REPORT

Relative effectiveness and durability of booster doses of SARS-CoV-2 vaccines: A systematic review and meta-analysis

Di Liu,[1,7] Yiwen Jiang,[1,7] Shiyu Wang,[1,7] Fuxiao Li,[1] Tengfei Lin,[1] Bingli Li,[1] Ziyi Zhao,[1,2] Qingping Yun,[1] Nana Peng,[1] Jiaxin Cai,[1,3] Lingling Zheng,[1,4] Yuanxi Jia,[1] Zuyao Yang,[5] Feng Sha,[1,*] Zhirong Yang,[1,6,*] and Jinling Tang[1,5]

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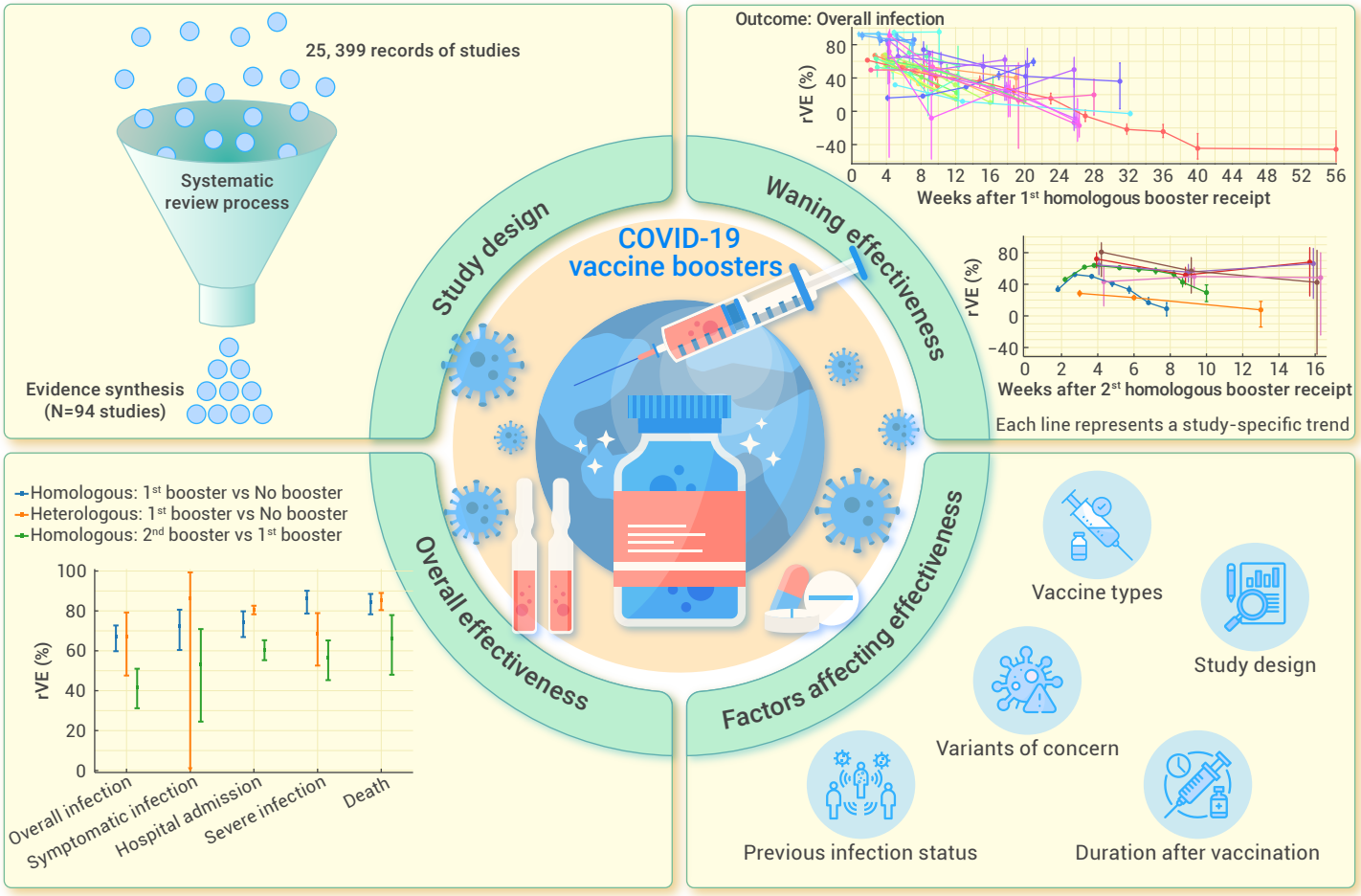
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Both the 1st and 2nd booster vaccination could offer additional protection against SARS-CoV-2 infections.
- The additional protection of the 1st booster vaccination may vary by variants of concern and vaccine types.
- The protection of the 1st booster waned fast but that of the 2nd booster remained stable in a short period.
- The sources of heterogeneity for the additional protection of the 2nd booster still remain uncertain.

