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Effectiveness of SARS-CoV-2 vaccines against Omicron infection and severe events: a systematic review and meta-analysis of test-negative design studies

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Background: A rapidly growing body was observed of literature evaluating the vaccine effectiveness (VE) against Omicron in test-negative design studies.

Methods: We systematically searched papers that evaluated VE of SARS-CoV-2 vaccines on PubMed, Web of Science, Cochrane Library, Google Scholar, Embase, Scopus, bioRxiv, and medRxiv published from November 26th, 2021, to June 27th, 2022 (full doses and the first booster), and to January 8th, 2023 (the second booster). The pooled VE against Omicron-associated infection and severe events were estimated.

Results: From 2,552 citations identified, 42 articles were included. The first booster provided stronger protection against Omicron than full doses alone, shown by VE estimates of 53.1% (95% CI: 48.0–57.8) vs. 28.6% (95% CI: 18.5–37.4) against infection and 82.5% (95% CI: 77.8–86.2) vs. 57.3% (95% CI: 48.5–64.7) against severe events. The second booster offered strong protection among adults within 60 days of vaccination against infection (VE=53.1%, 95% CI: 48.0–57.8) and severe events (VE=87.3% (95% CI: 75.5–93.4), comparable to the first booster with corresponding VE estimates of 59.9% against infection and 84.8% against severe events. The VE estimates of booster doses against severe events among adults sustained beyond 60 days, 77.6% (95% CI: 69.4–83.6) for first and 85.9% (95% CI: 80.3–89.9) for the second booster. The VE estimates against infection were less sustainable regardless of dose type. Pure mRNA vaccines provided comparable protection to partial mRNA vaccines, but both provided higher protection than non-mRNA vaccines.

Conclusions: One or two SARS-CoV-2 booster doses provide considerable protection against Omicron infection and substantial and sustainable protection against Omicron-induced severe clinical outcomes.

KEYWORDS

Omicron, vaccine effectiveness, meta-analysis, test negative, booster dose

Introduction

The Omicron variant (B.1.1.529) was first detected in early November 2021 in South Africa and was designated the fifth variant of concern by the World Health Organization (1). In contrast to the original wild-type variant, Omicron accumulated over 50 mutations in the whole genome, including 26-32 in the spike protein. This altered protein receptor-binding efficiency and immunogenicity, increasing infectivity, ability to evade neutralizing antibodies, and risk of reinfection (2). Additional mutations led to multiple Omicron subvariants with increased transmissibility including BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7, BQ.1, BQ.1.1, and XBB.1.5, the latter three of which accounted for most infections in the United States as of February 2023 (3). The effective reproduction number (R_t) and basic reproduction number (R_0) were estimated to be 3.8 and 2.5 times higher for Omicron than for Delta (4). Compared with the wild-type and Delta variants, Omicron replicates less efficiently in the lung parenchymal tissues and more efficiently in the bronchial tissues, which may contribute to increased transmissibility but decreased disease severity (5-7).

There is a rapidly growing body of literature of real-world vaccine effectiveness (VE) against Omicron. Studies reported that individuals vaccinated with two mRNA doses were less susceptible to Omicron infection, though the level of protection conferred was lower than that of earlier variants, and protection waned over time (8,9). The emergence of new variants coupled with waning vaccineinduced immunity prompted recommendations for booster doses and second booster doses based on the original Wuhan-Hu-1 strain, which were shown to confer greater protection against Omicron than two mRNA doses (10, 11). Omicron-specific bivalent mRNA booster doses were recently authorized for use in the U.S. by the Food and Drug Administration, and early data demonstrated stronger neutralizing antibody responses against Omicron than the original monovalent mRNA vaccines (12). The BNT162b2 bivalent BA.4/5 COVID-19 vaccine was recently shown to elicit greater neutralizing antibody titers against newer Omicron sublineages (BA.4.6, BA.2.75.2, BQ.1.1 and XBB.1) in adults older than 55 than a fourth dose of the original monovalent BNT162b2 (13). Uptake of the bivalent boosters, however, is low with only 15% of the U.S. adult population vaccinated as of February 2023 (14). Therefore, it is important to quantify the effectiveness of the original vaccines against Omicron.

Two early meta-analyses evaluated VE of a primary vaccine series or single booster dose and demonstrated greater protection for the third dose against symptomatic infection and severe events compared to a two-dose regimen (15, 16). However, they focused on hybrid immunity (immunity developed from SARS-CoV-2 infection and vaccination) (15) and relative vaccine effectiveness of the third dose compared to two doses (16) rather than nonvaccination. Nor did they evaluate VE for a second booster, longterm (>60 days) VE for the first booster, or adult- and child-specific VEs. Herein, we aggregate estimates in the literature to evaluate VE for the initial full doses, first booster dose, and second booster dose against Omicron-related infection and severe events for pure mRNA, partial (mixed) mRNA, and non-mRNA vaccines. We focus our review on test-negative design studies, an increasingly popular epidemiological study design for evaluating VE on infectious pathogens including influenza, rotavirus, pneumococcus, and others (17). In this design, the same clinical definition is used to enroll cases and controls and laboratory testing distinguishes "test positive" cases from "test negative" controls, thereby reducing bias from differential healthcare-seeking behavior between cases and controls (18).

Methods

This analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.

Data sources and searches

A systematic literature search was conducted of PubMed, Web of Science, Cochrane Library, Google Scholar, Embase, Scopus, and preprint servers (bioRxiv and medRxiv) for papers published from November 26th, 2021, when Omicron was classified as a World Health Organization Variant of Concern (1), to June 27th, 2022 (for full doses and booster), and to January 8th, 2023 (for the second booster). We applied Boolean combinations of the following keywords to identify relevant publications: "SARS-CoV-2", "COVID-19", "2019nCoV", "vaccine", "booster", "second booster", "effectiveness", "efficacy", "test-negative case-control", "test-negative design", "Omicron", "infection", "hospitalization"; the detailed search procedures were presented in the Supplementary material. Publication language was not restricted, and reference lists of selected papers were also screened for additional studies.

Study selection

The selection of studies followed Participant (P), Intervention (I), Comparator (C), Outcome (O), and Study Type (S), PICOS criteria (19) (Supplementary Table 1). Published studies were eligible for inclusion if they were original analyses with the test-negative design (TND) and reported VE or corresponding odds ratios (OR) of full doses, booster, or second booster against Omicron infection or severe events. We excluded studies that focused on special populations (e.g., patients with kidney disease); did not include circulation period of Omicron variant; combined VE estimates for Omicron with other viral variants such as Delta; reported relative VE between different vaccines, vaccination doses, or variants among vaccinated individuals; did not evaluate VE (e.g., instead, evaluated neutralizing antibodies); or evaluated outcomes other than infection or severe events. All available ages were included. We did not contact authors for additional data.

After removing duplicated results, we first screened studies by titles and abstracts to identify potentially eligible articles. Two pairs of researchers then independently evaluated full texts and selected those meeting the inclusion criteria. Any disagreements were discussed until a consensus was reached. Preprints were checked and updated with their most recent published version if available as of January 10th, 2023. Zotero was used for literature management.

Due to the scarcity of published TND studies involving Omicronspecific bivalent booster doses by the time this meta-analysis was conducted, we solely focused on monovalent vaccines and booster doses based on the original Wuhan-Hu-1 strain.

Data extraction and quality assessment

Two pairs of researchers independently extracted the following from the included studies: author names, publication year, study region, study design, dose, vaccine type, test time in reference to vaccination time, adjusted VE point estimate and 95% confidence intervals, and adjustment confounders; if available, the number of vaccinated and unvaccinated individuals in the cases and controls were also recorded.

Study quality and risk of bias were independently assessed by two researchers using the Newcastle-Ottawa Scale (NOS). Studies could earn up to 9 points composed of participant selection (4 points), study comparability (1 point), and outcome of interest (4 points). A score >7 was considered as high quality, 5–6 as medium, and <5 as low, and studies classified as low were excluded from the meta-analysis. Publication bias was also evaluated by Egger's test, Begg and Mazumdar rank correlation, and funnel plots when at least ten studies were available, with significance set at p < 0.1. If we detected publication bias, we used the Duval and Tweedie trimand-fill method (20) for adjustment, which consists of imputing missing effect sizes to achieve symmetry.

Data synthesis and analysis

We categorized full doses and booster VE into short-term, longterm, and overall to evaluate potential waning of VE over time. In the collected studies, there is no uniform definition for shortterm vs. long-term VE, but most adopted cut-off points of 60-120 days from last vaccination to lab-testing. Considering the lower and upper bounds of the post vaccination test dates, we used the following guidelines. For initial full doses, a lower bound \leq 30 days and an upper bound \leq 180 days constitute short term, and a lower bound ≥ 90 (except one study used ≥ 70 days) days and an upper bound that is either \geq 200 days or unspecified are considered long term. For booster doses, a lower bound \leq 30 days and an upper bound ≤ 120 days are considered short term, and a lower bound \geq 60 days and an upper bound > 120 days or unspecified are considered as long-term. To simplify description, we occasionally use "<90 days" and "≥90 days" to represent short-term vs. longterm VEs for the full doses, and use "<60 days" and "≥60 days" to represent short-term vs. long-term VEs for the booster doses. If a study reported VEs for finer time intervals than we needed, we used an inverse variance weighted (IVW) averaging approach to combine them.

For each time interval, we further categorized VE by the type of vaccine: pure mRNA vaccines, partial mRNA vaccines, and non-mRNA vaccines. Pure mRNA vaccines comprise of homogenous or heterogeneous BNT162b2 and mRNA-1273, or a population-level mixture of the two if a study does not discriminate between them. Partial mRNA vaccines include either a multidose course containing at least one mRNA vaccine dose, or the study indiscriminately reported VEs of a population-level mixture of vaccines including at least one mRNA vaccine. Non-mRNA vaccines refer to the regimens that do not involve mRNA vaccines at all (e.g., Ad26.COV2.S, ChAdOx1).

We evaluated VE against Omicron infection and severe events. Analyses of VE against infection or symptomatic infection combined studies that reported either VE against symptomatic infection or VE against any infection (symptomatic or asymptomatic). Severe events included hospitalizations, noncritical hospitalizations, deaths, emergency department (ED) or urgent care (UC) encounters, ED admissions, intensive care unit (ICU) admissions, and invasive ventilation.

We evaluated VE for the overall vaccine-eligible population as well as for age groups defined as adults (\geq 18 years) and children/adolescents (5–17 years). If VE was not reported but odds ratios (OR) were provided, we calculated VE as (1 – OR) ×100%. The pooled VE and 95% confidence intervals were calculated via a random effects meta-analysis with restricted maximum likelihood estimation. I^2 was used to evaluate between-study heterogeneity with thresholds of 25, 50, and 75% indicating low, moderate, and high heterogeneity, respectively. The *metafor* package in the R statistical software (version 4.0.5) was used for estimation and visualization in this meta-analysis (21).

Results

Study selection and characteristics

For full doses and booster doses, we obtained 1,139 articles from all searched databases (82 from PubMed, 23 from Web of Science, 89 from Embase, 721 from Scopus, 3 from Cochrane Library, 115 from medRxiv, 6 from bioRxiv, and 100 from Google Scholar). After removing duplicates, 952 articles remained, of which 136 were retained for full review following inspection of the title, abstract, and keywords. After full text review of these 136 articles, 33 articles (9, 10, 22-52) with 271 VE estimates were formally included in this meta-analysis (Figure 1A). For the second booster, we obtained 1,413 articles from all databases (56 from PubMed, 22 from Web of Science, 55 from Embase, 1,015 from Scopus, nine from Cochrane Library, 149 from medRxiv, seven from bioRxiv, and 100 from Google Scholar). After removing duplicates, 1,236 articles remained, of which 116 were considered relevant after inspection of the title, abstract, and keywords. These 116 relevant articles were then reviewed in full text for eligibility, and 11 articles (23, 37, 53-61) with 46 VE estimates were finally included in this meta-analysis (Figure 1B).

