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Protection of the third-dose and fourth-dose mRNA vaccines against SARS-CoV-2 Omicron subvariant: a systematic review and meta-analysis

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ABSTRACT

Objectives The rapid spread of the SARS-CoV-2 Omicron variant has raised concerns regarding waning vaccine-induced immunity and durability. We evaluated protection of the third-dose and fourth-dose mRNA vaccines against SARS-CoV-2 Omicron subvariant and its sublineages.

Design Systematic review and meta-analysis.

Data sources Electronic databases and other resources (PubMed, Embase, CENTRAL, MEDLINE, CINAHL PLUS, APA PsycINFO, Web of Science, Scopus, ScienceDirect, MedRxiv and bioRxiv) were searched until December 2022.

Study eligibility criteria We included studies that assessed the effectiveness of mRNA vaccine booster doses against SARS-CoV-2 infection and severe COVID-19 outcomes caused by the subvariant.

Data extraction and synthesis Estimates of vaccine effectiveness (VE) at different time points after the third-dose and fourth-dose vaccination were extracted. Random-effects meta-analysis was used to compare VE of the third dose versus the primary series, no vaccination and the fourth dose at different time points. The certainty of the evidence was assessed by Grading of Recommendations, Assessments, Development and Evaluation approach.

Results This review included 50 studies. The third-dose VE, compared with the primary series, against SARS-CoV-2 infection was 48.86% (95% CI 44.90% to 52.82%, low certainty) at ≥14 days, and gradually decreased to 38.01% (95% CI 13.90% to 62.13%, very low certainty) at ≥90 days after the third-dose vaccination. The fourth-dose VE peaked at 14–30 days (56.70% (95% CI 50.36% to 63.04%), moderate certainty), then quickly declined at 61–90 days (22% (95% CI 6.40% to 37.60%), low certainty). Compared with no vaccination, the third-dose VE was 75.84% (95% CI 40.56% to 111.12%, low certainty) against BA.1 infection, and 70.41% (95% CI 49.94% to 90.88%, low certainty) against BA.2 infection at ≥7 days after the third-dose vaccination. The third-dose VE against hospitalisation remained stable over time and maintained 79.30% (95% CI 58.65% to 99.94%, moderate certainty) at 91–120 days. The fourth-dose VE up to 60 days was 67.54% (95% CI 59.76% to 75.33%, moderate certainty) for hospitalisation and 77.88% (95% CI 72.55% to 83.21%, moderate certainty) for death.

Conclusion The boosters provided substantial protection against severe COVID-19 outcomes for at least 6 months, although the duration of protection remains uncertain, suggesting the need for a booster dose within 6 months of the third-dose or fourth-dose vaccination. However, the certainty of evidence in our VE estimates varied from very low to moderate, indicating significant heterogeneity among studies that should be considered when interpreting the findings for public health policies.

PROSPERO registration number CRD42023376698.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We evaluated the certainty of the evidence by the Grading of Recommendations, Assessments, Development and Evaluation approach for SARS-CoV-2 infection, symptomatic infection, hospitalisation and death outcomes caused by the Omicron subvariant.

⇒ Adhering to stringent methodology, we searched a range of electronic databases and other resources without any restrictions, and used the Risk of Bias in Non-randomised Studies of Interventions tool for assessing the quality of the case–control or cohort studies.

⇒ With robust analytical approaches, we rigorously assessed vaccine effectiveness (VE) at specific time periods and open-ended time points since booster vaccination to minimise bias and to provide more accuracy of the estimates.

⇒ Most of our pooled estimates were based on a limited number of studies with a 6-month follow-up after the last booster vaccination; therefore, the impact of waning booster dose VE beyond these periods are unknown.

INTRODUCTION

The SARS-CoV-2 Omicron variant (B.1.1.529) was reported as a variant of concern on 26 November 2021 by the WHO.[1] The SARS-CoV-2

Omicron variant carries over 34 mutations in the spike protein and has an increased capacity to escape immunity and cause reinfections or breakthrough infections.[2 3] Since its emergence, the Omicron variant has continued to evolve genetically and antigenically with an expanding range of sublineages such as BA.4 or BA.5 and has largely replaced all other variants globally, accounting for over 98% of publicly available sequences.[4]

Globally, vaccination has been considered a key public health intervention to control SARS-CoV-2 infections and cases of severe COVID-19. The first mass vaccination programme began in early December 2020, and over 13 billion vaccine doses have been administered worldwide as of 22 March 2023.[5] Based on available data on safety and efficacy, the WHO recommends several types of COVID-19 vaccines for emergent use, such as mRNA vaccines (BNT162b2, mRNA-1273), viral vector vaccines (ChAdOx1-S, Ad26.COV2) or other inactivated vaccines.[5] The pace of vaccine development was unprecedented, and early vaccine effectiveness (VE) studies demonstrated a high VE for both mRNA vaccines.[6 7] Although the primary series of mRNA vaccines greatly reduces the risk of SARS-CoV-2 infection and severe COVID-19 outcomes, protection against infection starts to wane within a few months of administration.[8–11] Further studies have reported that a booster dose administered at least 5 months after the primary series of mRNA vaccines restores protection against SARS-CoV-2 infection and severe COVID-19 outcomes,[12–14] and thus many countries have recommended booster doses 3–6 months after the primary series vaccination.[15]

Although booster doses of BNT162b2 and mRNA-1273 vaccines are widely administered to prevent severe COVID-19 outcomes and SARS-CoV-2 infection, the rapid spread of novel SARS-CoV-2 Omicron variant and its sublineages has raised concerns about waning vaccine-induced immunity and its durability. Recent evidence has shown a rapid decline in antibody titres over time following booster doses of mRNA vaccines.[16] Several systematic reviews of COVID-19 vaccine efficacy and effectiveness, with or without meta-analyses, have been published[11 17–22]; however, none have assessed the magnitude and duration of protection conferred by booster doses of mRNA vaccines, particularly for the fourth dose, for a comprehensive range of COVID-19 outcomes caused by the Omicron subvariant and its sublineages. To address this dearth of evidence, we aimed to conduct a systematic review and meta-analysis to assess the magnitude and duration of the protective effectiveness of the third dose versus the primary series and no vaccination, and the fourth dose against SARS-CoV-2 infection and severe COVID-19 outcomes caused by the Omicron subvariant and its sublineages, such as BA.1 and BA.2.