REPORT

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Relative effectiveness and durability of booster doses of SARS-CoV-2 vaccines: A systematic review and meta-analysis

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Billions of people worldwide have received booster doses of SARS-CoV-2 vaccines. Continuous monitoring of the relative vaccine effectiveness (rVE) and durability of booster vaccination over previous vaccinations is important for developing vaccination strategies during the post-pandemic era. We conducted a systematic review and meta-analysis of trials and observational studies to determine the rVE of the 1st booster over no booster and that of the 2nd booster over the 1st booster. Three trials and 91 observational studies were included in this systematic review. For the 1st booster homologous vaccination, the rVE at a median of 9 weeks after booster vaccination was 66.9% (95% confidence interval: 59.8%, 72.7%), 75.9% (62.6%, 84.5%), 74.1% (66.9%, 79.8%), 86.1% (78.7%, 90.9%) and 84.2% (78.3%, 88.5%) against overall infection, symptomatic infection, hospital admission, severe infection and COVID-19-related death, respectively. The rVE against overall infection was affected by variants of concern and vaccine types and waned by average of 4.3% (3.3%, 5.4%; *P-trend*<0.01) per week. Heterologous regimens for the 1st booster vaccination demonstrated effectiveness comparable to that of homologous regimens. The rVE of the 2nd booster homologous vaccination at a median of 7 weeks after booster vaccination was 41.9% (31.2%, 51.0%), 53.1% (24.5%, 70.9%), 60.6% (55.3%, 65.3%), 56.4% (45.3%, 65.2%) and 68.2% (51.2%, 79.2%) against the five outcomes above, respectively, with no significant decrease in the rVE of 2nd booster vaccination. In conclusion, both the 1st and 2nd booster homologous vaccinations provided additional protection against mild and severe infections. The rVE of the 1st booster rapidly waned over time. The rVE of the 2nd booster, including heterologous vaccination, its durability and the sources of heterogeneity, however, remains uncertain and more relevant studies are needed.

INTRODUCTION

Primary SARS-CoV-2 vaccine regimens are effective in reducing the risk of mild and severe COVID-19; however, their effectiveness diminishes rapidly after vaccination.[1-3] To maintain or increase vaccine effectiveness, receiving a homologous or heterologous booster dose after the primary full-dose vaccination is recommended.[4] Some countries have launched national campaigns for a second booster.[5] However, evidence of the efficacy of booster doses from randomized controlled trials (RCTs) was limited.[3,6,7] Most available evidence in this regard was derived from observational studies. The effectiveness and durability of a booster dose remained largely uncertain due to the wide variations in the findings of observational studies. This uncertainty may contribute to hesitancy and reluctance to receive a booster. The level of uncertainty further increased with the emergence of Omicron variants, which exhibit high immune evasion and have become the global predominant strains.

Quantitative systematic reviews suggested that booster vaccination was associated with a reduced risk of SARS-CoV-2 infections.[8-13] Two additional systematic reviews provided only a narrative summary of seroconversion rates and effectiveness against SARS-CoV-2 infections.[14,15] Two systematic reviews further showed the waning effectiveness of the 1st booster dose compared with no vaccination.[10,16] However, evaluating the relative vaccine effectiveness (rVE) of a booster dose versus no booster dose and its waning have now been of significance for practice as two thirds of the global population have received SARS-CoV-2 vaccines, according to the latest reports from the World Health Organization (WHO),[17] and there is an ongoing hesitancy towards booster vaccination. However, the conflicting findings in previous studies, the lack of systematic reviews on the waning effect of a booster dose compared with no booster dose and the limited systematic assessment of rVE of the 2nd booster dose contribute to uncertainty about future vaccination strategies. The influence of various potential sources of heterogeneity on rVE, such as vaccine regimens (homologous or heterologous), variants of concern (VOCs), age groups, vaccine types, prior infection status, study design and jab-interval time, is also largely unknown. Therefore, further comprehensive assessment of the rVE of the 1st and 2nd booster vaccination, taking into account the post-vaccination duration and potential sources of heterogeneity, is urgently needed to help adjust vaccination strategies and reduce vaccination hesitancy during the post-pandemic era.

This systematic review aimed to evaluate the rVE of a booster dose (including both the 1st and 2nd booster doses) in comparison to that of a previous vaccine regimen, the waning of the rVE over time and the sources of rVE heterogeneity.

MATERIALS AND METHODS

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42022347249). This systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Supplemental Appendix 1).[18]

Search strategy

The PubMed, Web of science, Embase, Cochrane Library, Scopus, medRxiv, bioRxiv and WHO COVID-19 Research Database were searched from January 1, 2020 to June 6, 2023 (The search strategies are shown in Supplemental Appendix 2). In addition, we manually retrieved studies from reference lists of relevant systematic reviews.

Eligibility criteria

Observational studies (including cohort and case-control studies) and RCTs were included if they: (1) evaluated the rVE of the 1st booster vaccination versus primary full vaccination (the 1st booster vs no booster) or the 2nd booster versus previous vaccination (the 2nd booster vs the 1st booster); (2) addressed at least one of the outcomes (overall infection, symptomatic infection, hospital admission, severe infection and death); (3) reported an estimate of the rVE with adjustment for potential confounders; (4) explicitly specified homologous or heterologous booster vaccination; and (5) were published in English. Meanwhile, we excluded (1) duplicate studies, comments, conference abstracts or protocols; (2) studies where SARS-CoV-2 infection was not