Among the 33 papers relevant to full doses and booster doses, 14 studies were conducted in the U.S., five in the U.K., four in Canada, three in South Africa, two in Qatar, two in Brazil, and one in each of Belgium, Netherlands and Scotland, respectively. A study could report multiple VEs for different vaccination types and outcomes. In total, there were 271 VE estimates including 124 for full doses and 147 for the first booster doses; 133 for pure mRNA vaccines, 100 for partial mRNA vaccines, and 38 the non-mRNA vaccines; 138 for symptomatic infection, 14 for any infection, and



119 for severe events. For the second booster, out of 11 papers, five studies conducted in the U.S., three in Canada, and three in Thailand. In total, there were 46 VE estimates including 32 for pure mRNA vaccines, 13 for partial mRNA vaccines, and one for non-mRNA vaccines; three for symptomatic infection, 24 for any infections, and 19 for severe events.

Vaccine effectiveness against Omicron symptomatic infection or any infection

The VE estimates for the initial full doses against Omicron symptomatic infection or any infection were summarized in Figure 2A. Pooling all vaccine types and time intervals, the overall VE was estimated to be 28.6% (95% CI: 18.5–37.4%, 25 studies) for all ages and 24.4% (95% CI: 16.2–31.8%, 15 studies) for adults. The overall VE of the pure mRNA vaccines was estimated to be 30.6% (95% CI: 17.1–41.8%, 18 studies) for all ages, 25.4% (95% CI: 11.5–37.1%, 8 studies) for adults, and 54.2% (95% CI: 35.2–67.7%, 5 studies) for children and adolescents. Overall VE estimates for partial mRNA vaccines and non-mRNA vaccines were only available for adults, 28.1% (95% CI: 19.8–35.6%, 5 studies) and 1.5% (95% CI: 0.4–2.7%, 2 studies) respectively. This is also why we do not have a separate overall VE estimate for children and adolescents pooling all vaccine types.

Short-term full-dose VE estimates pooling all vaccine types were 40.7% (95% CI: 34.3–46.5%, 19 studies) for all ages and 37.5% (95% CI: 31.4–43.1%, 10 studies) for adults (Supplementary Figure 1). Short-term VE of pure mRNA vaccines was estimated to be 43.5% (95% CI: 35.4–50.6%, 13 studies) for all ages, 41.3% (95% CI: 40.2–42.4%, 4 studies) for adults, and 45.3% (95% CI: 28.7–58.1%, 6 studies) for children and adolescents. Short-term VE estimate of partial mRNA vaccines was 34.7% (95% CI: 25.4–42.9%, 6 studies) for adults, slightly lower than that of the pure mRNA vaccines.

Long-term full-dose VE estimates against symptomatic or any infection were in general much lower than their short-term counterparts. Pooling all vaccine types, long-term full-dose VE was estimated to be 17.6% (95% CI: 13.2–21.8%, 22 studies) for all ages and 16.6% (95% CI: 10.5–22.3%, 15 studies) for adults (Supplementary Figure 2). Long-term full-dose VE of pure mRNA vaccines was estimated to be 16.4% (95% CI: 13.6–19.1%, 11 studies) for all ages, 13.1% (95% CI: 11.7–14.6%, 4 studies) for adults, and 22.3% (95% CI: 13.6–30.1%, 4 studies) for children and adolescents. Long-term full-dose VE among adults was estimated to be 22.6% (95% CI: 10.8–32.7%, 5 studies) for partial mRNA vaccines and 13.2% (95% CI: 2.6–22.6%, 6 studies) for nonmRNA vaccines.

Compared to unvaccinated controls, the overall VE of the first booster dose against Omicron symptomatic infection or any infection was 53.1% (95% CI: 48.0-57.8%, 31 studies) for

Author(s) and Year	Region	Omicron Subvariant	Vaccine	Case Event	Age Group (years)	Test Timing (days)		Estimate [95% C
Pure mRNA Vaccines, full dos	es							
Powell, et al. (2021)	UK	B.1.1.529	BNT162b2/BNT162b2	SI	12-15	≥14	⊢ ∎-	0.730 [0.664, 0.783
lorentino, et al. (2022)	Scotland	B.1.1.529	BNT162b2/BNT162b2	SI	12-17	≥14	H	0.638 [0.613, 0.661
Carazo, et al. (2022)	Canada	BA.2	Mixed (BNT162b2/mRNA-1273)	SI	≥18	≥7	⊢ ⊷⊣	0.610 [0.520, 0.690
owell, et al. (2021)	UK	B.1.1.529	BNT162b2/BNT162b2	SI	16-17	≥14	н	0.572 [0.553, 0.590
uchan, et al. (2022b)	Canada	BA.1/BA.1.1	BNT162b2/BNT162b2	SI	12-17	≥7	⊢•-	0.324 [0.269, 0.375
lorentino, et al. (2022)	Brazil	B.1.1.529	BNT162b2/BNT162b2	SI	12-17	≥14		0.316 [0.307, 0.325
ndrews, et al. (2022)	UK	B.1.1.529	mRNA-1273/mRNA-1273	SI	≥18	≥14	H	0.274 [0.260, 0.288
rewal, et al. (2022a)	Canada	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	SI	≥60	NR	—	0.230 [0.010, 0.400
ndrews, et al. (2022)	UK	B.1.1.529	BNT162b2/BNT162b2	SI	≥18	≥14		0.210 [0.204, 0.217
im, et al. (2022)	USA	Unspecified	Mixed (BNT162b2/mRNA-1273)	SI	≥18	≥14	H	0.210 [-0.060, 0.410
ind, et al. (2022)	Brazil	BA.1	Mixed (BNT162b2/mRNA-1273)	AI	≥5	≥14	l • l	0.181 [0.139, 0.222
hin, et al. (2022)	USA	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	AI	≥18	≥7	I =1	0.149 [0.123, 0.197
seng, et al. (2022a)	USA	B.1.1.529	mRNA-1273/mRNA-1273	AI	≥18	≥14	H	0.139 [0.105, 0.171
oung-Xu, et al. (2022)	USA	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	AI	≥18	≥14	H	0.120 [0.100, 0.150
hemaitelly, et al. (2022)	Qatar	BA.1/BA.2	BNT162b2/BNT162b2	SI	all ages	≥30	-	0.056 [0.018, 0.092
ltarawneh, et al. (2022)	Qatar	BA.1/BA.2	mRNA-1273/mRNA-1273	SI	all ages	14-300	H ≠ -	0.022 [-0.046, 0.085
hemaitelly, et al. (2022)	Qatar	BA.1/BA.2	mRNA-1273/mRNA-1273	SI	all ages	≥30	H	-0.000 [-0.053, 0.050
ltarawneh, et al. (2022)	Qatar	BA.1/BA.2	BNT162b2/BNT162b2	SI	all ages	14-300	H i l	-0.002 [-0.055, 0.049
ooled VE in adults: (Q = 198.8	3, df = 7, p < .01;	I ² = 99.6%, τ ² = 5.52e ⁻⁰²)					-	0.254 [0.115, 0.371
ooled VE in children and adole	scents: (Q = 758	.63, df = 4, p < .01; l ² = 99	0.6%, τ ² = 1.55e ⁻⁰¹)					0.542 [0.352, 0.677
ooled VE in all age groups: (Q	= 2179.16, df = 1	17, p < .01; $I^2 = 99.8\%$, τ^2	= 1.43e ⁻⁰¹)				-	0.306 [0.171, 0.418
artial mRNA Vaccines, full do	ses							
irsebom, et al. (2022a)	UK	BA.2	Mixed (BNT162b2/mRNA-1273/ChAdOx	1) SI	≥18	≥14	H	0.353 [0.340, 0.366
ndeweg, et al. (2022)	Netherlands	BA.1	Mixed (BNT162b2/mRNA-1273/ChAdOx	1) SI	≥18	≥14	н	0.330 [0.300, 0.350
ndeweg, et al. (2022)	Netherlands	BA.2	Mixed (BNT162b2/mRNA-1273/ChAdOx	1) SI	≥18	≥14	H	0.330 [0.300, 0.360
irsebom, et al. (2022a)	UK	BA.1	Mixed (BNT162b2/mRNA-1273/ChAdOx	1) SI	≥18	≥14		0.249 [0.236, 0.261
uchan, et al. (2022a)	Canada	B.1.1.529	Mixed (≥1 mRNA Vaccine)	SI	≥18	≥7	H=1	0.119 [0.076, 0.160
ooled VE in adults: (Q = 221.7	1, df = 4, p < .01;	I ² = 98.7%, τ ² = 1.55e ⁻⁰²					•	0.281 [0.198, 0.356
on-mRNA Vaccines, full dos	es							
unes, et al. (2022)	South Africa	B.1.1.529	Janssen	SI	≥18	≥14	◀ · · · ·	0.110 [-0.720, 0.540
ndrews, et al. (2022)	UK	B.1.1.529	ChAdOx1/ChAdOx1	SI	≥18	≥14		0.015 [0.004, 0.027
ooled VE in adults: (Q = 0.09,	df = 1, p = 0.76; l	$t^2 = 0.0\%, \ \tau^2 = 0.00e^{+00})$					•	0.015 [0.004, 0.02]