METHODS

Review registration and guidelines

The review protocol was registered in the 'International Prospective Register for Systematic Reviews' (PROSPERO) database (CRD42023376698).[23] To carry out this review, we followed the Cochrane guideline[24] and the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline[25] for reporting this systematic review and meta-analysis.

Search strategy

Using an extensive search strategy described in online supplemental table 1, we searched the following electronic databases from the inception of the COVID-19 pandemic to December 2022: PubMed, Embase, CENTRAL, MEDLINE, CINAHL PLUS, APA PsycINFO, Web of Science, Scopus and ScienceDirect. The primary search terms included but were not limited to the following keywords: COVID-19, Omicron, mRNA booster doses, BNT162b2, mRNA-1273, vaccine effectiveness, cross-sectional studies, case–control studies, retrospective or prospective cohort studies, and randomised controlled trials (RCTs). We did not limit the search by date, language or publication type to avoid missing published studies. Furthermore, we checked the reference lists of all included studies and relevant systematic reviews, including preprint servers (MedRxiv and bioRxiv) and citation tracking, to identify additional potential studies that were not captured by the above searches. For preprint studies, we reviewed peer-reviewed publications when available.

Eligibility criteria

The detailed study eligibility criteria were provided in the appendix (online supplemental table 2). In summary, we included real-world VE studies that assessed the effectiveness of mRNA vaccine booster doses (BNT162b2 and mRNA-1273) against SARS-CoV-2 infection and severe COVID-19 outcomes caused by the Omicron subvariant and its sublineages. We excluded clinical trials because VE measures how well vaccines work in real-world settings outside of a clinical trial.[26]

Study selection, data extraction and risk of bias assessment

Pairs of independent reviewers (MOR, FY, MMT, RH, MRI, JKMS, MS-F and TK) assessed the eligibility of the studies and extracted data from the included studies. Estimated VE at different time points after the third-dose and fourth-dose vaccination were extracted. Else, we calculated VE as one minus estimated ratio (ie, OR, risk ratio, incidence rate ratio and HR), which was estimated in studies then multiplied by 100. The associated 95% CIs for VE estimates were calculated using the recommendations for the use of Taylor expansion (the Delta method) for estimates of vaccine efficacy.[27] We planned to review and extract data from non-English studies with the assistance of our colleagues who are native speakers of the languages or English translator if required. Furthermore, we planned to use the Cochrane Collaboration Risk of Bias Assessment Tool to evaluate the risk of bias in the RCTs[28] and the Risk of Bias in Non-randomised Studies of Interventions tool for case–control or cohort studies[29]; however, we did not find any RCT in this review.

Disagreements were resolved through discussion or by a third reviewer, when required.

Data analysis

We narratively synthesised the study, participant and vaccination characteristics, and the principal findings of the included studies. Descriptive statistics were used to summarise study-level demographics. A pairwise random-effects meta-analysis was performed to pool data on VE against SARS-CoV-2 infection, symptomatic infection, hospitalisation, intensive care unit (ICU) admission, emergency department/urgent care (ED/UC) visit, oxygen support, mechanical ventilation and death due to the Omicron subvariant or its sublineages. The restricted maximum likelihood method was used for random-effects estimation. We compared the VE of the third dose versus the primary series, no vaccination and the fourth dose for each outcome at different time points after booster vaccination. We rigorously assessed VE at specific time periods (eg, 7–13, 14–30, 31–60, 61–90, 91–120, 121–150 and 151–180 days) and open-ended time points since booster vaccination (eg, ≥7, ≥14, ≥30, ≥60, ≥90, ≥120 and ≥150 days). Furthermore, we performed a subgroup analysis of adolescents (10–19 years old) and older adults (≥60 years old) and sublineages of the Omicron subvariant (BA.1 and BA.2) when multiple VE estimates were reported. We assessed heterogeneity between studies by visual inspection of forest plots, and tested statistically by tau-square statistic, quantifying with the value of I^2 and considered an I^2 value >50% to indicate substantial heterogeneity.[24] Publication bias was assessed using Funnel plots and Egger's tests. We applied the trim-and-fill method to estimate the effect of potentially missing studies leading to publication bias and adjusted the overall effect estimate accordingly. Statistical significance was defined as a $p<0.05$ for all analyses. Furthermore, we evaluated the certainty of evidence for estimates of our four main outcomes (SARS-CoV-2 infection, symptomatic infection, hospitalisation and death) using the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) system.[30]

Patient and public involvement

The patient and public were not involved in the design, conduct and reporting of this study, nor in the dissemination of its findings. As the study was a systematic review and meta-analysis, all data included were derived solely from publicly accessible evidence.

RESULTS

Of 17 267 non-duplicate records, 50 studies[12 31–79] were identified for this review after assessing the predefined study eligibility criteria (figure 1). Among them, 28 were case–control studies and 22 were cohort studies with national, subnational or hospital/medical centre/nursing home settings (online supplemental table 3). Most studies were conducted in the USA (19), Israel (8) and the UK (6). Three studies included healthcare personnel or front-line healthcare workers, while the others covered the general population of all ages, including children, adolescents and older adults. Most studies assessed VE against SARS-CoV-2 infection (25 studies), hospitalisation (20 studies), symptomatic infection (17 studies), death (8 studies), ED/UC visits (3 studies), oxygen support (2 studies), ICU admission (1 study) and mechanical