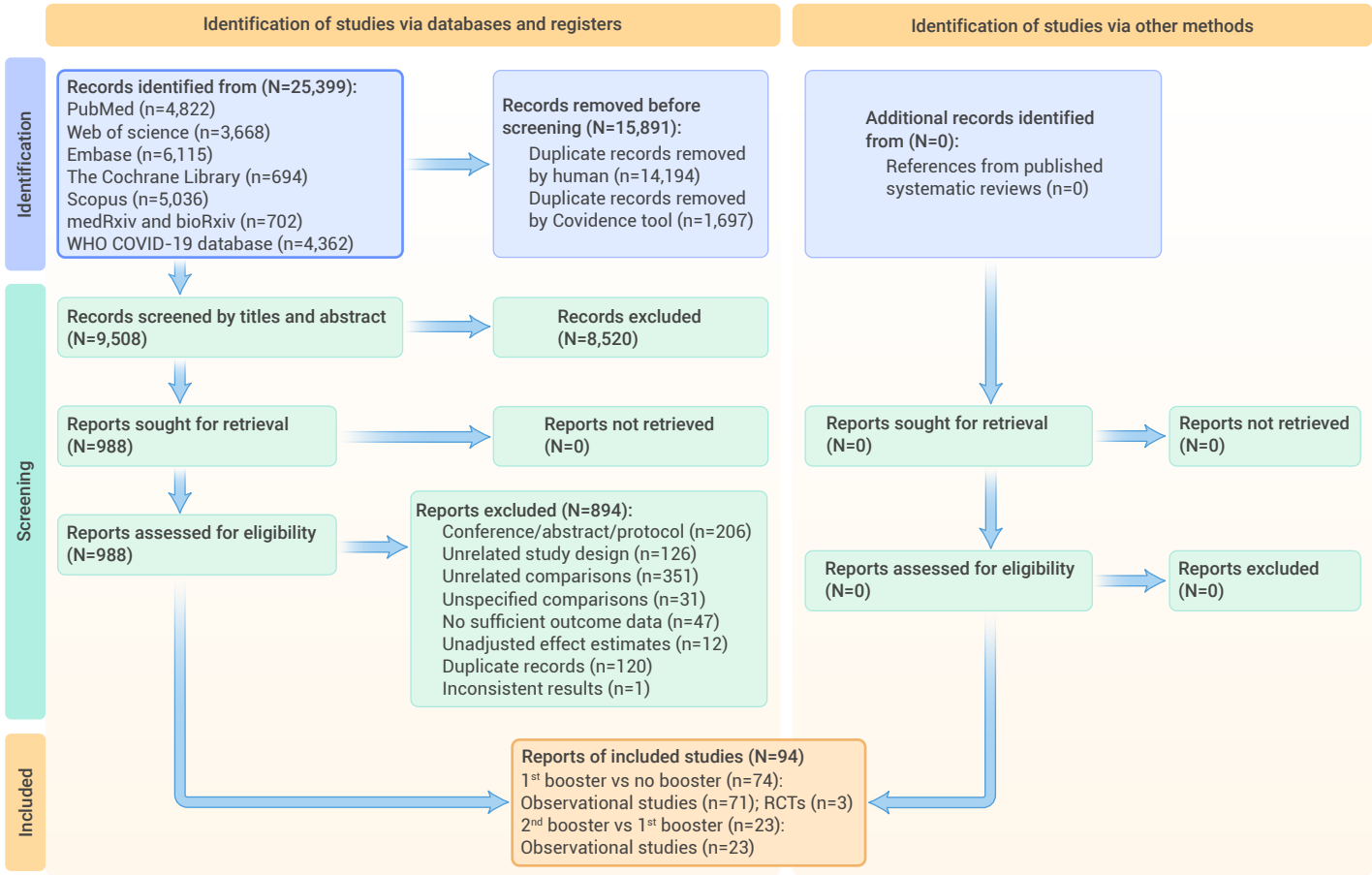

Figure 1. Flowchart of the study selection process Notes: COVID-19, Coronavirus disease 2019; RCT, Randomized controlled trial; WHO, World Health Organization. Among the 94 inlcuded studies, three provided both comparison of the 1st booster with no booster vaccination and comparison of the 2nd booster with the 1st booster vaccination.

detected using reverse transcription polymerase chain reaction; (3) studies where the comparison groups had previously received a different type of vaccine; or (4) studies where the results presented in the same publication were inconsistent in context.

Study selection and data extraction

Pairs of trained investigators (DL, YWJ, SYW, TFL, FXL, BLL, ZYZ, YXJ and FS) independently selected eligible studies by screening the titles, abstracts and full text. For eligible studies, pairs of trained researchers (DL, YWJ, SYW, FXL, QPY and TFL) independently extracted data using a pre-determined form. The information included study characteristics, participant characteristics, interventions/exposures, controls and outcomes of interest. The process of extracting data from duplicate databases or for multiple comparisons is provided in the Supplemental Methods 1. Any discrepancies in the study selection and data extraction were resolved by consensus with a third investigator (ZRY).

Risk of bias assessment

The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to rate the risk of bias for observational studies in seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of reported results (Supplemental Appendix 3).[19] Each domain was evaluated and categorized as having a low, moderate, serious, critical or unclear risk of bias. The Cochrane Risk of Bias (RoB) tool was used to assess the risk of bias in RCTs, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete data, outcome reporting and other biases (Supplemental Appendix 4).[20] Each domain was evaluated and categorized as having a low, high, or unclear risk of bias. For both the ROBINS-I and RoB tools, overall bias was divided based on the presence or absence of a high risk of bias (or serious/critical risk of bias).