est for VE Difference in All across Vaccine Types: Q_M = 1.21, df = 2, p = 0.55

-0.500 0.000 0.500 1.000 Vaccine Effectiveness

в

Author(s) and Year	Region	Omicron Subvariant	Vaccine	Case Event	Age Group (years)	Test Timing (days)		Estimate [95% CI]	
Pure mRNA Vaccines, booster dose									
Tseng, et al. (2022a)	USA	B.1.1.529	mRNA-1273/mRNA-1273/mRNA-1273	AL	≥18	≥14	н	0.700 [0.680, 0.719]	
Carazo, et al. (2022)	Canada	BA.2	Mixed (BNT162b2/mRNA-1273)	SI	≥18	≥7	⊢ +1	0.700 [0.620, 0.750]	
Young-Xu, et al. (2022)	USA	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	AI	≥18	≥14		0.640 [0.630, 0.650]	
Buchan, et al. (2022b)	Canada	BA.1/BA.1.1	BNT162b2/BNT162b2/BNT162b2	SI	12-17	≥7	H-H-I	0.620 [0.490, 0.720]	
Kim, et al. (2022)	USA	Unspecified	Mixed (BNT162b2/mRNA-1273)	SI	≥18	≥14	⊢ ⊷⊣	0.620 [0.480, 0.720]	
Andrews, et al. (2022)	UK	B.1.1.529	BNT162b2/BNT162b2/BNT162b2	SI	≥18	≥7	i i i i i i i i i i i i i i i i i i i	0.585 [0.581, 0.589]	
Grewal, et al. (2022a)	Canada	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	SI	≥60	≥0	⊢ •-	0.579 [0.504, 0.643]	
Lind, et al. (2022)	Brazil	BA.1	Mixed (BNT162b2/mRNA-1273)	AL	≥5	≥14	H+1	0.569 [0.521, 0.612]	
Chemaitelly, et al. (2022)	Qatar	BA.1/BA.2	mRNA-1273/mRNA-1273/mRNA-1273	SI	all ages	≥7	⊢ ⊷	0.444 [0.365, 0.514]	
Chin, et al. (2022)	USA	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	AL	≥18	≥7	н	0.432 [0.422, 0.474]	
Chemaitelly, et al. (2022)	Qatar	BA.1/BA.2	BNT162b2/BNT162b2/BNT162b2	SI	all ages	≥7	H	0.408 [0.376, 0.438]	
Pooled VE in adults: (Q = 371.80, dl	= 6, p < .01; I ²	$= 99.1\%, \tau^2 = 4.90e^{-02})$					•	0.614 [0.541, 0.675]	
Pooled VE in all age groups: (Q = 5)	3.00, df = 10,	$p < .01; I^2 = 98.9\%, \tau^2 = 5.45$	5e ⁻⁰²)				+	0.580 [0.514, 0.636]	
Partial mRNA Vaccines, booster d	ose								
Andeweg, et al. (2022)	Netherlands	BA.1	Mixed (BNT162b2/mRNA-1273/ChAdOx1) SI	≥18	≥7		0.680 [0.670, 0.690]	
Buchan, et al. (2022a)	Canada	B.1.1.529	Mixed (≥1 mRNA Vaccine)/mRNA-1273	SI	≥18	≥7	⊢ •-1	0.650 [0.550, 0.720]	
Andeweg, et al. (2022)	Netherlands	BA.2	Mixed (BNT162b2/mRNA-1273/ChAdOx1) SI	≥18	≥7	н	0.620 [0.610, 0.640]	
Stowe, et al. (2022)	UK	Unspecified	Mixed (BNT162b2/mRNA-1273/ChAdOx1) SI	18-64	≥7		0.619 [0.615, 0.623]	
Buchan, et al. (2022a)	Canada	B.1.1.529	Mixed (≥1 mRNA Vaccine)/BNT162b2	SI	≥18	≥7	H+I	0.600 [0.550, 0.650]	
Kirsebom, et al. (2022a)	UK	BA.2	Mixed (BNT162b2/mRNA-1273/ChAdOx1) SI	≥18	≥7		0.594 [0.589, 0.599]	
Kirsebom, et al. (2022a)	UK	BA.1	Mixed (BNT162b2/mRNA-1273/ChAdOx1) SI	≥18	≥7	•	0.589 [0.584, 0.593]	
Kirsebom, et al. (2022b)	UK	BA.1/BA.2	ChAdOx1/ChAdOx1/BNT162b2	SI	40-64	≥7		0.568 [0.563, 0.573]	
Andrews, et al. (2022)	UK	B.1.1.529	ChAdOx1/ChAdOx1/BNT162b2	SI	≥18	≥7	٠	0.561 [0.557, 0.565]	
Stowe, et al. (2022)	UK	Unspecified	Mixed (BNT162b2/mRNA-1273/ChAdOx1) SI	≥65	≥7	i hei	0.523 [0.483, 0.559]	
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/BNT162b2	SI	≥75	>7	н	0.515 [0.498, 0.531]	
Kirsebom, et al. (2022b)	UK	BA.1/BA.2	ChAdOx1/ChAdOx1/BNT162b2	SI	≥65	≥7	H	0.508 [0.488, 0.528]	
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/BNT162b2	SI	60-74	>7	H	0.485 [0.474, 0.495]	
Braeye, et al. (2022)	Belgium	BA.1/BA.2	Mixed (BNT162b2/mRNA-1273/ChAdOx1) SI	≥18 (C	0-50) & (100-150)		0.472 [0.467, 0.477]	
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/BNT162b2	SI	18-59	>7	•	0.431 [0.427, 0.436]	
Pooled VE in adults: (Q = 6460.27, c	if = 14, p < .01	; $I^2 = 99.8\%$, $\tau^2 = 2.47e^{-02}$)					•	0.564 [0.527, 0.598]	
Non-mRNA Vaccines, booster dos	e								
Kirsebom, et al. (2022b)	UK	BA.1/BA.2	ChAdOx1/ChAdOx1/ChAdOx1	SI	40-64	≥7	⊢+-	0.513 [0.446, 0.572]	
Kirsebom, et al. (2022b)	UK	BA.1/BA.2	ChAdOx1/ChAdOx1/ChAdOx1	SI	≥65	≥7		0.407 [0.244, 0.534]	
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/CoronaVac	SI	≥75	>7	┝╾┥	0.159 [0.118, 0.198]	
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/CoronaVac	SI	60-74	>7	+	0.079 [0.044, 0.112]	
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/CoronaVac	SI	18-59	>7	¥	0.005 [-0.023, 0.033]	
Pooled VE in adults: (Q = 148.91, di	= 4, p < .01; l ²	$\tau^2 = 99.3\%, \ \tau^2 = 8.98e^{-02})$						0.252 [0.022, 0.428]	
Pooled VE in adults across all vaccin Pooled VE in all age groups across a Test for VE Difference in All across V	e types: (Q = Il vaccine type: accine Types: (12327.86, df = 26, p < .01; l ² s: (Q = 12422.07, df = 30, p Q _M = 28.55, df = 2, p = 0.00	$r^{2} = 99.9\%, r^{2} = 9.28e^{-02})$ < .01; $I^{2} = 99.9\%, r^{2} = 8.47e^{-02})$				* *	0.534 [0.477, 0.586] 0.531 [0.480, 0.578]	

0.000 0.500 1.000 Vaccine Effectiveness

FIGURE 2

Overall vaccine effectiveness of full doses and first booster against infection or symptomatic infection. (A) Pooled VE of full doses estimated from all 25 studies combined as well as for each vaccine type. (B) Pooled VE of first booster estimated from all 31 studies combined as well as for each vaccine type. Statistics Cochran's Q, I^2 and τ^2 measure the heterogeneity between studies. End points of the studies are either symptomatic infection (SI) or any infection (A). Mixed vaccine type indicates the study reported VEs of these vaccines combined without distinguishing between them.

all ages and 53.4% (95% CI: 47.7–58.6%, 27 studies) for adults (Figure 2B). No studies included in this analysis reported VE of booster doses for children. When stratified by vaccine type, the overall first-booster VE estimates were 58.0% (95% CI: 51.4–63.6%, 11 studies) for all ages and 61.4% (95% CI: 54.1–67.5%, 7 studies) in adults for pure mRNA vaccination, 56.4% (95% CI: 52.7–59.8%, 15 studies) for adults for partial mRNA vaccines, and 25.2% (95% CI: 2.2–42.8%, 5 studies) for adults for non-mRNA vaccines.

In comparison to its overall VE, the short-term VE estimates of the first booster dose were slightly higher, 59.4% (95% CI: 55.1–63.3%, 33 studies) for all ages and 59.9% (95% CI: 55.1–64.1%, 28 studies) for adults (Supplementary Figure 3). When stratified by vaccine type, the short-term first-booster VE estimates were 63.7% (95% CI: 59.2–67.7%, 15 studies) for all ages and 67.3 % (95% CI: 64.5–69.9%, 10 studies) for adults for pure mRNA vaccination, 62.3% (95% CI: 59.2– 65.1%, 12 studies) for adults for partial mRNA vaccines, and 37.2% (95% CI: 19.5–51.0%, 6 studies) for adults for nonmRNA vaccines.

Long-term VE estimates of the first booster dose were moderately lower than their overall counterparts, 34.9% (95% CI: 27.6–41.5%, 22 studies) for all ages and 31.5% (95% CI: 22.7–39.4%, 20 studies) for adults (Supplementary Figure 4). Long-term firstbooster VE estimates stratified by vaccine type were 46.6% (95% CI: 36.8–54.8%, 7 studies) for all ages and 50.9% (95% CI: 45.0– 56.2%, 5 studies) for adults for pure mRNA vaccination, 34.6% (95% CI: 28.6–40.2%, 11 studies) for adults for partial mRNA vaccines, and 4.6% (95% CI:–9.5–16.9%, 4 studies) for adults for non-mRNA vaccines.

Due to lack of data, we were only able to estimate short-term and long-term VE but not overall VE of the second booster (Figure 3). Furthermore, we were unable to distinguish between vaccine types for the second booster, but the majority of these studies were based on four doses of mRNA vaccines. The short-term second-booster VE against symptomatic infection or any infection for Omicron was 59.6% (95% CI: 52.0–66.1%, 17 studies) in adults, similar to the overall and the short-term first-booster VE estimates in adults. The long-term second-booster VE was 32.7% (95% CI: 15.4–46.4%, 10 studies) in adults, comparable to that of the first booster.

Vaccine effectiveness against omicron-associated severe events

The overall VE of the full doses against Omicron-associated severe events was estimated to be 57.3% (95% CI: 48.5–64.7%, 24 studies) for all ages and 57.9% (95% CI: 51.5%-63.4%, 16 studies) for adults (Figure 4A). The overall VE estimates of pure mRNA vaccines were 60.9% (95% CI: 50.7–68.9%, 18 studies) for all ages, 60.1% (95% CI: 53.1–66.0%, 10 studies) for adults, and 59.9% (95% CI: 24.7–78.6%, 6 studies) for children and adolescents. The overall VE of partial mRNA vaccines for adults was slightly lower than that of pure mRNA vaccines, 54.5% (95% CI: 41.1–64.8%, 6 studies).

We did not find studies estimating the overall VE of non-mRNA vaccines against Omicron-related severe events.

The short-term VE of the full doses against Omicron-associated severe events was estimated to be 66.9% (95% CI: 58.3–73.8%, 16 studies) for all ages and 69.9% (95% CI: 62.8–75.6%, 10 studies) for adults (Supplementary Figure 5). Stratified by vaccine type, the short-term VE estimates were 64.0% (95% CI: 50.2–74.0%, 9 studies) for all ages, 70.5% (95% CI: 64.9–75.2%, 3 studies) for adults, 60.7% (95% CI: 36.6–75.6%, 6 studies) for children and adolescents for pure mRNA vaccines and 70.7% (95% CI: 59.2%-78.9%, 7 studies) for adults for partial mRNA vaccines.

Long-term VE estimates of the full doses against Omicronassociated severe events were comparable to the overall VE estimates, 58.3% (95% CI: 45.5–68.1%, 18 studies) for all ages and 59.0% (95% CI: 49.0–67.1%, 13 studies) for adults (Supplementary Figure 6). Stratified by vaccine type, the long-term VE estimates were 62.4% (95% CI: 38.9–76.8%, 9 studies) for all ages, 67.7% (95% CI: 56.3–76.1%, 4 studies) for adults, and 56.4% (95% CI:–3.6–81.7%, 5 studies) for children and adolescents for pure mRNA vaccines, 50.7% (95% CI: 29.9–65.2%, 6 studies) for adults for partial mRNA vaccines, and 60.1% (95% CI: 39.7–73.6%, 3 studies) for adults for non-mRNA vaccines.

First booster doses generally showed higher VEs against Omicron-associated severe disease than full doses. The pooled overall VE of the first booster dose was estimated to be 82.5% (95% CI: 77.8%-86.2%, 28 studies) for all ages and 82.0% (95% CI: 77.0%-86.0%, 25 studies) for adults (Figure 4B). Pure mRNA vaccines and partial mRNA vaccines showed similar overall VEs against severe events, 83.6% (95% CI: 77.0–88.2%, 11 studies) for all ages, 82.5% (95% CI: 74.7–88.0%, 8 studies) for adults for the former, and 84.6% (95% CI: 77.6–89.5%, 12 studies) for adults for the latter. The overall VE was moderately lower for non-mRNA vaccines, 71.4% (95% CI: 52.1–82.9%, 5 studies) for adults.

Short-term and long-term VEs of the booster dose against Omicron-associated severe events were only available for adults (Supplementary Figure 7). We estimated the short-term VE to be 84.8% (95% CI: 80.4–88.1%, 17 studies) and the long-term VE to be 77.6% (95% CI: 69.4–83.6%, 16 studies) for all vaccine types combined. Short-term vs. long-term booster VE estimates were 85.3% (95% CI: 79.8–89.3%, 6 studies) vs. 80.1% (95% CI: 64.6–88.8%, 5 studies) for pure mRNA vaccines, 88.1% (95% CI: 83.4–91.4%, 7 studies) vs. 78.0% (95% CI: 64.3–86.4%, 8 studies) for partial mRNA vaccines, and 73.0% (95% CI: 53.7–84.3%, 4 studies) vs. 70.5% (95% CI: 47.3–83.5%, 3 studies) for non-mRNA vaccines.