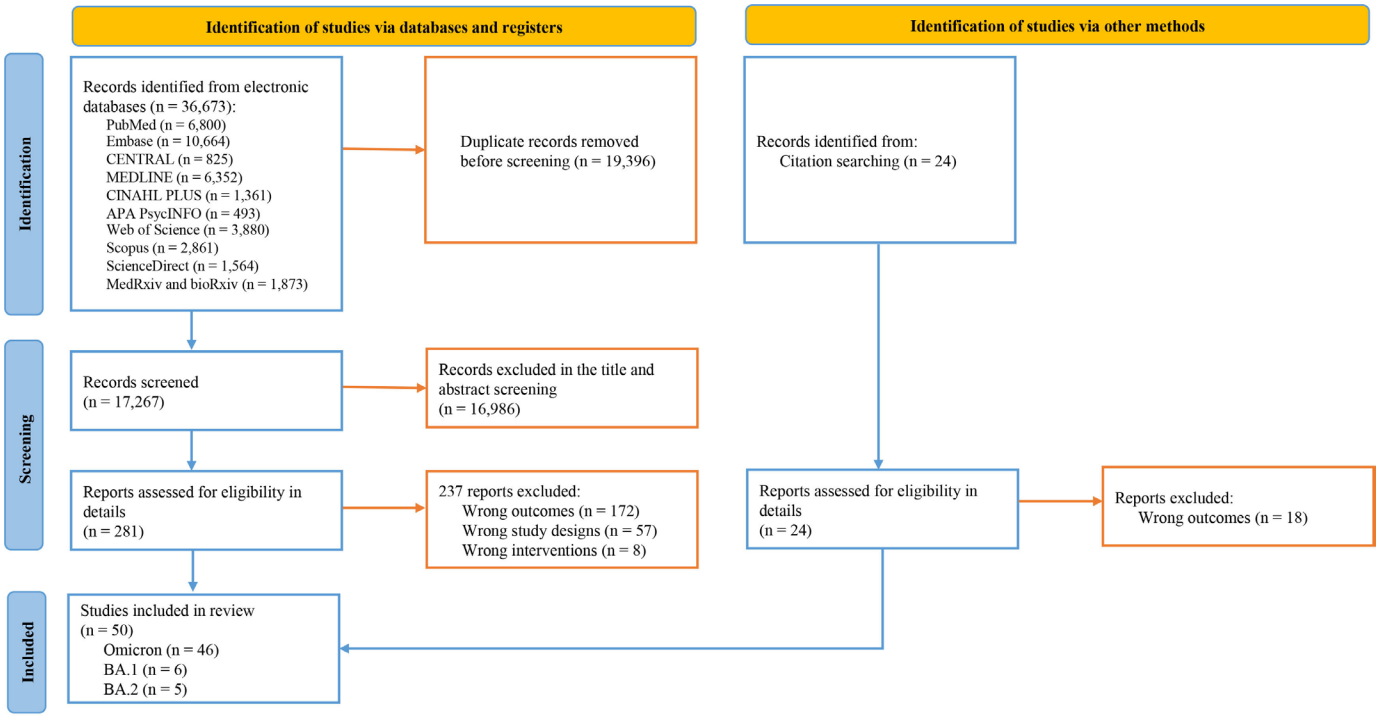

Figure 1 Study flow chart.

ventilation (1 study). The studies compared the VE of the third dose versus the primary series, no vaccination and the fourth dose for outcomes at different time points and periods. The risk of bias in the included studies is presented in online supplemental table 4.

Protection of third-dose mRNA vaccines against SARS-CoV-2 Omicron subvariant: compared with the primary series

Eighteen studies[12 31 32 35 38 46 47 62–69 72 73 78] compared VE of the third-dose with the primary series of mRNA vaccines against SARS-CoV-2 infection and its severe outcomes. Among these, 11 studies[12 35 38 62 64–66 69 72 73 78] reported VE against SARS-CoV-2 infection at different time periods or points after booster dose vaccination. Our pooled estimates revealed that, compared with the primary series, the third dose exhibited a VE against SARS-CoV-2 infection of 42.11% (95% CI 32.84% to 51.37%, I^2=98.43%, low certainty), 48.86% (95% CI 44.90% to 52.82%, I^2=95.79%, low certainty) and 38.01% (95% CI 13.90% to 62.13%, I^2=68.14%, very low certainty) at ≥7, ≥14 and ≥90 days after the third dose of vaccination, respectively. It peaked at ≥30 days after the third-dose vaccination (VE 59.40% (95% CI 55.10% to 63.70%), moderate certainty), and gradually declined to 16% (95% CI 12.40% to 19.60%, low certainty) at ≥150 days (table 1, figure 2). For older people aged ≥60 years, the third-dose VE against SARS-CoV-2 infection was 41.81% (95% CI 25.28% to 58.33%, I^2=98.51%, very low certainty) at ≥7 days after the third-dose vaccination (table 1, online supplemental figure 1).

Seven studies[31 32 46 47 65 67 73] assessed third-dose VE against symptomatic infections, and it was higher than the primary series. The pooled VE against symptomatic infection was 58.24% (95% CI 50.24% to 66.07%, I^2=54.04%) at 7–13 days, which remained almost stable until 31–60 days after the third-dose vaccination (table 1, online supplemental figures 2 and 3).

Four studies assessed third-dose VE against hospitalisation.[38 46 47 66] Compared with the primary series, the third-dose VE against hospitalisation was higher, with an estimated VE of 65.35% (95% CI 53.10% to 77.60%, I^2=96.26%, moderate certainty) at ≥7 days after the third-dose vaccination. For older adults, the third-dose VE at ≥7 days was 74.25% (95% CI 59.02% to 89.49%, I^2=96.56%, moderate certainty) against hospitalisation (table 1, online supplemental figures 4 and 5).

Two studies[38 68] showed a higher VE against oxygen support for the third dose than for the primary series of mRNA vaccines. The third-dose VE against oxygen support was 88% (95% CI 80% to 88%) at >60 days after the third dose. Another study[38] assessed the VE of the third dose relative to the primary series against mechanical ventilation and reported a VE of 31% (95% CI 30% to 64%) at 7 days after the third dose of vaccination.

Only two studies[38 66] reported the VE of the third dose versus the primary series of mRNA vaccines against death. One study reported 27% VE (95% CI 25.50% to 79.50%) 7 days after the third dose of vaccination among people of all ages, while another study found a 77.79% VE (95% CI 69.39% to 86.19%) of the third dose compared with the primary series of mRNA vaccines against death outcome among older people at 7–120 days. The pooled VE of the third dose against death was 76.52% (95% CI 68.23% to 84.82%, I^2=0%, moderate certainty) (table 1, online supplemental figure 6). However, no study has reported ICU admission and ED/UC visit outcomes for this comparison.