Data analysis

A meta-analysis was conducted according to the type of booster vaccination regimen (homologous or heterologous) administered. We expected that heterogeneity would exist across the SARS-CoV-2 vaccine studies due to various VOCs, vaccine types, previous infection status and other potential factors, which may introduce differences in rVE estimates. We therefore used random-effects models with restricted maximum likelihood estimation to calculate the pooled effect estimate (odds ratio [OR], risk ratio [RR] or hazard ratio [HR]) and 95% confidence interval (CI) for each outcome of interest by comparing the 1st booster with no booster or the 2nd booster with the 1st booster when two or more eligible studies were available. Subsequently, the effect estimates were converted to rVE using the following formula: (1 – effect estimate) × 100%. The rVE was calculated based on the time lag for developing immunological protection after booster vaccination when data were available. I^2 statistics and Q test were used to quantify heterogeneity between studies, with an I^2 value of >50% or a *P*-value of <0.05 representing a significant heterogeneity. Meta-regression and subgroup analyses were performed to explore the sources of heterogeneity (i.e., VOCs, age groups, vaccine types, previous infection status and study design). Due to the sufficient number of studies, we only conducted meta-regression analysis for homologous vaccination regimens in preventing overall infection. When data were available, between-study and within-study subgroup analyses were performed. Funnel plot and Egger's test were employed to evaluate potential publication bias when the number of comparisons was greater than or equal to 10. A *P*-value of <0.05 was considered statistically significant. All analyses were performed using the R software (version 4.0.5).

To test the robustness of the results, four sensitivity analyses were

Figure 2. Relative vaccine effectiveness of booster vaccination in preventing infections of different severities, stratified by the median period after the receipt of the latest booster dose Notes: rVE, Relative vaccination effectiveness. There is no evidence for the 2nd booster compared with the 1st booster vaccination in heterologous vaccine regimens in preventing infections of different severities. The effectiveness were estimated only for the periods when data were available. Data are represented as relative vaccine effectiveness and 95% confidence interval.

conducted: (1) excluding studies without peer reviews; (2) excluding studies with a high risk of bias in at least one domain; (3) excluding studies conducted in specific populations (i.e., healthcare workers, patients with a specific disease, pregnant women and nursing home residents); or (4) excluding studies that reported infections occurring within less than 14 days of follow-up to account for the immunization time lag.

We plotted the rVE over time, utilizing within-study repeated measurement data on outcomes for discrete time intervals post-booster vaccination. The average change in the rVE over time was estimated using linear mixed-effects meta-regression.[21] This meta-regression regressed the logarithmic form of effect estimates on the weeks after the latest vaccination.

Certainty of evidence

We assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation approach.[22] The certainty of the overall evidence was rated as high, moderate, low, or very low. The hierarchy of evidence from RCTs and observational studies was initially deemed high and low, respectively, and it could be downgraded due to violations in the following five domains: risk of bias, inconsistency, indirectness, publication bias and imprecision. For observational studies, the level of evidence could also be upgraded if the effect size was large, the study showed a dose-response relationship, or the effect size was underestimated owing to negative bias. Once the evidence is downgraded on a domain, it cannot be upgraded on any other domain.

RESULTS

Study characteristics

Of the 9,508 studies retrieved, 94 studies (71 comparing the 1st booster with no booster, 20 comparing the 2nd booster with the 1st booster and three examining both) were included in this review (Figure 1). The list of included references is in Supplemental Appendix 5. Seventy-four studies compared the 1st booster with no booster vaccination (46 cohort studies, 25 case-control studies and 3 RCTs, with 62 on homologous vaccine regimens, 4 on heterologous vaccine regimens and 8 on both). The median jab-interval between the completion of the primary vaccination and the 1st booster vaccination was 6 months, with a median time of 9 weeks after the booster vaccination (Table S1). Twenty-three studies compared the 2nd booster with the 1st booster vaccination (16 cohort studies and 7 case-control studies). The median jab-interval between the 1st booster and 2nd booster dose vaccination was 4 months, with a median time of 7 weeks after the booster vaccination (Table S1). The definitions of severe infection varied across studies (Supplemental Appendix 6). The estimates of rVE for individual studies are shown in Figures S1-S3.

Risk of bias

Fifty-three observational studies (39 studies comparing the 1st booster with

Table 1. Meta regression analysis for heterogeneity sources of relative vaccine effectiveness of the 1st booster versus no booster against overall infection in the homologous vaccine regimens

Factors	n	rVE (95%CI), %	Univariable *P* for heterogeneity	Multivariable *P* for heterogeneity
VOCs			<0.001	<0.0001
Delta	15	82.6 (75.9, 87.4)		
Omicron	37	47.2 (37.8, 55.1)		
Unspecified	20	77.7 (66.3, 85.2)		
Age groups			0.099	0.066
<65y	9	81.9 (69.5, 89.2)		
≥65y	8	64.6 (42.4, 78.2)		
Unspecified	55	63.7 (54.8, 70.8)		
Vaccine types			0.097	0.035
mRNA	68	68.1 (61.1, 73.9)		
non-mRNA	4	33.1 (4.7, 53.6)		
Prior infection status			0.507	0.068
No prior infection	30	68.6 (59.6, 75.6)		
Prior infection	36	67.3 (55.4, 76.0)		
Unspecified	6	49.3 (19.3, 68.1)		
Study design			0.039	0.205
Cohort study	46	73.0 (65.2, 79.0)		
Case-control study	25	51.6 (39.0, 61.6)		
RCT	1	51.1 (29.5, 66.5)		