Pooled short-term and long-term VE estimates for the second booster against Omicron-associated severe events among adults were 87.3% (95% CI: 75.5–93.4%, 14 studies), and 85.9% (95% CI: 80.3–89.9%, 5 studies) respectively (Figure 3), both of which are comparable to those of the first booster, though the long-term VE of the second booster appears to decay at a slower rate.

Assessment of publication bias

Publication bias was detected in the pooled estimates of overall VE of the full doses against severe events (Egger's test p = 0.073, Begg's test p = 0.208), long-term VE of the full doses against severe

Infection, short term, 2nd booster Interwort, et al. (2022) Thailand Unsp Chariyalertsak, et al. (2022) Thailand Unsp Chariyalertsak, et al. (2022) Thailand Unsp Grewal, et al. (2022) Thailand Unsp Grewal, et al. (2022) Thailand Unsp Grewal, et al. (2022) Canada B.1. Grewal, et al. (2022) US BA4 Tartor, et al. (2022) US BA4 Grewal, et al. (2022) US BA4 Tartor, e	Omicron Subvaria	nt Vaccine	Case Event	Age Group (years)	Test Timing Median (IQR) or Mean (SD) (days)		Estimate [95% CI]
Intawong, et al. (2022) Thailand Unsp. Chariyajettsak, et al. (2022) Canada B.1. Tarfor, et al. (2022b) USA B.4. Tseng, et al. (2022b) USA B. Grewal, et al.							
Chariyalertsak, et al. (2022) Thailand Unsp. Thatilyasoot, et al. (2022) Thailand Unsp. Chariyalertsak, et al. (2022) Thailand Unsp. Chariyalertsak, et al. (2022) Thailand Unsp. Grewal, et al. (2022b) Canada Unsp. Tartof, et al. (2022b) US BAA Tartof, et al. (2022b) US BAA Tartof, et al. (2022b) US BAA Grewal, et al. (2022b) USA BA Fareng, et al. (2022b) USA BA Grewal, et al. (2022b) USA BA Tartof, et al. (2022b) USA BA Pooled VE in adults accoss all vaccine types against AI or SI, short te Infection, Ionge term, 2nd Booster Tartof, et al. (2022b) USA BAA Tartof, et al. (2022b) US BAA Tartof, et al. (2022b) Canada BA. (BAZ Grewal, et al. (2022	Unspecified	Mixed (BNT162b2/mRNA-1273/ChAdOx1)	AI	≥18	40 (26, 57)	. H-I.	0.750 [0.710, 0.800]
Nategrasot, et al. (2022) Thailand BA1 Charvignetrask, et al. (2022) Thailand Unsp. Charvignetrask, et al. (2022) Thailand Unsp. Grewal, et al. (2022) Canada Unsp. Tartof, et al. (2022) Canada Unsp. Tartof, et al. (2022) USA BA4 Tseng, et al. (2022b) USA BA Grewal, et al. (2022b) USA BA Tartof, et al. (2022b) USA BA4 Tseng, et al. (2022b) USA BA Tartof, et al. (2022b) USA BA4 Tseng, et al. (2022b) USA BA4 Tartof, et al. (2022b) USA BA4 Tartof, et al. (2022b) USA BA4 Tseng, et al. (2022b) USA BA4 Tseng et al. (2022b	Unspecified	ChAdOx1	AI	≥18	≥14 40 (26-57)		0.730 [0.480, 0.890]
Chargementsake, et al. (2022) Instaland Unsp. Grewal, et al. (2022) Canada Unsp. Tartof, et al. (2022b) US BA Tartof, et al. (2022b) US BA Grewal, et al. (2022b) USA BA Tartof, et al. (2022b) USA BA Grewal, et al. (2022b) USA BA Tartof, et al. (2022b) US BA Canada Unsp Grewal, et al. (2022b) US BA Canada Unsp Tartof, et al. (2022b) US BA Canada Unsp Grewal, et al. (2022b) US BA Canada Unsp Tartof, et al. (2022b) US BA Canada Unsp Grewal, et al. (2022b) US BA Canada Unsp Tartof, et al. (2022b) US BA Canada Unsp Canada BA 1862. Grewal, et al. (2022b) US BA Canada BA 1862. Grewal, et al. (2022b) US A BA Canada BA 1862. Grewal, et al. (2022c) Canada BA 1862. Grewal, et al. (2022b) US A BA 2055 Grewal, et al. (2022b) US A BA 2055 Grewal, et al. (2022b) US A BA 2055 Grewal, et al. (2022b) Canada BA 1862. Grewal, et al. (2022b) US A BA 2055 Grewal, et al. (2022b) US A BA 2055 Grewal, et al. (2022b) Canada BA 1862. Grewal, e	BA.1/BA.2	Mixed (BN1162b2/mRNA-12/3/ChAdOx1/CoronaVa	ic) Al	Majority is 18-59	68.49 (28.2)	, . .	0.711 [0.706, 0.717]
Crewal, et al. (2022b) Canada Unsp. Tartof, et al. (2022b) USA BAA Tareng, et al. (2022b) USA BAA Tareng, et al. (2022b) USA BAA Grewal, et al. (2022b) USA BAA Tareng, et al. (2022b) USA BAA Grewal, et al. (2022b) USA BAA Tareng, et al. (2022b) USA BAA Crewal, et al. (2022b) USA BAA Tareng, et al. (2022b) USA BAA Grewal, et al. (2022b) USA BAA Tareng, et al. (2022b) USA BAA Grewal, et al. (2022b) Canada BAA HBAA Grewal, et al. (2022b) Canada BAA HBAA Grewal,	Unspecified	BN116202	AI	218	214 40 (26-57)		0.710[0.600, 0.790]
Crewai, et al. (2022b) Canada Uring Tartof, et al. (2022b) US BAA Tartof, et al. (2022b) US BAA Tartof, et al. (2022b) US BAA Tartof, et al. (2022b) US BAA Tartof, et al. (2022b) USA B Tartof, et al. (2022b) US BAA Pooled VE: nadults across all vaccine types against Al cords I. whore the transpare to the transparet to the trad transpare to the transpare to the trad transpare	B 1 1 520	Mixed (BNT162b2/mRNA=1273)	AI SI	210	>7 40 (30)		0.690 [0.610 0.760]
Tarde, et al. (2022b) US BAA Taren, et al. (2022b) US BAA Tseng, et al. (2022b) USA B Grewal, et al. (2022b) USA B Grewal, et al. (2022b) USA B Tarent, et al. (2022b) Canada B1, Tarent, et al. (2022b) Canada B1, Tarent, et al. (2022b) USA BA Crewal, et al. (2022b) USA BA Grewal, et al. (2022b) USA BA Taroft, et al. (2022b	Unspecified	Mixed (BNT162b2/mRNA-1273)	SI	≥60	<84		0.690 [0.610, 0.750]
Tardot, et al. (2022b) US BAA. Treng, et al. (2022b) USA B Treng, et al. (2022b) USA B Grewal, et al. (2022b) USA B Teng, et al. (2022b) USA B Teng, et al. (2022b) Canada USA Teng, et al. (2022b) USA B Teng, et al. (2022b) USA B Tardot, et al. (2022b) USA B Tardot, et al. (2022b) US BA Pooled VE: nadults across all vaccine types against Al or SI, short te Indication, ong terma, 2nd al. (2022b) US BA Tardot, et al. (2022b) US BA Tardot et al. (2022b) US Tardot, et al. (2022b) US BA Tardot et al. (2022b) US Tardot, et al. (2022b) US BA Tardot et al. (2022b) US BA Tardot, et al. (2022b) USA BA Tardot et al. (2022b) USA BA Tardot, et al. (2022b) USA BA Tardot et al. (2022b) USA BA	BA.4/BA.5	Mixed (BNT162b2/mRNA-1273/Janssen)	Al in hospital	≥50	<90		0.660 [0.200, 0.850]
Tener, et al. (2022b) USA B Grewal, et al. (2022b) Canada B.1. Tenr, et al. (2022b) Canada B.1. Tenr, et al. (2022b) Canada B.1. Tenr, et al. (2022b) USA B.2. Tenr, et al. (2022b) USA B.3. Tenr, et al. (2022b) USA B.3. Tenr, et al. (2022b) USA B.3. Tenr, et al. (2022b) US B.4. Tenr, et al. (2022b) US B.4. Tenr, et al. (2022b) US B.4. Grewal, et al. (2022b) US B.4. Tenrof, et al. (2022b) US B.4. Tenrof, et al. (2022b) US B.4. Tenrof, et al. (2022b) US B.4. Tearg, et al. (2022b) USA B.4. Tearg, e	BA.4/BA.5	Mixed (BNT162b2/mRNA-1273/Janssen)	Al in ED	≥50	<90	i i -i	0.650 [0.350, 0.820]
Tener, et al. (2022b) USA B Grewal, et al. (2022b) Canada USA BA Grewal, et al. (2022b) Canada USA BA Taeng, et al. (2022b) USA BA BA Pooled VE in adults across all vaccine types against AI or SI, short te Indection, nog term, 2nd booster BA BA Tarof, et al. (2022b) US BA BA Grewal, et al. (2022b) USA BA Tarof, et al. (2022b) USA BA Tarof, et al. (2022b) USA BA Tarof, et al. (2022b) USA BA Tarof, et al. (2022b) USA BA Tarof, et al. (2022b) USA BA Tarof, et al. (2022b) USA BA Tarof, et al. (2022b) USA BA Tarof, et al. (2022b) USA BA Tarof, et al. (2022b) USA BA Pooled	BA.4	mRNA-1273	AI	≥18	14-90	⊢ • · · · · · · · · · · · · · · · · · ·	0.587 [0.325, 0.747]
Grewal, et al. (2022a) Canada B.1. Tarang, et al. (2022b) Canada Unsp. Tarang, et al. (2022b) USA BAJ Tarang, et al. (2022b) USA BAJ Tarang, et al. (2022b) USA BAJ Tardit, et al. (2022b) US BAJ Pooled VE: Tardit, et al. (2022b) US BAJ Tardit, et al. (2022b) US BAJ Grewal, et al. (2022b) US BAJ Grewal, et al. (2022b) US BAJ Tardit, et al. (2022b) USA BA Tardit, et al. (2022b) USA BA Tareng, et al. (2022b) USA B Pooled VE: ndults across all vaccine types against AJ, long territ, UR Nittayasoot, et al. (2022) Thailand BA, 1162, 2 Theng, et al. (2022b) USA B Fereval, et al. (2022b) U	BA.2	mRNA-1273	AI	≥18	14-90		0.572 [0.472, 0.653]
Grewal, et al. (2022b) USA BAA Tardor, et al. (2022c) Tahaliand BAA Tardor, et al. (2022c) Canada BAA Tardor, et al. (2022c) Canada BAA Tardor, et al. (2022c) USA BAA Grewal, et al. (2022c) USA BAA Tardor, et al. (2022c) USA BAA BAA Grewal, et al. (2022c) Canada BAA Tardor, et al. (2022c) Canada BAAA Tardor, et al. (2022c) Canada BAAA Tardor, et al. (2022c) Canada B	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	AI	≥60	≥7 40 (30)		0.490 [0.430, 0.540]
Tardin, rat. (2022b) USA BA. Tardix of al. (2022b) US BA. Procled VE: In dults across all vaccine types against Al or SI, short term ford, et al. (2022b) US BA. Tardix of al. (2022b) US BA. BA. Tardix of al. (2022b) US BA. Tardix of al. (2022b) US BA. Grewal, et al. (2022b) US BA. Tardix of al. (2022b) US BA. Tardix et al. (2022b) US BA. Tardix et al. (2022b) US BA. Tardix et al. (2022b) US BA. Tareng, et al. (2022b) USA BA. Fang, et al. (2022b) USA BA. Severo uccome, short term, 2nd booster Thiland BA. Nittayasoot, et al. (2022) Thailand BA. Theng, et al. (2022b) USA B Severo uccome, short term, 2nd booster Nittayasoot, et al. (2022) Thailand BA. Theng, et al. (2022b) USA BA. BA. Fererulandt al. (2022b	Unspecified	Mixed (BN1162b2/mRNA-1273)	AI	≥60	<84		0.490 [0.440, 0.540]
Tarang, et al. (2022b) USA BA Tarlot, et al. (2022b) USA BA Tarlot, et al. (2022b) USA BA Reveal, et al. (2022b) USA BA Tarlot, et al. (2022b) Canada Unsp Grewal, et al. (2022b) USA BA Tarlot, et al. (2022c) Thailand BA Tarlot, et al. (2022c) Thailand BA Tarlot, et al. (2022c) Canada BA TBA2 Grewal, et al. (2022c) USA BA Grewal, et al. (2022c) USA BA Canada BA TBA2 Grewal, et al. (2022c) USA BA Da Canada BA TBA2 Grewal, et al. (2022c) USA BA Da Canada BA TBA2 Grewal, et al. (2022c) USA BA Da Canada BA TBA2 Grewal, et al. (2022c) USA BA DA Da Canada BA TBA2 Grewal, et al. (2022c) Canada BA TBA2 Grewal, et al. (2022	BA.2.12.1	Mixed (BNT162b2/mBNA=1273 (Japaneon)	AL	218	14-90		0.472 [0.346, 0.574]