Protection of third-dose mRNA vaccines against SARS-CoV-2 Omicron subvariant: compared with no vaccination

Thirty-one studies[32–36 38 41–45 48 50 51 53–57 59 61 65 66 70 71 74–79] compared VE of third-dose mRNA vaccines with the outcome under no vaccination against SARS-CoV-2 infection and its severe outcomes. Of these, 13 studies[35 38 42 53 54 59 61 65 66 70 77–79] reported a third-dose VE against SARS-CoV-2 infection for different periods or points after the third-dose vaccination. All studies showed a higher third-dose VE compared with the outcome under no vaccination against SARS-CoV-2 infection, irrespective of the time after the third-dose vaccination. The pooled VE of third-dose mRNA vaccines against SARS-CoV-2 infection was 76.17% (95% CI 61.79% to 90.5%6, I^2=92.69%, moderate certainty), 52.07% (95% CI 41.62% to 62.53%, I^2=99.72%, moderate certainty), 60.42% (95% CI 51.97% to 68.86%, I^2=98.86%, moderate certainty), 51.07% (95% CI 46.27% to 55.86%, I^2=60.10%, moderate certainty), 44.46% (95% CI 30.46% to 58.46%, I^2=95.15%, low certainty) and 52.34% (95% CI 48.28% to 56.41%, I^2=0%, moderate certainty) at ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days and ≥120 days after the third dose of vaccination, respectively (table 1, online supplemental figure 7). A similar trend in third-dose VE against SARS-CoV-2 infection was observed in older adults (online supplemental figure 8). The VE of third-dose mRNA vaccines was 75.84% for BA.1 infection (95% CI 40.56% to 111.12%, I^2=98.62%, low certainty) and 70.41% (95% CI 49.94% to 90.88%, I^2=88.87%, low certainty) against BA.2 infection at ≥7 days after the third-dose vaccination (table 1, online supplemental figure 9).

Thirteen studies[32–34 36 44 45 48 51 54 55 71] assessed the VE of third-dose mRNA vaccines against symptomatic infection compared with the outcome under no vaccination. The pooled VE estimates indicated that the third-dose VE against symptomatic infection peaked at ≥14 days after the third-dose vaccination (VE 66.94% (95% CI 63.75% to 70.14%), I^2=98.27%, moderate certainty), and then gradually decreased to 40.58% (95% CI 34.39% to 46.74%, I^2=97.04%, low certainty) at ≥120 days (table 1, online supplemental figure 10). However, the third dose of VE against symptomatic infection remained stable over time when considering specific time periods after the third-dose vaccination, and an almost similar VE was observed for adolescents and older adults. A similar trend of third-dose VE against symptomatic BA.1 and BA.2 infection was observed (online supplemental figures 11–15).

Table 1 Summary of findings

Population	Outcome	SARS-CoV-2 variant	Time after the last dose vaccination	No of studies	VE (95% CI)	GRADE/certainty of evidence	Reasons for upgrading or downgrading GRADE
Comparison: third dose versus primary series of mRNA vaccines							
All aged population	SARS-CoV-2 infection	Omicron	≥7 days	5 studies	42.11 (32.84 to 51.37)	Low	*†
			≥14 days	6 studies	48.86 (44.90 to 52.82)	Low	*†
			≥30 days	1 study	59.40 (55.10 to 63.70)	Moderate	*§**
			≥60 days	1 study	43.20 (38.40 to 48.00)	Low	*§
			≥90 days	2 studies	38.01 (13.90 to 62.13)	Very low	*†§
			≥120 days	1 study	18.30 (15.30 to 21.30)	Low	*§
			≥150 days	1 study	16 (12.40 to 19.60)	Low	*§
Older people (≥60 years)	SARS-CoV-2 infection	Omicron	≥7 days	2 studies	41.81 (25.28 to 58.33)	Very low	*†§
People aged ≥50 years	Symptomatic infection	Omicron	≥7 days	2 studies	75.26 (54.84 to 95.67)	Low	*†§**
			≥14 days	1 study	57 (52 to 62)	Moderate	*§**
All aged population	Hospitalisation	Omicron	≥7 days	4 studies	65.35 (53.10 to 77.60)	Moderate	*†**
Older people (≥60 years)	Hospitalisation	Omicron	≥7 days	2 studies	74.25 (59.02 to 89.49)	Moderate	*†**
All aged population	Death	Omicron	Overall (7–120 days)	2 studies	76.52 (68.23 to 84.82)	Moderate	*§**
Comparison: third dose mRNA vaccines versus no vaccination							
All aged population	SARS-CoV-2 infection	Omicron	≥7 days	4 studies	76.17 (61.79 to 90.56)	Moderate	*†**
			≥14 days	8 studies	52.07 (41.62 to 62.53)	Moderate	*†**
			≥30 days	3 studies	60.42 (51.97 to 68.86)	Moderate	*†**
			≥60 days	2 studies	51.07 (46.27 to 55.86)	Moderate	*†**
			≥90 days	2 studies	44.46 (30.46 to 58.46)	Low	*†
			≥120 days	2 studies	52.34 (48.28 to 56.41)	Moderate	***
Older people (≥60 years)	SARS-CoV-2 infection	Omicron	≥7 days	1 study	90.40 (79.62 to 101.18)	Moderate	*§**
			≥14 days	4 studies	54.07 (45.08 to 63.07)	Moderate	*†**
			≥30 days	1 study	54.40 (52.75 to 56.05)	Moderate	*§**
			≥60 days	1 study	57.90 (56.15 to 59.65)	Moderate	*§**
			≥90 days	2 studies	46.71 (28.10 to 65.33)	Very low	*†§
			≥120 days	1 study	53.20 (49.70 to 56.70)	Moderate	*§**
All aged population	SARS-CoV-2 infection	BA.1	Overall (≥7 days)	2 studies	75.84 (40.56 to 111.12)	Low	*†**§
All aged population	SARS-CoV-2 infection	BA.2	Overall (≥7 days)	2 studies	70.41 (49.94 to 90.88)	Low	*†§**
All aged population	Symptomatic infection	Omicron	≥7 days	6 studies	56.37 (51.07 to 61.67)	Moderate	*†**
			≥14 days	6 studies	66.94 (63.75 to 70.14)	Moderate	*†**
			≥30 days	3 studies	52.10 (45.19 to 59.02)	Moderate	*†**
			≥60 days	4 studies	51.18 (41.03 to 61.33)	Moderate	*†**