Notes: CI, Confidence interval; RCT, Randomized controlled trial; rVE, Relative vaccine effectiveness; VOCs, Variants of concern. n refers to the number of comparisons. Multivariable included VOCs, age groups, vaccine types, prior infection status and study design.

no booster vaccination and 14 studies for comparing the 2nd booster with the 1st booster vaccination) were rated as having a high risk of bias in at least one domain. The primary concerns included confounding bias, selection bias and measurements bias for outcomes. One RCT was rated as having a high risk of bias due to insufficient blinding of the participants and personnel and insufficient coverage of SARS-CoV-2 infection testing in all study participants (Tables S2-S3).

Relative vaccine effectiveness of the 1st booster compared with no booster vaccination

For homologous booster regimens, the combined rVE was 66.9% (95% CI: 59.8%, 72.7%;) for overall infection, 75.9% (95% CI: 62.6%, 84.5%) for symptomatic infection, 74.1% (95% CI: 66.9%, 79.8%) for hospital admission, 86.1% (95% CI: 78.7%, 90.9%) for severe infection and 84.2% (95% CI: 78.3%, 88.5%) for death (Figures 2 & S1). These estimates showed substantial heterogeneity (most I^2>50% and P <0.05). Sensitivity analyses also showed similar effect estimates and heterogeneity (Tables S4-S7). VOCs and vaccine types could affect the rVE of homologous booster regimens, with lower rVE in preventing Omicron infection than Delta infection and higher rVE for mRNA booster vaccination than for non-mRNA booster vaccination (Tables 1 & S8). Pooled analysis of RCTs yielded an rVE of 51.1% (95% CI: 29.5%, 66.5%) for overall infection and 75.2% (95% CI: 54.6%, 87.3%) for severe infection (Table S9). The protection decreased after the 1st booster dose significantly by average of 4.3% per week (95% CI: 3.3%, 5.4%; 1-56 weeks) for overall infection, 2.7% per week (95% CI: 1.5%, 4.0%; 2-49 weeks) for symptomatic infection, 6.5% per week (95% CI: 2.6%, 10.5%; 2-29 weeks) for hospital admission, 1.5% per week (95% CI: -3.0%, 6.2%; 3-30 weeks) for severe infection and 30.9% per week (95% CI: 12.1%, 52.7%; 8-10 weeks) for death (Figures 2-3). Only two studies reported the impact of the time interval between primary vaccination completion and the 1st booster vaccination on the rVE; however, the results were inconsistent (Table S10).

For heterologous booster regimens, the combined rVE was 71.7% (95% CI: 50.3, 83.8%) for overall infection, 86.3% (95% CI: -167.2%, 99.3%) for symptomatic infection, 80.6% (95% CI: 78.3%, 82.6%) for hospital admission, 68.4% (95% CI: 52.6%, 78.9%) for severe infection and 85.3% (95% CI: 80.4%, 89.0%) for death (Figures 2 & S2). The combined rVE of the heterologous vaccination regimens was similar to that of the homologous vaccination regimens for all five outcomes (Table 2). Insufficient data were available for a robust subgroup analysis (Table S11). A decreasing trend in the rVE was observed for overall infection (by average of 11.5% per week, 95% CI: 0.2%, 24.2%) and symptomatic infection (by average of 10.0% per week, 95% CI: 1.3%, 19.4%) during a maximum of 22 weeks after the 1st booster vaccination (Figures 2-3).

Relative vaccine effectiveness of 2nd booster compared with 1st booster vaccination

All included studies used a booster with homologous vaccination regimens. The combined rVE was 41.9% (95% CI: 31.2%, 51.0%) for overall infection, 53.1% (95% CI: 24.5%, 70.9%) for symptomatic infection, 60.6% (95% CI: 55.3%, 65.3%) for hospital admission, 56.4% (95% CI: 45.3%, 65.2%) for severe infection and 68.2% (95% CI: 51.2%, 79.2%) for death (Figures 2 & S3). Heterogeneity was high for all outcomes (I^2>80% and P<0.05) except for hospital admission. No significant sources of heterogeneity were identified in the subgroup analysis (Table S12). No significant decrease was observed in the rVE of the 2nd booster vaccination: average of 1.5% per week (95%CI: -2.3%, 5.3%; 2-16 weeks) for overall infection, 0.9% per week (95%CI: -0.3%, 2.0%; 2-24 weeks) for symptomatic infection, 1.7% per week (95%CI: -1.9%, 5.4%; 3-11 weeks) for hospital admission, 2.0% per week (95%CI: -4.7%, 9.2%; 2-13 weeks) for severe infection and 6.0% per week (95%CI: -8.1%, 22.4%; 5-14 weeks) for death (Figures 2-3). No studies reported the impact of the interval