Tardie, dra (2022b) US EA Procled VE: Induits across all vaccine types against AI or SI, short te Infection, long term, 2nd booster Infection, long term, 2nd booster Tarof, et al. (2022b) US BAA Grewal, et al. (2022b) US BAA Tarof, et al. (2022b) USA BA Tarage, et al. (2022b) USA BA Tareng, et al. (2022b) USA BA Severo uccome, short term, 2nd booster Thialand BA Nittayasoot, et al. (2022) Thailand BA Tareng, et al. (2022b) USA B Severo uccome, short term, 2nd booster Nittayasoot, et al. (2022) Thailand BA Tareng, et al. (2022b) USA BA BA BA Tereng et al. (2022b) USA BA BA BA	BA.4/BA.5	mRNA=1273	ALINOC	≥30	14-90		0.349[0.158_0.497]
Pooled VE in adults across all vaccine types against Al or SI, short VE in induction, ong term, 2nd boostor BA Tartof, et al. (2022b) US BAA Grewal, et al. (2022b) Canada Unsp. Tartof, et al. (2022b) US BAA Tartof, et al. (2022b) USA BA Tartof, et al. (2022b) USA BA Tartof, et al. (2022b) USA BA Tartof, et al. (2022c) USA BA Tartof, et al. (2022c) USA BA Severo outcome, short torm, 2nd booster BA 1992A Grewal, et al. (2022c) Canada BA 1992A Grewal, et al. (2022c) Canada BA 1992A Grewal, et al. (2022c) USA BA 2992A Admas, et al. (2022c)	BA 4/BA 5	Mixed (BNT162b2/mRNA-1273/Janssen)	Al in outpatient	≥50	<90		0.280 [0.100, 0.430]
Infection, long term, 2nd Booster Tartof, et al. (2022b) US BAA Grewal, et al. (2022b) Canada Unsp Tartof, et al. (2022b) US BAA Tartof, et al. (2022b) US BA Trentof, et al. (2022b) USA BA Tenng, et al. (2022b) USA B Pooled VE: nadults across al vaccine types against AI, long term: (Nittayaoot, et al. (2022) Nittayaoot, et al. (2022) Thailand BA. Treng, et al. (2022b) USA B Grewal, et al. (2022) Thailand BA. Tareng, et al. (2022b) USA B Grewal, et al. (2022b) Canada BA. Tareng, et al. (2022b) Canada USA Tareng, et al. (2022b) Canada USA Tareng, et al. (2022b) USA US	igainst AI or SI, short term: (Q =	373.19, df = 16, p < .01; l ² = 94.6%, l ² = 1.05e ⁻⁰¹)				★	0.596 [0.520, 0.661]
Tardor, et al. (2022b) US BAA. Grewal, et al. (2022b) Canada Unsp. Grewal, et al. (2022b) Canada Unsp. Tartor, et al. (2022b) US BAA. Tartor, et al. (2022b) USA BAA. Tartor, et al. (2022b) USA BAA. Tartor, et al. (2022b) USA BAA. Severo outcome, abort torm, 2nd booster BAA. Ba Nithayaoot, et al. (2022c) Thaliand BAA. Nithayaoot, et al. (2022c) Canada BA.1196.2 Grewal, et al. (2022c) USA BA.20 Grewal, et al. (2022c) USA BA.20 Jank-Grewal, et al. (2022c) USA BA.196.2 Grewal, et							
Grewal, et al. (2022b) Canada Unsp. Tarof, et al. (2022b) US BAA. Tarof, et al. (2022b) US A B Tarof, et al. (2022b) US A B Pooled VE: nadults across all vaccine types against Al. (ong term.) Nittayasoot, et al. (2022) Nittayasoot, et al. (2022) Thailand BA. Treng, et al. (2022b) USA B Grewal, et al. (2022) Thailand BA. Taraf, et al. (2022b) USA B Grewal, et al. (2022b) USA B Grewal, et al. (2022b) USA B Fordmands, et al. (2022b) Canada BA. 1954.2 Grewal, et al. (2022b) USA USA Fordmands, et al. (2022b) USA USA Adams, et al. (2022b)	BA.4/BA.5	Mixed (BNT162b2/mRNA=1273/Janssen)	AI in ED	≥50	≥90		0.780 [0.500, 0.910]
Grewal, et al. (2022b) US BAA Tartof, et al. (2022b) USA BA Tartof, et al. (2022b) USA BA Tenen, et al. (2022c) USA BA Tenen, et al. (2022c) USA BA Severo outcome, short torm, 2nd booster BAA BA Tenen, et al. (2022c) Thailand BA BA Grewal, et al. (2022c) Canada BA (196.) Grewal, et al. (2022c) Canada BA (196.) Grewal, et al. (2022c) USA BA BA BA Grewal, et al. (2022c) USA BA BA Grewal, et al. (2022c) USA BA BA Grewal, et al. (2022c) USA BA BA	Unspecified	Mixed (BNT162b2/mRNA-1273)	SI	≥60	≥84	. H+I	0.535 [0.465, 0.596]
lafot et al. (2022b) US BA/A Taeng, et al. (2022b) USA B Pooled VE in adults across all vaccine types against Al. (ong term.) Nittayasoot, et al. (2022) Thailand Severo uccome, short term, 2nd booster Nittayasoot, et al. (2022) Thailand BA. 116A.2 Severo utcome, short term, 2nd booster USA B BA/16A.2 Grewal, et al. (2022) Thailand BA.116A.2 Grewal, et al. (2022) Canada BA.116A.2 Grewal, et al. (2022b) USA B BA.116A.2 Grewal, et al. (2022b) USA BA.116A.2 Fordmands, et al. (2022b) USA BA.116A.2 Grewal, et al. (2022b) USA BA.116A.2 Fordmands, et al. (2022b) USA USA USA BA.202 Fordmands, et al. (2022b) USA USA USA Madmar, et al. (2022b) USA <	Unspecified	Mixed (BNT162b2/mRNA-1273)	Al	≥60	≥84	. I+I .	0.355 [0.313, 0.394]
Halling and (2002) USA BBA Harring et al. (2022b) USA BAA Tarlot et al. (2022b) USA BAA Tarlot, et al. (2022b) USA BAA Tarlot, et al. (2022b) USA BA Tarlot, et al. (2022b) USA BA Pooled VE in adults across all vaccine types against AL long term: (In Severe outcome, short term, 2nd booster Titigrasot, et al. (2022) Thailand BA.1 Tereng, et al. (2022c) Thailand BA.1 Tereng, et al. (2022c) Canada BA.1 Grewal, et al. (2022) Canada BA.1 Grewal, et al. (2022c) Canada BA.1 Grewal, et al. (2022c) USA BA Grewal, et al. (2022c) USA BA.1 Grewal, et al. (2022c) USA BA.1 Grewal, et al. (2022c) USA BA.2 Marins et al. (2022c) USA BA.1 Grewal, et al. (2022c) USA BA.1 Adams et al. (2022c) USA BA.1 Grewal, et al. (2022	BA.4/BA.5	Mixed (BNT162b2/mRNA=1273/Janssen)	Al in hospital	≥50	290		0.330 [-1.120, 0.790]
Tareng, et al. (2022b) USA BA Tseng, et al. (2022b) USA BA Pooled VE in adults access all vaccine types against AI, long term. (f Severe outcome, short term, 2nd booster Nittayasot, et al. (2022) Thailand BA 1 Tseng, et al. (2022b) USA BA Severe outcome, short term, 2nd booster Nittayasot, et al. (2022) Thailand BA 1 Tseng, et al. (2022) Thailand BA 1 Tseng, et al. (2022) Canada BA 1BA 2 Grewal, et al. (2022) Canada BA 1BA 2 Grewal, et al. (2022) Canada BA 1BA 2 Grewal, et al. (2022) Canada BA 1BA 3 Tseng, et al. (2022b) USA BA 2 Ferdinands, et al. (2022b) Canada BA 1BA 2 Grewal, et al. (2022b) Canada BA 1BA 3 Grewal, et al. (2022b) Canada BA 1BA 4 Grewal, et al. (2022b) Canada BA 1BA 4 Grewal, et al. (2022b) Canada BA 1BA 4 Grewal, et al. (2022b) USA BA 2 Ferdinands, et al. (2022b) USA BA 2 Ferdinands, et al. (2022b) USA BA 2 Grewal, et al. (2022b) USA BA 1BA 4 Grewal, et al. (2022b) Canada B	BA.4/BA.5	Mixed (BN116202/mRNA=1273/Janssen)	AI in UC	250	290		0.200 [-0.230, 0.480]
Tartof, et al. (2022b) USA BA Tseng, et al. (2022b) USA B Tseng, et al. (2022b) USA B Pooled VE in adults across all vaccine types against Al, long term. (Severe outcome, short term, 2nd booster Nittayascot, et al. (2022) Thailand BA (Tiseng, et al. (2022) Thailand BA (Treewal, et al. (2022) Canada BA /156.2 Grewal, et al. (2022) USA BA BA (Grewal, et al. (2022) USA BA (Grewal, et al. (2022) USA BA (Grewal, et al. (2022) USA BA (Grewal, et al. (2022) Canada BA /156.2 Grewal, et al. (2022) Canada BA /156.2 Grewal, et al. (2022) Canada BA /156.2 Grewal, et al. (2022) USA BA (Grewal, et al. (2022) Canada BA /156.2 Grewal, et al. (2022) Canada CA /156.2 Grewal, et al.	BA.2 BA.2.12.1	mRNA-1273	AL	218	>90		0.173 [=0.453, 0.626]
Tseng, et al. (2022b) USA B Tseng, et al. (2022b) USA B Pooled VE in adults across all vaccine types against AI, long term. (f Severe outcome, short term, and thooster Nittayasot, et al. (2022) Thailand B A1 Tiseng, et al. (2022) Thailand B A1 Tiseng, et al. (2022) Thailand B A1 Tiseng, et al. (2022) USA B Grewal, et al. (2022) Canada B A1BA Grewal, et al. (2022) Canada B A1BA Grewal, et al. (2022) Canada B A1BA Tiseng, et al. (2022) Canada B A1BA Grewal, et al. (2022) Canada B A1BA Tiseng, et al. (2022) USA B A1BA Ferdinands, et al. (2022) USA B A1BA Ferdinands, et al. (2022) USA B A1BA Ferdinands, et al. (2022) USA B A1BA Crewal, et al. (2022) USA B A1BA Crewal, et al. (2022) USA B A1BA Crewal, et al. (2022) Canada B A1BA Crewal, et a	BA 4/BA 5	Mixed (BNT162b2/mRNA-1273/Janssen)	Al in outpatient	>50	>90		0.110 [-0.180, 0.340]
Tseng, et al. (2022b) USA B Pooled VE in adults across all vaccine types against Al, long term: (V Severe outcome, short term, 2nd booster Nittayasoot, et al. (2022) Thailand BA1 Tiseng, et al. (2022) Thailand BA1 Grewal, et al. (2022) Canada BA1/BA2 Grewal, et al. (2022) USA BA2 Ferdinands, et al. (2022) USA BA2 Ferdinands, et al. (2022) USA Usp Ferdinands, et al. (2022) USA Usp Pooled VE in adults across all vaccine types against severe outcome Grewal, et al. (2022) Grewal, et al. (2022) Canada BA1/BA2 Grewal, et al. (2022) Canada	BA.4	mRNA-1273	Al	≥18	>90		0.063 [-0.663, 0.704]
Pooled VE in adults across all vaccine types against AI, long term: (f Severe outcome, short term, 2nd booster Nittayasot, et al. (2022) Thailand BA 1 Taeng, et al. (2022) Thailand BA 1 Taeng, et al. (2022) USA B Grewal, et al. (2022) Canada BA 1BA 2 Grewal, et al. (2022) Canada BA 1BA 2 Grewal, et al. (2022) Canada BA 1BA 2 Grewal, et al. (2022) USA BA 1BA 2 Grewal, et al. (2022) USA BA A Grewal, et al. (2022) USA BA 2 Ferdinands, et al. (2022) USA BA 2 Ferdinands, et al. (2022) USA BA 2 Grewal, et al. (2022) USA BA 2 Ferdinands, et al. (2022) USA BA 2 Grewal, et al. (2022) USA BA 2 Ferdinands, et al. (2022) USA BA 2 Grewal, et al. (2022) USA Canada BA 1BA 2 Grewal, et al. (2022) USA Canada CA Grewal, et al. (2022)	BA.5	mRNA-1273	AI	≥18	>90		0.050 [-0.569, 0.611]