Continued

Table 1 Continued

Population	Outcome	SARS-CoV-2 variant	Time after the last dose vaccination	No of studies	VE (95% CI)	GRADE/certainty of evidence	Reasons for upgrading or downgrading GRADE
			≥90 days	2 studies	44.33 (22.41 to 66.26)	Very low	*†§
			≥120 days	1 study	40.56 (34.39 to 46.74)	Low	*§
Adolescent aged 12–17 years	Symptomatic infection	Omicron	Overall (≥7 days)	2 studies	68.07 (59.66 to 76.48)	Moderate	*†**
Older people (≥60 years)	Symptomatic infection	Omicron	Overall (≥7 days)	2 studies	54.96 (49.58 to 60.35)	Moderate	*§**
All aged population	Symptomatic infection	BA.1	≥7 days	3 studies	61.75 (54.92 to 68.58)	Moderate	*†**
			≥14 days	1 study	68.70 (67.95 to 69.45)	Moderate	*§**
			≥30 days	2 studies	51.05 (35.12 to 66.99)	Low	*†§**
			≥60 days	1 study	53 (51.95 to 54.05)	Moderate	*§**
			≥120 days	1 study	37.4 (35.8 to 39.0)	Low	*§
All aged population	Symptomatic infection	BA.2	≥7 days	3 studies	53.09 (41.16 to 65.02)	Moderate	*†**
			≥14 days	1 study	74.1 (72.9 to 75.3)	Moderate	*§**
			≥30 days	2 studies	50.20 (32.82 to 67.58)	Low	*†§**
			≥60 days	1 study	59.4 (58.5 to 60.3)	Moderate	*§**
			≥120 days	1 study	43.7 (42.3 to 45.1)	Low	*§
All aged population	Hospitalisation	Omicron	7–13 days	3 studies	82.07 (73.76 to 90.38)	Moderate	*†**
			14–30 days	4 studies	88.71 (82.32 to 95.10)	Moderate	*†**
			31–60 days	3 studies	88.35 (81.61 to 95.10)	Moderate	*†**
			61–90 days	4 studies	82.79 (75.77 to 89.81)	Moderate	*†**
			91–120 days	1 study	79.30 (58.65 to 99.94)	Moderate	*§**
Older people (≥60 years)	Hospitalisation	Omicron	≥7 days	1 study	92.30 (81.70 to 102.90)	Moderate	*§**
			≥14 days	4 studies	89.04 (83.74 to 94.33)	Moderate	*§
			≥30 days	2 studies	92.24 (83.09 to 101.39)	Moderate	*†**
			≥60 days	2 studies	89.74 (80.05 to 99.43)	Moderate	*†**
			≥90 days	3 studies	80.15 (67.35 to 92.95)	Moderate	*†**
			≥120 days	1 study	83.30 (78.05 to 88.55)	Moderate	*§**
All aged population	Death	Omicron	≥14 days	4 studies	86.57 (79.07 to 94.08)	Moderate	*†**
Comparison: fourth-dose versus third-dose of BNT162b2 vaccine							
Older people (≥60 years)	SARS-CoV-2 infection	Omicron	7–13 days	2 studies	35.36 (–8.41 to 79.12)	Very low	*†§
			14–30 days	3 studies	56.70 (50.36 to 63.04)	Moderate	*†**
			31–60 days	2 studies	34.56 19.89 to 49.23)	Very low	*†§
			61–90 days	1 study	22 (6.40 to 37.60)	Low	*§
	Symptomatic infection	Omicron	≥7 days	2 studies	43.56 (20.07 to 67.06)	Very low	*†§
			≥14 days	1 study	61 (58 to 64)	Moderate	*§**

Continued

Table 1 Continued

Population	Outcome	SARS-CoV-2 variant	Time after the last dose vaccination	No of studies	VE (95% CI)	GRADE/certainty of evidence	Reasons for upgrading or downgrading GRADE
	Hospitalisation	Omicron	Overall (14–60 days)	2 studies	67.54 (59.76 to 75.33)	Moderate	*†**
	Death	Omicron	Overall (14–60 days)	2 studies	77.88 (72.55 to 83.21)	Moderate	***

High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: Any estimate of effect is very uncertain.
*Risk of bias.
†Inconsistency.
‡Indirectness.
§Imprecision.
¶Publication bias.
**Large effect.
††Plausible confounding.
‡‡Dose response gradient.
GRADE, Grading of Recommendations, Assessments, Developments and Evaluation; VE, vaccine effectiveness.

Twelve studies[38 50 53 55 59 61 66 71 74 76 77 79] reported the VE of third-dose mRNA vaccines against hospitalisation and showed a higher VE compared with the outcome under no vaccination. The third-dose VE against hospitalisation remained stable over time and retained 79.30% (95% CI 58.65% to 99.94%, I^2=88.10%, moderate certainty) at 91–120 days after the third dose vaccination (table 1, figure 3). A similar VE against hospitalisation was observed in older individuals (online supplemental figure 16).

Five studies[38 56 59 66 79] reported the VE of third-dose mRNA vaccines against death relative to no vaccination. The pooled VE was 86.57% (95% CI 79.07% to 94.08%, I^2=94.46%, moderate certainty) against death at ≥14 days after the third-dose vaccination (table 1, online supplemental figure 17). One study[38] showed a higher VE of third-dose mRNA vaccines, compared with no vaccination, against oxygen support (VE 66% (95% CI 31% to 83%)) and mechanical ventilation (VE 34% (95% CI 51% to 71%)) due to the Omicron subvariant 7 days after the third-dose vaccination. Another study[68] reported a higher VE of third-dose mRNA vaccines, when compared with the outcome in unvaccinated individuals and in those with prior infection, against ICU admission at ≤60 days (VE 83% (95% CI 75% to 89%) and >60 days (VE 60% (95% CI 37% to 74%)) after the third dose.

Three studies[50 57 76] assessed the VE of third-dose mRNA vaccines against ED/UC visits due to the Omicron subvariant. Compared with unvaccinated individuals, the third-dose VE against ED/UC visits was 84.60% (95% CI 79.71% to 89.50%, I^2=91.15%) ≥14 days after the third-dose vaccination, and retained 31% VE (95% CI 28% to 90%) ≥150 days after the booster dose (online supplemental figure 18).

Protection of fourth-dose mRNA vaccines against SARS-CoV-2 Omicron subvariant: compared with the third dose

Nine studies evaluated the VE of the fourth dose compared with the third dose of mRNA vaccines but only among older people (≥60 years).[37 40 43 49 52 54 56 58 60] Six studies assessed VE against SARS-CoV-2 infection at different time points after the last booster dose.[40 52 54 56 58 60] Most of them estimated the VE of the BNT162b2 vaccine against SARS-CoV-2 infection; however, two studies[54 56] assessed the VE of mixed doses of BNT162b2 and mRNA-1273 vaccines. All studies showed a higher VE for the fourth dose than for the third dose of mRNA vaccines against SARS-CoV-2 infection, regardless of the time since the last booster dose vaccination. Our meta-analysis estimates indicated that the fourth-dose VE against SARS-CoV-2 infection peaked at 14–30 days (VE 56.70% (95% CI 50.36% to 63.04%), I^2=98.02%, moderate certainty) and then decreased at 61–90 days after the last booster dose vaccination (VE 22% (95% CI 6.40% to 37.60%), low certainty) (table 1, figure 4). A similar trend was observed when we pooled the data considering open-end time points since the last booster dose vaccination (online supplemental figure 19).