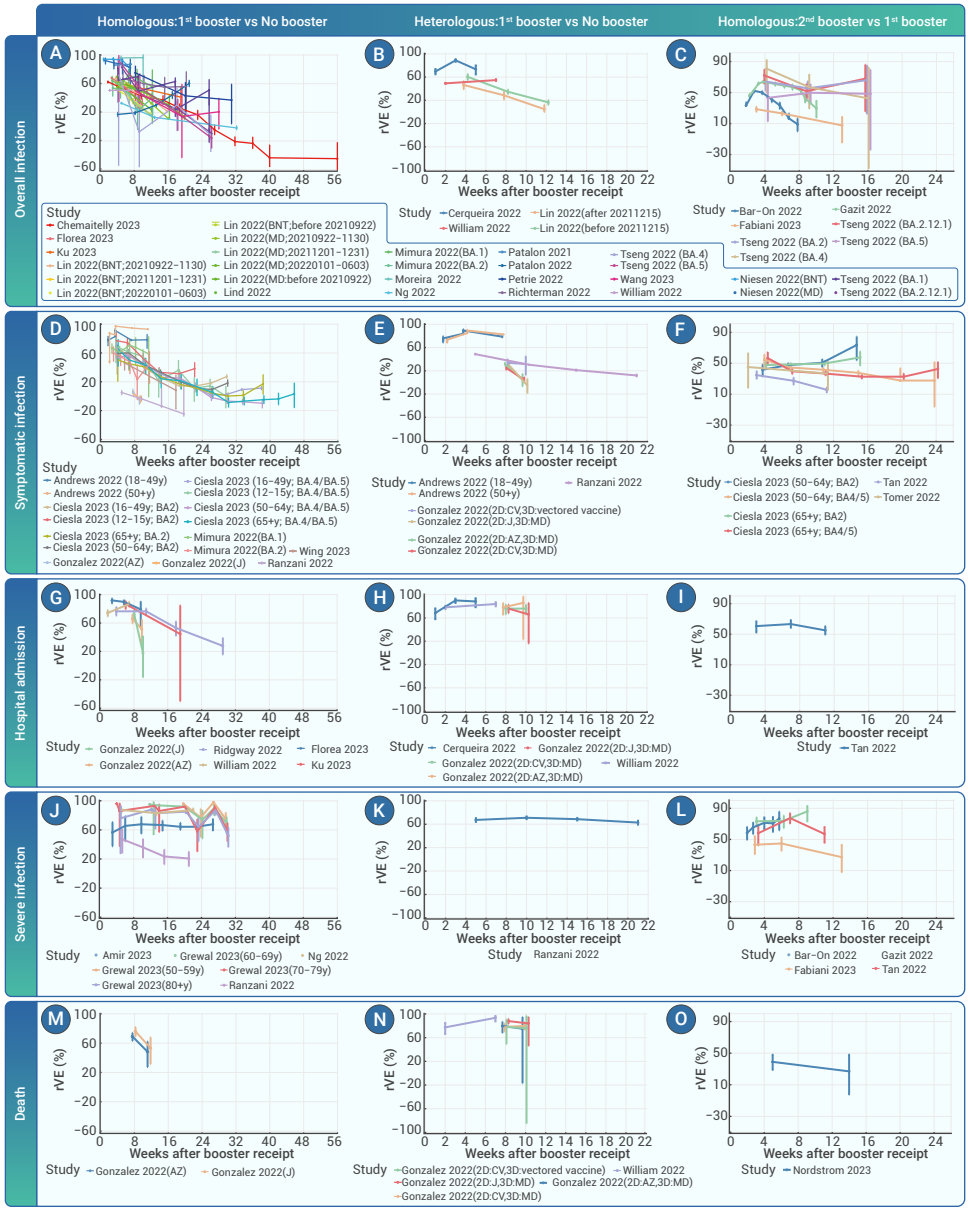

Figure 3. Changes over time in relative vaccine effectiveness of booster vaccination in preventing infections of different severities Notes: rVE, Relative vaccination effectiveness. There is no evidence for the 2nd booster compared with the 1st booster vaccination in heterologous vaccine regimens in preventing infections of different severities. Each line represents a study-specific trend. Data are represented as relative vaccine effectiveness and 95% confidence interval.

time between the 1st booster and 2nd booster doses on the rVE.

Publication bias

The Egger's tests and the funnel plots for the rVE of the 1st or 2nd booster vaccination in preventing different outcomes did not suggest obvious publication bias (Figures S4-S6).

Evidence level

The quality of evidence for the rVE against different outcomes ranged from very low to high (Tables S13-S15). The RCT demonstrated high-quality evidence. The main factors responsible for lowering the quality of the evidence in observational studies were inconsistency and imprecision.

DISCUSSION

Main findings of this study

This systematic review found that both the 1st and 2nd booster vaccinations were associated with a lower risk of mild and severe SARS-CoV-2 infections. Heterologous and homologous regimens with the 1st booster dose seemed to exhibit comparable effectiveness in preventing SARS-CoV-2 infection. The rVE of the 1st booster against Omicron variants was lower than that against Delta variants and a higher rVE was observed for mRNA vaccines than for non-mRNA vaccines. The rVE waned after the 1st booster vaccination, whereas it remained stable in the short-term period after the 2nd booster vaccination. The heterogeneity between studies may also stem from VOCs, vaccine types, previous infection status and study design. Limited evidence was available regarding the rVE of the 2nd booster vaccination in terms of the long-term durability, heterologous regimen and sources of heterogeneity.