Severe outcome, short term, 2nd booster Nittayasoot, et al. (2022) Thailand BA. Nittayasot, et al. (2022) Thailand BA. Taeng, et al. (2022) USA BA Grewal, et al. (2022) Canada BA.116A.2 Grewal, et al. (2022) Canada BA.116A.2 Grewal, et al. (2022) Canada BA.116A.2 Grewal, et al. (2022) Canada BA.116A.2 (2022) Canada BA.116A.2 (2022) USA BA.116A.2 USA BA.116A.2 Display the al. (2022) USA BA.116A.2 Display the al. (2022) USA BA.2 Display the al. (2022) USA BA.2 Display the al. (2022) USA BA.116A.2 Display the al. (2022) USA BA.116A.2 Display the al. (2022) USA BA.116A.2 Product B.2 Grewal, et al. (2022) USA BA.116A.2 Pooled VE In adults across all vaccine types against severe outcome Grewal, et al. (2022) Canada BA.116A.2 Grewal, et al. (against AI, long term: (Q = 34.37	df = 9, p < .01; l ² = 78.8%, l ² = 6.81e ⁻⁰²)				-	0.327 [0.154, 0.464]
Nittayasot, et al. (2022) Thailand BA. Tareng, et al. (2022) Canada BA. Starwal, et al. (2022) Canada BA. Grewal, et al. (2022) USA USA Ferdinands, et al. (2022) USA USA Ferdinands, et al. (2022) USA USA Severe outcome. Iong term, 2nd booster Severe outcome. BA. Grewal, et al. (2022) Canada BA. HA. Grewal, et al. (2022) Canada BA. HA. Severe outcome. Iong term, 2nd booster Grewal, et al. Canada HA. Grewal, et al. (2022) Canada BA. HA. Grewal, et al. (2022)							
Nittayasot, et al. (2022) Thailand BA:1 Treeng, et al. (2022b) USA B Grewal, et al. (2022b) USA Grewal, et al. (2022b) Canada BA:1BA:2 Grewal, et al. (2022b) Canada BA:1BA:2 Ferdinands, et al. (2022b) USA BA:20 Ferdinands, et al. (2022b) USA USA Pooled VE in adults across all vaccine types against severe outcome Severe outcome, long term, <i>Indooster</i> Grewal, et al. (2022b) Canada BA:1BA:2 Grewal, et al. (2022b) USA USA Pooled VE in adults across all vaccine types against severe outcome Grewal, et al. (2022b) Canada BA:1BA:2 Grewal, et al. (2022b) Canada BA:1BA:2 Grewal, et al. (2022c) Canada BA:1BA:2 Grewal, et al.(2022c) C	BA.1/BA.2	Mixed (BNT162b2/mRNA-1273/ChAdOx1/CoronaVa	ic) INV	Majority are 18-59	9 42 (0)		0.996 [0.970, 0.999]
Teng, et al. (2022) Canada BA / IBA 2 Grewal, et al. (2022c) Canada BA / IBA 2 Grewal, et al. (2022c) Canada BA / IBA 2 Grewal, et al. (2022c) Canada BA / IBA 2 Grewal, et al. (2022c) Canada BA / IBA 2 Ferdiands, et al. (2022b) USA BA / IBA 2 Ferdiands, et al. (2022b) USA USA Ferdiands, et al. (2022b) USA USA Ferdiands, et al. (2022b) USA USA Severe outcome. fong term, 2nd booster Severe outcome. Grewal, et al. (2022b) Canada DA / IBA 2 Grewal, et al. (2022b) USA USA Severe outcome. fong term, 2nd booster Grewal, et al. (2022b) Canada Grewal, et al. (2022c) Canada DA / IBA 2 Grewal, et al. (2022c) Canada DA / IBA 2 Grewal, et al. (2022b) Canada DA / IBA 2 Grewal, et al. (2022c) Canada DA / IBA 2 Grewal, et al. (2022b) Canada DA / IBA 2 Grewal, et al. (2022b)	BA.1/BA.2	Mixed (BN1162b2/mRNA=1273/ChAdOx1/CoronaVa	ic) D	Majority are 18-59	42 (0)	, H	0.993 [0.945, 0.999]
Grewal, et al. (2022) Grewal, et al. (2022) USA Bereval, et al. (2022) Canada BA.1/BA.2 Grewal, et al. (2022) Canada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Conada Cona	BA.2	mRNA-12/3	н	218	214 Majority < 90		0.964 [0.884, 0.989]
Crewal, et al. (2022c) Graval, et al. (2022c) Graval, et al. (2022c) Graval, et al. (2022b) Graval, et al. (2022c) Graval, et al. (2022c) Graval	BA.1/BA.2/BA.4/BA	5 Mixed (BNT162b2/mRNA=1273) 5 Mixed (BNT162b2/mRNA=1273)	H/D	50-59	7-119		0.935 [0.901, 0.962]
Grewal, et al. (2022b) USA B.1/BA. Grewal, et al. (2022b) USA B.1/BA. Grewal, et al. (2022b) USA B.1/BA. Grewal, et al. (2022b) USA B.A.2/B. Ferdinands, et al. (2022b) USA USA B.A.2/B. Ferdinands, et al. (2022b) USA USA Pooled VE in adults across all vaccine types against severe outcome Severe outcome, long term, And booster Grewal, et al. (2022b) USA B.A.1/BA.2 Grewal, et al. (2022b) USA B.A.1/BA.2 Grewal, et al. (2022b) USA B.A.1/BA.2 Grewal, et al. (2022c) Canada B.A.1/BA.2 Grewal	BA 1/BA 2/BA 4/BA	5 Mixed (BNT162b2/mRNA=1273)	H/D	60-69	7-119	ġ.	0.919 [0.892, 0.940]
Tseng, et al. (2022b) USA BA Grewal, et al. (2022a) Canada BA1 Grewal, et al. (2022b) Canada Unsp. Link-Gelles, et al. (2022) USA BA2, 202 Ferdinands, et al. (2022b) USA Unsp. Jadams, et al. (2022b) USA Unsp. Adams, et al. (2022b) USA Unsp. Grewal, et al. (2022b) USA Unsp. Grewal, et al. (2022c) USA Unsp. Grewal, et al. (2022c) Canada BA 1/BA2 Grewal, et al. (2022c) Canada Unsp. Pooled VE in adults across all vaccine types against severe outcome Second Unsp. FIGURE 3 Overall vaccine effectiveness of second Second	BA.1/BA.2/BA.4/BA	5 Mixed (BNT162b2/mRNA-1273)	H/D	≥80	7-119	H	0.910 [0.893, 0.925]
Grewal, et al. (2022a) Canada B.1. Grewal, et al. (2022b) Canada Unsp. Link-Gelles, et al. (2022) USA BA.2/B Ferdinands, et al. (2022) USA Unsp. Adams, et al. (2022) USA Unsp. Adams, et al. (2022) USA BA.1/BA.2 Force UC in adults across all vaccine types against severe outcome <i>Severe outcome</i> , <i>long term, Zarb dooster</i> Grewal, et al. (2022) Canada BA.1/BA.2 Grewal,	BA.4/BA.5	mRNA-1273	н	≥18	≥14 Majority < 90	⊢ ` ⊣	0.885 [0.518, 0.972]
Grewal, et al. (2022b) Canada Unsp. Link-Gelles, et al. (2022b) USA BA.272 Ferdinands, et al. (2022b) USA Unsp. Ferdinands, et al. (2022b) USA Unsp. Adams, et al. (2022b) USA Unsp. Grewal, et al. (2022c) Canada BA.176A.2 Grewal, et al.2 Grewal, e	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	SO	≥60	≥7 40 (30)	+	0.860 [0.810, 0.900]
Link-Gelles, et al. (2022) USA BA205 Ferdinands, et al. (2022b) USA Unsp Ferdinands, et al. (2022b) USA Unsp Adams, et al. (2022b) USA BA108-2 Pooled VE in adults across all vaccine types against severe outcome Severe outcome, fong term, And booster Grewal, et al. (2022b) Canada BA108-2 Grewal, et	Unspecified	Mixed (BNT162b2/mRNA-1273)	SO	≥60	<84		0.820 [0.770, 0.860]
Ferdinands, et al. (2022b) USA Unap Adams, et al. (2022b) USA Unap Adams, et al. (2022b) USA Unap Adams, et al. (2022b) USA USA Severe aucome. Iong ferm, 2nd boaster Greval, et al. (2022c) Canada BA 1/BA2 Greval, et al. (2022c) Canada CANA Greval, et al. (2022c) Canada CANA Greval, et al. (2022c) Canada CANA Greval, et al. (2022c) CANA Grev	BA.2/BA.2.12.1	Mixed (BNT162b2/mRNA-1273)	н	≥50	≥7 27 (17-41)		0.800 [0.710, 0.850]
Ferdinands, et al. (2022) USA Uniph Pooled VE: n adults across all vaccine types against severe outcome Severe outcome, forg (tern, And Deoster Grewal, et al. (2022) Canada BA 1/86.2 Pooled VE in adults across all vaccine types against severe outcome FIGURE 3 Overall Vaccine effectiveness of sec Overall vaccine set	Unspecified	Mixed (BNT162b2/mRNA-1273)	н	≥65	7-60 33 (19-50)	, H•1,	0.760 [0.710, 0.800]
Pooled VE in adults across all vaccine types against severe outcome Severe automo. Iong ferri, 2nd Doaster Greval, et al. (2022c) Greval,	Unspecified	Mixed (BN1162D2/mRNA=1273)	н	50-64	27 33 (19-50)		0.720 [0.510, 0.830]
Severe outcome, long term, 2nd booster Greval, et al. (202c) Greval, et al. (202c) Freval, et al. (202c) Found VE in adults across all vaccine types against severe outcome Figure 3 Overall vaccine effectiveness of sector	BA. I/BA.2/BA.4/BA against severe outcomes short te	rm: ($\Omega = 183.40$ df = 15 n < $\Omega \cdot 1^2 = 97.9\%$ $\Pi^2 = 1.54e^{+00}$		210	27 26 (15-42)		0.873 [0.376, 0.786]
Greval et al. (2022c) Greval et al. (2022c) Granada BA.168A. Greval et al. (2022c) Granada Unsp Pooled VE in adults across all vaccine types against severe outcome		in the restriction with restriction restriction in the	,				0.010[0.100, 0.004]
Grewal et al. (2022c) Canada BA (1962). Grewal et al. (2022c) Canada BA (1962). Grewal et al. (2022c) Canada BA (1962). Grewal et al. (2022c) Canada Unsp Pooled VE in adults across all vaccine types against severe outcome FIGURE 3 Overall vaccine effectiveness of sec	BA.1/BA.2/BA.4/BA	5 Mixed (BNT162b2/mRNA-1273)	H/D	70-79	≥120	H	0.890 [0.840, 0.920]
Grewal, et al. (2022c) Canada BA.178.4 Grewal, et al. (2022c) Canada BA.178.4 Grewal, et al. (2022c) Canada Unep Pooled VE in adults across all vaccine types against severe outcome	BA.1/BA.2/BA.4/BA	5 Mixed (BNT162b2/mRNA-1273)	H/D	≥80	≥120	i-i	0.880 [0.850, 0.910]
Greewal, et al. (2022c) Canada BA.186.4 Greewal, et al. (2022b) Canada Unsp. Pooled VE in adults across all vaccine types against severe outcome FIGURE 3 Overall vaccine effectiveness of sec	BA.1/BA.2/BA.4/BA	5 Mixed (BNT162b2/mRNA=1273)	H/D	60-69	≥120	i i i i i i i i i i i i i i i i i i i	0.880 [0.790, 0.930]
Grewal, et al. (2022b) Canada Unsp Pooled VE in adults across all vacine types against severe outcome FIGURE 3 Overall vaccine effectiveness of sec	BA.1/BA.2/BA.4/BA	5 Mixed (BNT162b2/mRNA=1273)	H/D	50-59	≥120		0.860 [0.440, 0.960]
FIGURE 3 Overall vaccine effectiveness of sec	Unspecified	Mixed (BNT162b2/mRNA-1273)	SO	≥60	≥84	H H	0.780 [0.738, 0.815]
FIGURE 3 Overall vaccine effectiveness of sea	against severe outcomes, short te	rm: (Q = 23.09, df = 4, p < .01; l ⁺ = 76.9%, l ⁺ = 9.28e ⁻⁰²)				•	0.859 [0.803, 0.899]
FIGURE 3 Overall vaccine effectiveness of sea	BA.1/BA.2/BA.4/BA Unspecified against severe outcomes, short te		H/D SO	50-59 ≥60	≥120 ≥84		0.860 [0.4 0.780 [0.7 0.859 [0.8
Overall vaccine effectiveness of sec					-0,500 0 Va	0.000 0.500 1.000 accine Effectiveness	
Overall vaccine effectiveness of see							
	eness of second	booster dose against infection	or sympt	omatic infe	ction and against severe	events Pooled VF es	timates are
		booster dose against inflection	Si Sympt		a and against severe	CVCING. I OOICU VE CS	cimates are
stratified by short-term (<60 davs)	n (<60 days) vs. lo	ng-term (>60 days). Statistics (Cochran's	Q, I ² and τ	² measure the heteroae	neity between studies	. For
the fact that the second s			(CI)	. the for a star of		a sette terrene en el se e tret	

