three doses of BNT162b2, three doses of mRNA-1273, or two doses of ChAdOx1 with one dose of BNT162b2 were the least likely to be admitted to hospital because of covid-19 (odds ratio 0.018, 0.001 to 0.224 for four doses of BNT162b2; 0.046, 0.011 to 0.203 for three doses of BNT162b2; 0.030, 0.005 to 0.159 for three doses of mRNA-1273; and 0.064, 0.013 to 0.322 for two doses of ChAdOx1 with one dose of BNT162b2; supplementary table 5D). Results showed that four doses of BNT162b2 was the most effective compared with other regimens in this study (odds ratio 0.018, 0.001 to 0.224; supplementary table 5D). However, this estimate was contributed by only one study.[80] Additional evidence needs to be considered to obtain a more precise estimate. Studies that reported covid-19 hospital admissions were mainly observational, which also added uncertainty to the estimates. We analysed the vaccine effectiveness for regimens before and during the delta or omicron outbreak (table 2).

Effect of vaccine regimens against covid-19 related deaths
Nine studies were evaluated for vaccine effectiveness against covid-19 related deaths. Estimates for the prevention of deaths were 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 and deaths, we only performed subgroup analyses on studies that investigated non-severe SARS-CoV-2 infections and hospital admissions. We were able to stratify studies by variants (delta or omicron versus other strains). We further stratified each variant group by age groups (<18 years, 18-65 years, and >65 years) and immunocompromised status or not. Sex and ethnicity were not investigated because of limited data.

We found that three dose regimens conferred protection in all age groups for non-delta or non-omicron related asymptomatic or symptomatic infections. The youngest age group (<18 years) had a similar protection level to the adult group aged 18-65 years (odds ratio ≤0.01) for all regimens. The oldest age group (>65 years) had the highest protection level after any three dose regimen (odds ratio 0.01) (supplementary table 8A). A three dose regimen of mRNA vaccine was effective in all age groups for the delta variant (odds ratio <0.1 for all age groups); however, the effectiveness of the same regimen decreased significantly for the omicron variant (odds ratio ranges from 0.23 to 0.44; supplementary table 8B). For prevention of hospital admission, a three dose regimen (either three doses of a mRNA vaccine or two doses of an adenovirus vector vaccine with one of mRNA vaccine) was highly effective in all age groups (odds ratio <0.1 for all age groups) for non-delta or non-omicron related hospital admission (supplementary table 8C). A slight average decrease of 0.03 in odds ratio was observed for three doses of mRNA vaccine when compared with delta or omicron related hospital admissions.

We compared vaccine effectiveness for prevention of non-delta or non-omicron related hospital admission. A three dose mRNA vaccine regimen was significantly effective in both the immunocompromised group (odds ratio 0.07, 0.01 to 0.27) and the immunocompetent group (odds ratio 0.03, 0.01 to 0.13; supplementary table 8C). Similar effectiveness was seen for delta or

omicron related hospital admissions (odds ratio 0.1, 0.02 to 0.49 for immunocompromised group; and 0.03, 0 to 0.89 for immunocompetent group; supplementary table 8D). We were unable to draw conclusions about vaccine effectiveness among patients who were immunocompromised owing to the limited number of studies when grouping by study period.

From the comparisons in this study, we found that vaccine regimens with two or more vaccine doses were more effective than one dose during the delta and omicron outbreaks. However, a three dose regimen was less effective in preventing omicron related infections than delta related infections (supplementary table 8A-D). Our findings suggest that three or more vaccine doses are needed to increase protection against omicron. In our second iteration, we included 10 studies that investigated vaccine effectiveness against the delta or omicron variant.[76-85] Incorporation of the new evidence provided us with more information on the effects of vaccine regimens on the variants; hence we are more certain with the estimates in the variant subgroups than we were in the first round of the review.

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 for the five outcomes (supplementary fig 4). An Egger's test P value indicated that statistical significance was not reached for all five outcomes (P>0.05).

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.[28 41 42 46 48 56 64 72 74] 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 vaccine effectiveness in preventing five outcomes: covid-19 related documented infections, symptomatic infections, severe infections, hospital admissions, and deaths. In this update, we were able to obtain more evidence for covid-19 related infections and hospital admissions. We could also analyse the true estimates for vaccine effectiveness against the delta and omicron variants with current included studies. We confirmed that a three dose vaccine regimen effectively reduces the risk of covid-19 with all SARS-CoV-2 strains. The results consistently showed a considerable reduction in covid-19 infections across different subgroups.

Three dose mRNA vaccine regimens (three doses of BNT162b2 or mRNA-1273) appear to be the most effective in preventing non-severe covid-19 infections, among all regimens we compared in this study. A heterologous regimen with an mRNA booster in recipients of two doses of adenovirus vector vaccines also had more than 80% protection against covid-19. Among all two dose regimens, mRNA vaccines remain the ideal for prevention against all covid-19 related outcomes. With more evidence added to this update, we have better certainty in the vaccine effectiveness of a three dose vaccine regimen against covid-19 related hospital admission. Both three doses of an mRNA vaccine and two doses of an adenovirus vector vaccine with one dose of mRNA vaccine prevent covid-19 related hospital admissions. Our results show that a three dose regimen reduces the risk of hospital admission even during outbreaks of variants. Consistent with the first publication, an mRNA vaccine continues to be the preferred vaccine type for a booster dose. When we compared vaccine effectiveness between age groups, we found that people younger than 18 years 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.[86] 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 oldest age group (>65 years). If several boosters are to be administered to any age group, a heterologous or homologous regimen does not make much difference in improving immunity. Although we estimated the overall effectiveness of a fourth mRNA vaccine dose to be more than 90%, the estimate was uncertain because only one study contributed to the estimation. We will include more studies on four vaccine doses in the coming update.

Vaccine effectiveness in patients who are immunocompromised
In the comparison of vaccine effectiveness between immunocompromised and non-immunocompromised groups, we found that a two dose mRNA vaccine regimen had lower effectiveness against hospital admission in people with immunosuppression or immunodeficiency whether or not an outbreak was related to delta or omicron, compared with a three dose mRNA. Our review suggests that a third booster

dose, as part of a heterologous or homologous regimen, greatly improves 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.[87]

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.[88] Our study found that homologous and heterologous three dose regimens successfully reduced covid-19 infections cause by the omicron variant. One study found that people who received an mRNA booster after two doses of CoronaVac had a 1.4-fold increase in neutralisation activity against omicron.[89] 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 improved from receiving a third dose to a fourth dose in adults aged 60 or older.[90] One included study in our update also assessed the risk of covid-19 among elderly people who received a fourth dose.[80] 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 were less likely to become infected with 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.[91] 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.[92]

Limitations of this 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 vaccine regimen comprising a third or more doses 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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Web appendix: Supplementary materials