Interpretations and implications

Our review suggested that both the 1st and 2nd booster vaccinations could provide additional protection against mild and severe SARS-CoV-2 infections. These findings aligned with those of earlier immunogenicity studies which found that the immunity of the primary vaccine series could wane over time, but booster vaccination could re-induce higher neutralizing immunity.[23,24] However, considerable heterogeneity was observed across studies, which was also noted in previous RCTs.[3] Such heterogeneity may originate mainly from the VOCs, vaccine types, prior infection status, study design and time after booster vaccination. These findings substantiated the previous hypothesis, suggesting that variability in vaccine effectiveness was likely a result of the combined impact of variations in study design, population characteristics, VOCs and duration after vaccination, as well as the types of vaccines themselves.[3]

The 1st and 2nd booster vaccinations can only additionally prevent 40-50% of Omicron-induced infections, which was much lower than their effectiveness against Delta-induced infections. The reduced effectiveness against Omicron variants was associated with multiple mutations in the receptor-binding domain of the spike protein that can lead to immune evasion, increased transmissibility and reduced response to vaccination. This reduced effectiveness could also be the result of neutralizing antibodies dampened by the SARS-CoV-2 vaccine booster.[25] Although a booster with existing vaccines could still be recommended for eligible individuals, prioritizing the development of a modified booster vaccine candidate targeting the emerging Omicron strains may enhance protection against the super-contagious Omicron family of variants.[26] However, further evidence is needed to confirm their effectiveness.

To assist in the adjustment of booster strategies, the effectiveness of homologous and heterologous booster vaccination should be determined. Although a homologous regimen has been conventionally recommended, immunogenicity studies have suggested a higher immune response to heterologous boosting regimens.[23,27,28] Additionally, heterologous regimens could serve as an alternative strategy to homologous regimens in response to fluctuations in vaccine supply.[29] However, our findings did not support the superiority of heterologous booster regimens over homologous booster regimens in terms of their real-world effectiveness. This finding aligned with a recent network meta-analysis,[8] demonstrating comparable effectiveness between heterologous and homologous three-dose regimens in preventing

Table 2. Subgroup analysis on relative vaccine effectiveness of the 1st booster versus no booster according to the homologous and heterologous vaccine regimens

Subgroup/Outcome	Between-studies comparison				Within-study comparison			
	n_{Hom} : n_{Het}	Homologous: rVE (95%CI), %	Heterologous: rVE (95%CI), %	*P*-value	n	Homologous: rVE (95%CI), %	Heterologous: rVE (95%CI), %	*P*-value
Overall infection	72: 10	66.9 (59.8, 72.7)	71.7 (50.3, 83.8)	0.602	7	63.4 (50.2, 73.2)	70.2 (40.9, 84.9)	0.107
Symptomatic infection	24: 2	75.9 (50.3, 83.8)	86.3 (-167.2, 99.3)	0.713	1	94.0 (95.0, 97.0)	97.0 (96.0, 97.0)	0.054
Hospital admission	27: 1	74.1 (66.9, 79.8)	80.6 (78.3, 82.6)	0.036	1	79.3 (76.1, 82.1)	80.6 (78.3, 82.6)	0.485
Severe infection	13: 1	86.1 (78.7, 90.9)	68.4 (52.6, 78.9)	0.101	0	NA	NA	NA
Death	18: 3	84.2 (78.3, 88.5)	85.3 (80.4, 89.0)	0.742	2	88.4 (84.9, 91.1)	85.3 (80.4, 89.0)	0.070

Notes: CI, Confidence interval; NA, Not available; rVE, Relative vaccine effectiveness. n_{Hom} and n_{Het} refer to the number of comparisons for booster vaccination with homologous and heterologous regimens respectively. n refers to the number of within-study comparisons.

SARS-CoV-2 infection. Notably, the current evidence was only applicable to homologous regimens with three doses of mRNA vaccines, adenovirus-vector vaccines and inactivated SARS-CoV-2 vaccines and to heterologous regimens with two doses of adenovirus-vector vaccines or inactivated SARS-CoV-2 vaccines plus an mRNA booster. Future research may shed light on the effectiveness of heterologous booster regimens involving other types of SARS-CoV-2 vaccines.

Current relevant studies predominantly focused on booster vaccination with mRNA vaccines, leaving non-mRNA vaccines under-represented in the actual application. The available evidence suggested that the 1st booster of homologous mRNA vaccination regimens was more effective against overall infection and death. This finding was consistent with a recent ecological study in Hong Kong, which showed that a booster with non-mRNA inactivated vaccines was less effective than mRNA vaccines against mild infection,[30] implying lower rVE with inactivated vaccines. Further evidence is required to ascertain whether vaccine type could also influence the rVE of the1st booster with a heterologous regimen and that of the 2nd booster with a homologous or heterologous regimen.