hospitalization (H), death (D), severe outcomes (SO) or invasive procedures (INV). Mixed vaccine type indicates the study reported VEs of these vaccines combined without distinguishing between them.

events (Egger's test p = 0.027, Begg's test p = 0.369), short-term VE of the first booster dose against severe events (Egger's test p = 0.098, Begg's test p = 0.49), and short-term VE of the second booster dose against severe events (Egger's test p = 0.001, Begg's test p = 0.747), as shown in Supplementary Figures 8–11. Additionally, publication bias was found in four subgroups defined by age group and vaccine type (Supplementary Figure 12). Results were corrected for these biases using the trim-and-fill method.

Discussion

In this systematic review and meta-analysis of 42 studies, we found that one or two booster doses in addition to the initial full COVID-19 vaccine series provided substantial protection against Omicron infection with VE \geq 50% and severe events with VE \geq 80%, compared to no vaccination. In general, pure and partial mRNA vaccines provided comparable protection levels against infection or severe disease, and both were more effective than non-mRNA vaccines, though the difference was less dramatic in terms of protection against severe disease. The VEs of the full doses and the booster doses against severe disease only wane slightly after 3 months, but the VEs against infection wane more quickly.

Both the first and second booster doses provided considerably higher VE against infection and severe events compared to completion of the initial full series only. Studies have reported higher anti-receptor binding domain specific memory B cells and anti-spike antibodies after booster doses compared to full series only (23, 62). Similarly, T cell immunity against Omicron is provided by booster doses though at a reduced level compared to ancestral variants (63). While the initial full doses provided inadequate protection against infection (Figure 2A), they did render practically meaningful (\geq 50%) VE against severe disease (Figure 4A).

Pure and partial mRNA vaccines offered comparable protection levels against infection, 25.4% vs. 28.1% for the full doses and 61.4% vs. 56.4% for the first booster among adults, and both were much more effective than the non-mRNA vaccines (1.5% for the full doses and 25.2% for the first booster). Studies included in this analysis reported lower binding activities between antispike and anti-receptor among Ad26.COV2 recipients compared to mRNA recipients (23). Similar trends were observed against severe events, though the gap between mRNA and non-mRNA vaccines was much narrower. In particular, full-dose non-mRNA vaccines provided a similar level of sustained protection against severe disease (VE = 60%) compared to full-dose mRNA vaccines (Supplementary Figure 6), suggesting that the initial full doses of

Author(s) and Year	Region	Omicron Subvariant	Vaccine	Case Event	Age Group (vears)	Test Timing (davs)			Estimate [95% C
Pure mRNA Vaccines, full doses					0	(
Buchan, et al. (2022b)	Canada	BA.1/BA.1.1	BNT162b2/BNT162b2	H/D	12-17	≥7		⊢ •-1	0.850 [0.740, 0.91
Tseng, et al. (2022a)	USA	B.1.1.529	mRNA-1273/mRNA-1273	н	≥18	≥14			0.845 [0.230, 0.96
Florentino, et al. (2022)	Brazil	B.1.1.529	BNT162b2/BNT162b2	H/D	12-17	≥14			0.829 [0.798, 0.85
Altarawneh, et al. (2022)	Qatar	BA.1/BA.2	BNT162b2/BNT162b2	H/D	all ages	≥14		⊢ •-	0.735 [0.605, 0.82
Collie, et al. (2022) So	outh Africa	B.1.1.529	BNT162b2/BNT162b2	н	≥18	≥14		H=H	0.700 [0.620, 0.76
Gary, et al. (2022) So	outh Africa	B.1.1.529	BNT162b2/BNT162b2	н	≥18	≥14			0.696 [0.673, 0.71
Price, et al. (2022)	USA	B.1.1.529	BNT162b2/BNT162b2	н	5-11	≥14		⊢ −−	0.680 [0.420, 0.82
Itarawneh, et al. (2022)	Qatar	BA.1/BA.2	mRNA-1273/mRNA-1273	H/D	all ages	≥14		——————————————————————————————————————	0.663 [0.383, 0.81
auring, et al. (2022)	USA	B.1.1.529/BA lineages	Mixed (BNT162b2/mRNA-1273)	н	≥18	≥14		⊢•	0.650 [0.510, 0.75
′oung-Xu, et al. (2022)	USA	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	н	≥18	≥14		Hel	0.630 [0.580, 0.67
artof, et al. (2022a)	USA	B.1.1.529	BNT162b2/BNT162b2	н	≥18	≥7		+•+	0.620 [0.530, 0.69
erdinands, et al. (2022a)	USA	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	н	≥18	≥14		H=H	0.550 [0.500, 0.60
Grewal, et al. (2022a)	Canada	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	H/D	≥60	NR		⊢-•	0.520 [0.330, 0.65
dams, et al. (2022)	USA	BA.1/BA.2/BA.4/BA.5	mRNA-1273/mRNA-1273	н	≥18	≥14		⊢ •−1	0.410 [0.250, 0.54
rice, et al. (2022)	USA	B.1.1.529	BNT162b2/BNT162b2	н	12-18	≥14		⊢ •−−1	0.400 [0.090, 0.60
dams, et al. (2022)	USA	BA.1/BA.2/BA.4/BA.5	BNT162b2/BNT162b2	н	≥18	≥14		⊢ •−1	0.360 [0.210, 0.48
lein, et al. (2022)	USA	B.1.1.529	BNT162b2/BNT162b2	ED/UC	12-15	≥14		⊢ •−1	0.210 [0.076, 0.32
(lein, et al. (2022)	USA	B.1.1.529	BNT162b2/BNT162b2	ED/UC	16-17	≥14	H		0.107 [-0.080, 0.26
ooled VE in adults: (Q = 64.19, df =	= 9, p < .01;	$I^2 = 86.0\%$, $\tau^2 = 4.71e^{-02}$)					•	0.601 [0.531, 0.66
ooled VE in children and adolescer	nts: (Q = 25	4.73, df = 5, p < .01; l ² =	97.9%, τ ² = 5.88e ⁻⁰¹)						0.599 [0.247, 0.78
ooled VE in all age groups: (Q = 3	57.51, df = 1	17, p < .01; $I^2 = 95.8\%$, τ^2	= 2.14e ⁻⁰¹)					-	0.609 [0.507, 0.68
Partial mRNA Vaccines, full doses									
Buchan, et al. (2022a)	Canada	B.1.1.529	Mixed (≥1 mRNA Vaccine)	H/D	≥18	≥7		⊢ •⊣	0.732 [0.596, 0.82
towe, et al. (2022)	UK	Unspecified	Mixed (BNT162b2/mRNA-1273/ChAdOx1	EC -> H	≥65	≥14		⊢•+	0.676 [0.575, 0.75
irsebom, et al. (2022a)	UK	BA.1	Mixed (BNT162b2/mRNA-1273/ChAdOx1	н	≥18	≥14		⊢•	0.560 [0.455, 0.64
towe, et al. (2022)	UK	Unspecified	Mixed (BNT162b2/mRNA-1273/ChAdOx1	EC -> H	18-64	≥14		Hel	0.468 [0.421, 0.51
dams, et al. (2022)	USA	BA.1/BA.2/BA.4/BA.5	Mixed (BNT162b2/mRNA-1273/Janssen)	н	≥18	≥14		⊢ •-	0.385 [0.277, 0.47
(irsebom, et al. (2022a)	UK	BA.2	Mixed (BNT162b2/mRNA-1273/ChAdOx1	н	≥18	≥14		⊢ • − 1	0.371 [0.076, 0.57
ooled VE in adults: (Q = 29.23, df =	= 5, p < .01;	$I^2 = 89.6\%, \tau^2 = 8.55e^{-0.2}$)					-	0.545 [0.411, 0.64
ooled VE in adults across all vaccin	ie types: (Q	e = 164.41, df = 15, p < .0	1; I ² = 89.4%, τ ² = 6.15e ⁻⁰²)					•	0.579 [0.515, 0.63
ooled VE in all age groups across a	all vaccine ty	vpes: (Q = 454.85, df = 2	5, p < .01; $I^2 = 95.6\%$, $\tau^2 = 2.03e^{-01}$)					•	0.573 [0.485, 0.64
est for VE Difference in All across V	accine Type	es: Q _M = 0.41, df = 1, p =	0.52						