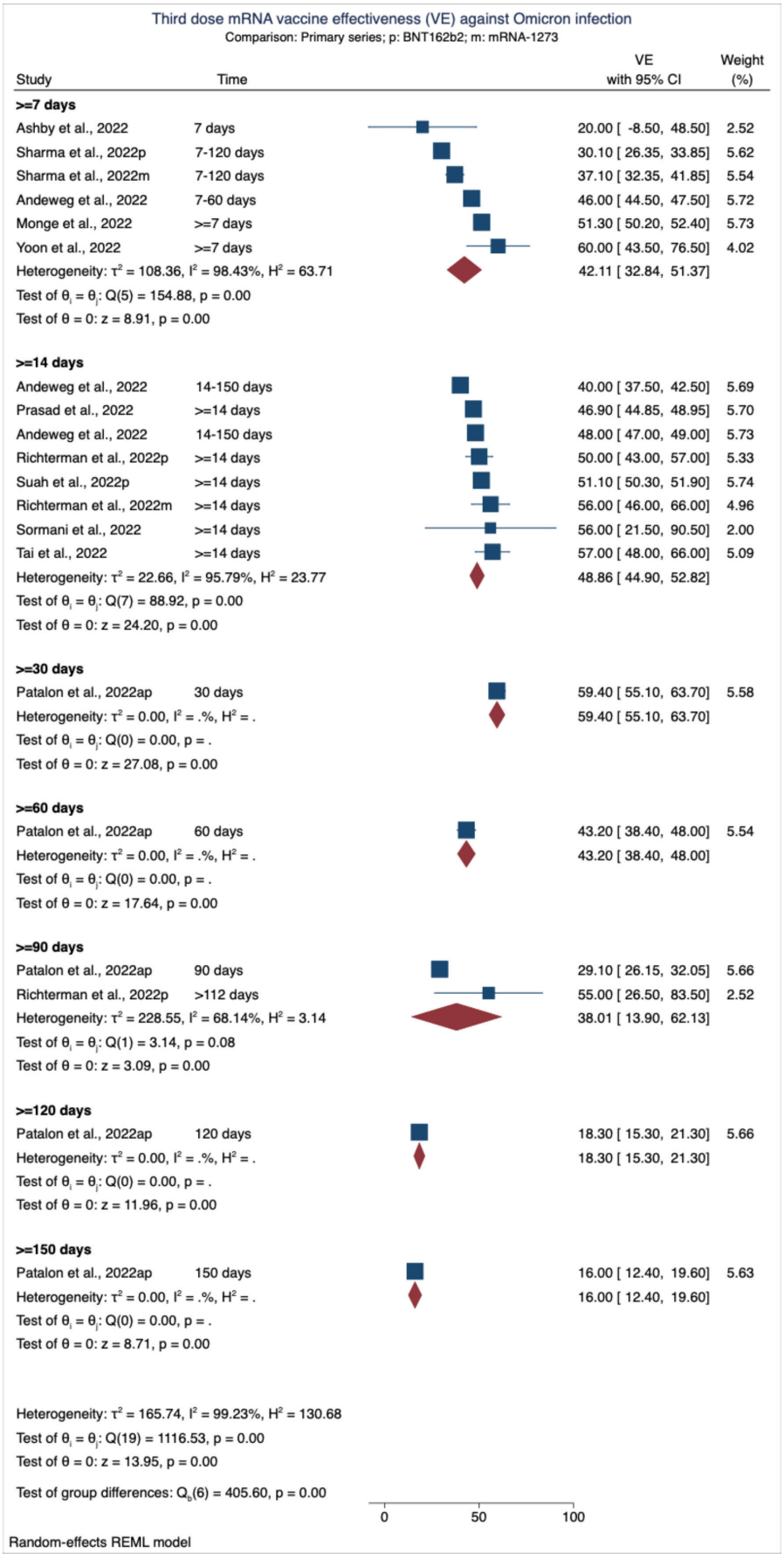

Figure 2 Third-dose mRNA vaccine effectiveness (VE) against SARS-CoV-2 infection due to Omicron variant, compared with the primary series. REML, Restricted maximum likelihood.