Regardless of the type of SARS-CoV-2 vaccines, the effectiveness of primary full vaccination against mild infection waned within 6 months post-vaccination, as reported in both RCTs and observational studies.[1-3] This waning effect was also noted after the 1st booster vaccination.[10,16] Although our meta-analysis suggested the 2nd booster dose may enhance the effectiveness and provide short-term stability, the duration of this protection remains uncertain due to limited evidence and short follow-up periods. Furthermore, the durability of booster vaccine effectiveness against severe outcomes remains uncertain owing to the scarcity of studies reporting these outcomes. Although the effectiveness of a booster dose against severe outcomes is likely to persist longer than that against symptomatic infections as per experience with primary vaccine series,[10] continuous monitoring of the effectiveness of booster vaccination over an extended period against SARS-CoV-2 infections of different severities is still essential for adjusting vaccination strategies.

Determining the optimal time for booster vaccination is vital for updating vaccination strategies. Current evidence could not specify the optimal timing for receiving the 1st booster because direct comparisons between the completion of primary full vaccination and the 1st booster doses were still limited, with only four studies available. These studies have reported inconsistent results, with some suggesting that a longer interval may induce a higher effectiveness whereas others suggesting the opposite. When waning effectiveness was considered, the 1st booster dose at 6th month from the completion of primary vaccination might be appropriate when the effectiveness against Omicron infection was lower than 20%.[2] No evidence on direct comparisons between the 1st and 2nd booster doses was available to support any recommendation for the optimal timing of the 2nd booster dose. By contrast, our findings showed that the rVE of the 1st booster would decrease to nearly null at 8th month after booster vaccination, suggesting this timing might be suitable for the 2nd booster. Furthermore, concerns have been raised that the administration of the 2nd booster dose within a shorter interval after the 1st booster dose could lead to a weaker immune response, potentially reducing broad protection against increasingly diverging variants.[31] Thus, there is an urgent need to determine the optimal timing for the 2nd booster vaccination before intensifying the 2nd booster dose vaccination campaign in practice.

Strengths and limitations

This is the most comprehensive assessment of all currently available evidence from RCTs and real-world studies regarding the rVE of the 1st booster vaccination to prevent SARS-CoV-2 infection. Additionally, it was the first to summarize the evidence for the rVE of the 2nd booster vaccination. In comparison to previous meta-analyses, our assessment of rVE took account for different vaccine regimens (homologous or heterologous), time intervals after booster vaccination and various potential sources of heterogeneity.

Our study has some limitations. First, the current evidence on the rVE of SARS-CoV-2 booster vaccination primarily came from observational studies rather than from RCTs. The limitations that originated in the primary individual studies may have affected our results, such as residual confounding (e.g., behavioral differences and coexisting conditions), the lack of stringent surveillance testing for SARS-CoV-2 infection, partial coverage of the study population for nucleic acid testing and the lack of standardized definitions of severe infections across studies. Confounding and detection bias should be reduced in future studies for more rigorous assessment of the rVE. Second, a notable heterogeneity existed in the effect estimates for preventing of SARS-CoV-2 infections. However, our analysis identified certain factors that may partially account for heterogeneity, such as duration after vaccination, vaccine type and VOCs. Third, some subgroup analysis and meta-regression may have low power to detect statistically significant associations when there was a small number of included studies. Fourth, existing evidence was unable to fully resolve some crucial issues, such as the prolonged waning of the rVE and the optimal timing of the 1st and 2nd booster vaccinations.

CONCLUSION

Both the 1st and 2nd booster vaccinations provided additional protection against mild SARS-CoV-2 infections and severe infections, although the heterogeneity in protection was large. The protection provided by the 1st booster dose against Omicron variants was significantly lower than that against Delta variants. Furthermore, mRNA vaccines exhibited a higher rVE compared with non-mRNA vaccines. The rVE waned over time following the 1st booster dose but demonstrated stability in the short period after the 2nd booster dose. Current evidence supported the recommendation for booster vaccination. The rVE of the 2nd booster, including heterologous vaccination, its durability and the sources of heterogeneity, still remains uncertain. Additional studies are needed to evaluate the longevity of the rVE over an extended period and optimize the timing and regimens of the 1st and 2nd booster vaccinations.

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AUTHOR CONTRIBUTIONS

JLT, ZRY, and FS conceived the research question and designed the study. ZRY, DL and YWJ conducted the literature search. DL, YWJ, SYW, FXL, TFL, BLL, ZYZ, YXJ, and FS screened articles. DL, YWJ, SYW, FXL, TFL and QPY read the full texts for eligibility. DL, YWJ, SYW, FXL, BLL, QPY and TFL extracted data from the original trials. DL, NNP, JXC and SYW evaluated the risk of bias and quality of evidence. ZRY solved any discrepancies in study selection and data extraction. DL, YWJ, SYW, and ZRY performed the analyses and evaluated quality of evidence. JLT, FS, ZYY, ZRY, DL, YWJ, YXJ contributed to the interpretation of the results. DL, YWJ and SYW wrote the first draft of the manuscript. JLT, ZRY, FS and ZYY critically revised the manuscript. All authors acknowledge full responsibility for the analyses and interpretation of the report. All authors have read and approved the final manuscript. JLT is the guarantor. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DECLARATION OF INTERESTS

Jinling Tang, as The Innovation Medicine Editorial Board members, were not involved in the manuscript's review or decision. Peer review was conducted independently. The other authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

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This systematic review was registered in the International ProspectiveRegister of Systematic Reviews (PROSPERO registration number: CRD42022347249). Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

SUPPLEMENTAL INFORMATION

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