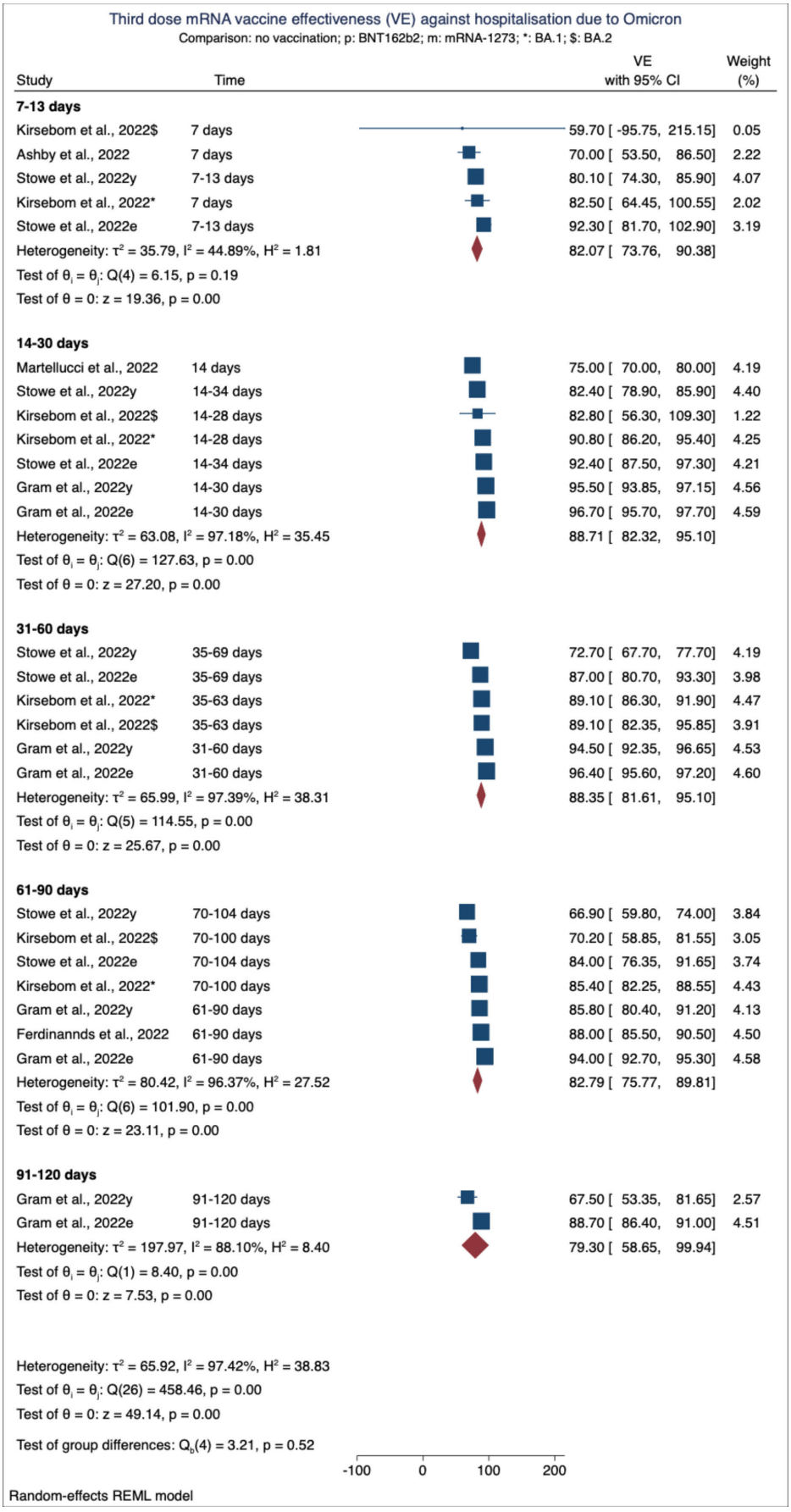

Figure 3 Third-dose mRNA vaccine effectiveness (VE) against hospitalisation due to Omicron variant, compared with no vaccination. REML, Restricted maximum likelihood.

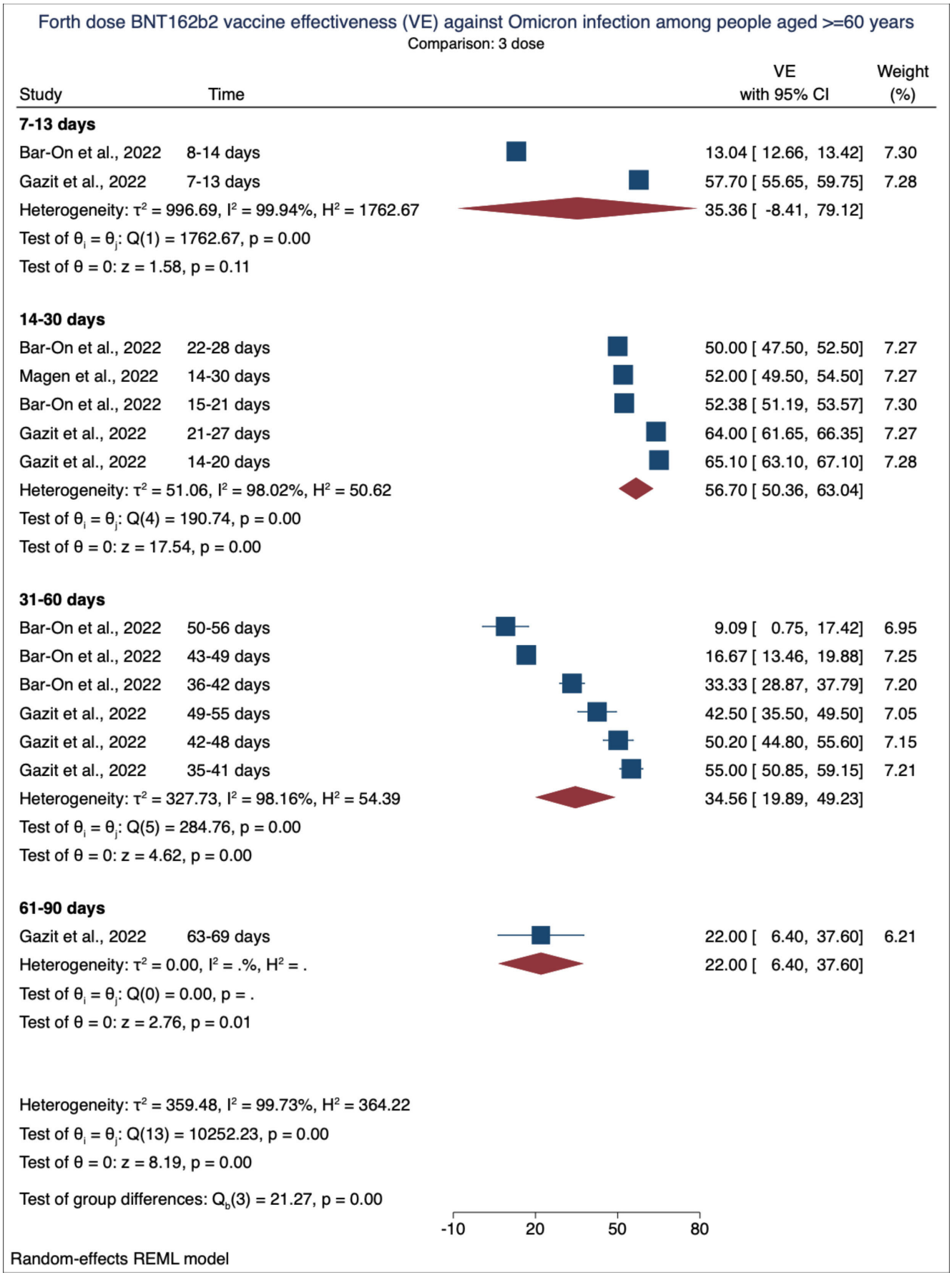

Figure 4 Fourth-dose BNT162b2 vaccine effectiveness (VE) against SARS-CoV-2 infection due to Omicron variant among older people, compared with the third dose. REML Restricted maximum likelihood.

Two studies[54 58] assessed the VE of the fourth dose relative to the third dose of mRNA vaccines against symptomatic infection among older people, and we could only estimate VE for the early time points postvaccination. The fourth-dose VE was 43.56% (95% CI 20.07% to 67.06%, I^2=94.74%, very low certainty) and 61% (95% CI 58% to 64%, moderate certainty) at ≥7 days and ≥14 days since the last booster dose, respectively (table 1, online supplemental figure 20).

Three studies[37 58 60] estimated the VE of the fourth dose compared with that of the third dose of the BNT162b2 vaccine against hospitalisation, and the VE remained stable from 14 to 60 days after the last booster dose vaccination. The pooled VE of the fourth dose of BNT162b2 vaccine against hospitalisation was 67.54% (95% CI 59.76% to 75.33%, I^2=59.33%, moderate certainty) 14–60 days after the last booster dose vaccination (table 1, online supplemental figure 21).

Four studies[37 56 58 60] showed a higher VE for the fourth dose than for the third dose of the BNT162b2 vaccine against death among older people. The overall VE of fourth dose BNT162b2 vaccine against death was 77.88% (95% CI 72.55% to 83.21%, I^2=0%, moderate certainty) and remained stable across 7–60 days after the last booster dose vaccination (table 1, online supplemental figures 22 and 23). However, none of the studies reported ICU admission, oxygen support, mechanical ventilation or ED/UC visit outcomes for this comparison.

DISCUSSION

This is the first comprehensive systematic review and meta-analysis to provide evidence on the VE and duration of protection of third-dose and fourth-dose mRNA vaccines against SARS-CoV-2 infection and severe COVID-19 outcomes due to the Omicron subvariant and its sublineages. Our meta-analysis estimates indicated a decline in the VE of the third-dose mRNA vaccines against SARS-CoV-2 infection and symptomatic infections over time. Compared with no vaccination, the VE of third-dose mRNA vaccines against SARS-CoV-2 infection declined from 76.17% at ≥7 days to 52.34% at ≥120 days after the third-dose vaccination; however, it fell below the WHO minimal criterion of 50% at ≥150 days (16%) when compared with primary series vaccination. A similar trend was observed for symptomatic infections following the third-dose vaccination. These findings are broadly consistent with a recent review that reported that a booster dose of mRNA vaccines restored protection against Omicron infection up to 51% and up to 57% against symptomatic infection within 3 months; however, this declined to 33% within 6 months.[18] Furthermore, compared with the third dose, the fourth dose of mRNA vaccine provides an additional, even better, protection and the durability of the protection was similar to that of three doses versus the primary series, although studies were among people over 60 years and the long-term effects are unclear. These findings suggest that a waning effect is also present for both third and fourth-dose vaccination against SARS-CoV-2 infection and symptomatic infection, corroborating recent studies conducted during the Omicron-dominant period.[20–22 53 79 80]

A recent study conducted in Japan[80] reported high-level protection against Omicron infection by an mRNA booster dose (74% at 14 days after the third dose), which is consistent with our findings. Our meta-analyses estimated that a third dose provided 75.84% protection against BA.1 infection and 70.41% against BA.2 infection at seven or more days postvaccination. However, the protection sharply declined below the WHO minimal criteria of 50% within 6 months following the third or fourth dose of vaccination, supporting the need for a booster dose within 6 months after the fourth-dose vaccination. Furthermore, our findings suggest that an mRNA booster, either the third or fourth dose, can provide longer protection for up to 6 months against severe COVID-19 outcomes such as hospitalisation, ICU admission, oxygen support, mechanical ventilation or death. For instance, the third dose of VE for hospitalisation remained high and stable over time, maintaining a VE of 79.30% at 91–120 days. For older adults, the fourth-dose VE up to 60 days was 67.54% for hospitalisation and 77.88% for death due to Omicron subvariant compared with that of the third dose. Similar to our findings, prior evidence has reported robust protection of up to 86% against severe disease caused by the Omicron subvariant after a single dose of mRNA booster, for up to 6 months.[18 19 81] We also noticed that the third-dose mRNA vaccines provided substantial protection with respect to ED/UC visits, which persisted over time, indicating that booster doses of mRNA vaccines can reduce the burden on healthcare facilities.

Similar to our findings, recent systematic review and meta-analyses[20–22] reported that the third dose mRNA vaccines provided additional protection against the Omicron subvariant compared with the primary series or no vaccination, however, the effectiveness waned over time. These findings were limited to a small number of studies and most of them followed-up for a period of 3 months after the booster vaccination.[20–22] Compared with the existing meta-analyses, the added value of our study is that we rigorously compared VE of the third dose versus the primary series, no vaccination, and the fourth dose at specific time periods and open-ended time points until 6 months after the last booster vaccination. This approach minimises bias and provides more accurate estimates. Furthermore, we assessed the certainty of the evidence using the GRADE approach for a comprehensive range of outcomes, which supports evidence-based recommendations for the use of fourth-dose and fifth-dose mRNA COVID-19 vaccines.

WHO recommends additional booster doses either 6 or 12 months after the last dose vaccination for the high priority groups (eg, older adults with some comorbidities or moderate/severe immunocompromised people).[82] Most of our pooled estimates were based on a limited

number of studies with a follow-up period of 6 months after the third or fourth dose of vaccination; therefore, the impact of waning booster dose VE on SARS-CoV-2 infection and severe COVID-19 outcomes beyond these periods are unknown. Nevertheless, not all severe COVID-19 outcomes have been reported in these studies, and few studies have reported VEs at specific time points after booster dose vaccination. Owing to the limited number of studies included in our meta-analyses, further long-term follow-up studies beyond 6 months are needed to confirm the durability of mRNA vaccine booster dose protection against all severe COVID-19 outcomes, as the outcomes can drive decisions on the stringency of COVID-19 policies in countries.

Our findings should be interpreted with caution for public health policies due to high statistical heterogeneity between the included studies, caused by factors such as diverse study populations, designs, geographical variations, different statistical approaches employed to estimate VE or analysed time points after vaccination. A subgroup analysis was performed for adolescent and older people, but limited data prevented subgroup analysis on different populations. The studies were predominantly conducted in America and Europe, but differences in study demographics, reinfection immunity and pandemic control measures could affect VE. Furthermore, our findings are specific to mRNA vaccines and cannot be generalised to other types. Additionally, the risk of bias in the included studies, publication bias, and small-study effects can also introduce variations in the VE. Although the certainty of evidence in our estimates for severe COVID-19 outcomes, such as hospitalisation and death, was moderate, it was very low to moderate for SARS-CoV-2 infection and symptomatic infection (table 1), indicating that future research is likely to change the estimates.

CONCLUSION

This systematic review and meta-analysis demonstrates that the VE of third-dose and fourth-dose mRNA vaccines against SARS-CoV-2 Omicron subvariant infection and symptomatic infection wanes over time; however, it offers substantial protection for at least 6 months against severe COVID-19 outcomes, although the duration of protection remains uncertain.

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