-0.500 0.000 0.500 Vaccine Effectiveness

в

Author(s) and Year	Region	Omicron Subvariant	Vaccine	Case Event	Age Group (years)	Test Timing (days)			Estimate [95% CI]
Pure mRNA Vaccines, booster o	lose								
Tseng, et al. (2022a)	USA	B.1.1.529	mRNA-1273/mRNA-1273/mRNA-1273	н	≥18	≥14		H-1	0.992 [0.763, 1.000]
Altarawneh, et al. (2022)	Qatar	BA.1/BA.2	BNT162b2/BNT162b2/BNT162b2	H/D	all ages	≥7		⊢+(0.925 [0.844, 0.963]
Young-Xu, et al. (2022)	USA	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	н	≥18	≥14			0.890 [0.880, 0.910]
Ferdinands, et al. (2022a)	USA	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	н	≥18	≥14		H	0.880 [0.860, 0.900]
Lauring, et al. (2022)	USA	B.1.1.529/BA lineages	Mixed (BNT162b2/mRNA-1273)	н	≥18	≥7		H-4	0.860 [0.770, 0.910]
Grewal, et al. (2022a)	Canada	B.1.1.529	Mixed (BNT162b2/mRNA-1273)	H/D	≥60	≥0			0.830 [0.824, 0.837]
Altarawneh, et al. (2022)	Qatar	BA.1/BA.2	mRNA-1273/mRNA-1273/mRNA-1273	H/D	all ages	≥7	-		0.827 [-0.802, 0.983]
Tartof, et al. (2022a)	USA	B.1.1.529	BNT162b2/BNT162b2/BNT162b2	н	≥18	≥14		⊢ -	0.820 [0.770, 0.870]
Klein, et al. (2022)	USA	B.1.1.529	BNT162b2/BNT162b2/BNT162b2	ED/UC	16-17	≥7		⊢ −+	0.810 [0.590, 0.910]
Adams, et al. (2022)	USA	BA.1/BA.2/BA.4/BA.5	mRNA-1273/mRNA-1273/mRNA-1273	н	≥18	≥7		⊢⊷⊣	0.650 [0.550, 0.730]
Adams, et al. (2022)	USA	BA.1/BA.2/BA.4/BA.5	BNT162b2/BNT162b2/BNT162b2	н	≥18	≥7		H•	0.640 [0.550, 0.720]
Pooled VE in adults: (Q = 125.86,	df = 7, p < .0	01; I ² = 96.9%, τ ² = 2.39e ⁻⁰	")					•	0.825 [0.747, 0.880]
Pooled VE in all age groups: (Q =	130.77, df =	10, p < .01; I ² = 95.7%, τ ²	= 2.33e ⁻⁰¹)					•	0.836 [0.770, 0.882]
Partial mRNA Vaccines, booster	r dose								
Buchan, et al. (2022a)	Canada	B.1.1.529	Mixed (≥1 mRNA Vaccine)/BNT162b2	H/D	≥18	≥7		⊢+	0.950 [0.870, 0.980]
Buchan, et al. (2022a)	Canada	B.1.1.529	Mixed (≥1 mRNA Vaccine)/mRNA-1273	H/D	≥18	≥7		⊢ +	0.930 [0.740, 0.980]
Stowe, et al. (2022)	UK	Unspecified	Mixed (BNT162b2/mRNA-1273/ChAdOx1)	EC -> H	≥65	≥7			0.913 [0.899, 0.925]
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/BNT162b2	H/D	18-59	>7			0.910 [0.897, 0.921]
Kirsebom, et al. (2022b)	UK	BA.1/BA.2	ChAdOx1/ChAdOx1/BNT162b2	н	≥65	≥7		н	0.909 [0.887, 0.927]
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/BNT162b2	H/D	60-74	>7			0.898 [0.887, 0.907]
Kirsebom, et al. (2022a)	UK	BA.1	Mixed (BNT162b2/mRNA-1273/ChAdOx1)	н	≥18	≥7		н	0.855 [0.835, 0.872]
Stowe, et al. (2022)	UK	Unspecified	Mixed (BNT162b2/mRNA-1273/ChAdOx1)	EC -> H	18-64	≥7		H	0.782 [0.766, 0.797]
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/BNT162b2	H/D	≥75	>7		н	0.782 [0.761, 0.800]
Kirsebom, et al. (2022a)	UK	BA.2	Mixed (BNT162b2/mRNA-1273/ChAdOx1)	н	≥18	≥7		⊢•-	0.703 [0.627, 0.764]
Adams, et al. (2022)	USA	BA.1/BA.2/BA.4/BA.5	Mixed (BNT162b2/mRNA-1273/Janssen)	н	≥18	≥7		⊢⊷∣	0.650 [0.580, 0.710]
Adams, et al. (2022)	USA	BA.1/BA.2/BA.4/BA.5	Janssen/Any mRNA dose	н	≥18	≥7		⊢	0.520 [0.250, 0.690]
Pooled VE in adults: (Q = 486.32,	df = 11, p <	.01; I ² = 98.7%, τ ² = 4.01e	-01)					•	0.846 [0.776, 0.895]
Non-mRNA Vaccines, booster o	lose								
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/CoronaVac	H/D	18-59	>7		⊢•-	0.843 [0.736, 0.907]
Kirsebom, et al. (2022b)	UK	BA.1/BA.2	ChAdOx1/ChAdOx1/ChAdOx1	н	≥65	≥7		⊢ •	0.823 [0.642, 0.913]
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/CoronaVac	H/D	60-74	>7		•	0.768 [0.721, 0.807]
Ranzani, et al. (2022)	Brazil	BA.1/BA.2	CoronaVac/CoronaVac/CoronaVac	H/D	≥75	>7		⊢•-	0.512 [0.446, 0.570]
Adams, et al. (2022)	USA	BA.1/BA.2/BA.4/BA.5	Janssen/Janssen	н	≥18	≥7	-	• 1	0.350 [-0.540, 0.730]
Pooled VE in adults: (Q = 59.42, o	df = 4, p < .0	1; $I^2 = 93.1\%$, $\tau^2 = 2.78e^{-01}$)					-	0.714 [0.521, 0.829]
Deeled VE is adulta serect all use	oloo hunos: /	0 = 800 22 46 = 24 0	$1 \cdot 1^2 = 0.9 \cdot 60^2 = 2 \cdot 47 - 01$						0.000 (0.770, 0.000)
Pooled VE in adults across all vac	one types: (w = 099.22, at = 24, p < .0	1, 1 - 30.0%, T = 3.4/6%					•	0.820 [0.770, 0.860]
Test for VE Difference in All across	s all vaccine s Vaccine Typ	types: (Q = 904.58, df = 2 bes: Q _M = 3.74, df = 2, p = 1	7, p < .01; I ⁻ = 98.3%, t ⁻ = 3.39e ⁻⁰¹) 0.15					•	0.825 [0.778, 0.862]
							ſ		
							-0.500 0.0	000 0.500 1.000	

-0.500 0.000 0.500 Vaccine Effectiveness

FIGURE 4

Overall vaccine effectiveness of full doses and first booster against severe events. (A) Pooled VE of full doses estimated from all 24 studies combined as well as for each vaccine type. (B) Pooled VE of first booster estimated from all 28 studies combined as well as for each vaccine type. Statistics Cochran's Q, I² and τ^2 measure the heterogeneity between studies. Possible end points of the studies are hospitalization (H), hospitalization or death (H/D), emergency department or urgent care encounter (ED/UC), or hospital admissions from emergency care (EC \rightarrow H). Mixed vaccine type indicates the study reported VEs of these vaccines combined without distinguishing between them.

non-mRNA vaccines should be encouraged among unvaccinated individuals in regions where mRNA vaccine supply is insufficient.

The VEs of the initial full doses and the first booster dose against Omicron infection waned substantially over time, from 40.7% within 3 months of boosting to 17.6% for full doses and 59.4 to 34.9% for the first booster. The VEs against Omicronassociated severe disease waned at a slower pace, from 66.9% to 58.3% for the full doses and from 84.8% to 77.6% (in adults) for the first booster dose. Our findings are consistent with other studies reporting waning immunity of COVID-19 vaccines for earlier variants (19, 58) as well as for Omicron regardless of age, immunocompromised status, and vaccine product (55). One study reported that VE against symptomatic infection waned more rapidly among older adults (64), which was also reflected in this meta-analysis, e.g., the full-dose VE of pure mRNA vaccines against infection declined from 45.3 to 22.3% among children and from 41.3 to 13.1% among adults (Supplementary Figures 1, 2). These age differences in decay rates were not observed for the VEs against severe disease (Supplementary Figures 5, 6).

The second booster of pure or partial mRNA vaccines protected adults from Omicron infection with a VE of 59.6% which is slightly lower than the short-term VE of the first booster for pure mRNA (67.3%) or partial mRNA vaccines (62.3%) among adults. A similar gap was seen for the long-term VE among adults as well, 32.7% for the second booster vs. 50.9% for pure mRNA and 34.6% for partial mRNA first boosters. This seemingly unexpected gap (not statistically significant) may result from the fact that the dominant Omicron subvariants were mostly BA.1 and BA.2 for the first booster studies but BA.4 and BA.5 were taking over for the second booster studies. BA.4 and BA.5 are known to be associated with high immune escape and transmissibility compared to BA.1 and BA.2, e.g., the effective reproductive number was estimated to be 5.11 and 5.22 for BA.4 and BA.5 compared to 3.22 and 5.04 for BA.1 and BA.2 (65).

In terms of protection against severe disease among adults, we observed comparable VE estimates between the second booster and the first booster doses for both short term (87.3% for the second booster vs. 85.3% and 88.1% for pure and partial mRNA first boosters) and long term (85.9% for second booster vs. 80.1% and 78.0 for pure and partial mRNA first boosters). The second booster appears to wane to a lesser extent over time. However, a caveat is that nearly all data used to estimate the long-term VE of the second booster against severe disease came from the same study among elderly residents of long-term care facilities in Ontario, Canada (60). In addition, this long-term VE is against BA.1 and BA.2, the dominant subvariants during the study period of 31 December 2021 to 27 April 2022, according to the Ontario Ministry of Health.

Our study had several limitations. First, in several testnegative studies, we included, the same control group for multiple vaccine groups, which introduces dependence among the VE estimates. However, such dependence was not accounted for in our analysis due to lack of covariance estimates. Second, there was significant heterogeneity in VE estimates, which may be attributable to differences between studies in terms of a whole host of characteristics, including study design, followup duration, definitions of VE, time since vaccination, dosing intervals, confounders adjusted for, and others. Finally, as most studies did not provide subvariant-specific VE estimates and there is ambiguity in which Omicron subvariants were dominant for many studies, we were not able to stratify the meta-analysis by subvariant.

Our findings demonstrate that completion of a full COVID-19 vaccine series plus one or two booster doses provides considerable VE against Omicron infection and strong VE against severe events compared to non-vaccination. Although VEs generally wane after 2-3 months, the second booster clearly generates more sustainable protection. As the Omicron family continues to evolve with more genetic and antigenic variation, e.g., the XBB* and BQ.1* sublineages, lower VEs and faster waning of protection of the Wuhan-Hu-1-based boosters should be expected. Meanwhile, the level and longevity of efficacies of Omicron-specific bivalent vaccines should be closely monitored using meta-analytic approaches. To facilitate comparison and synthesis of VE estimates across studies, we recommend the following improvements to future vaccine studies: (i) longer follow-up to better understand long-term VE; (ii) stratification of VE by age group, vaccine type and variant whenever possible; and (iii) when multiple VE estimates are reported, providing covariance or correlation among the estimates via, e.g., resampling the data.

Data availability statement

Publicly available datasets were analyzed in this study. The raw summary-level data were derived from publicly available papers cited in the reference. Extracted data and programming codes will be made available upon request by email to the corresponding authors.

Author contributions

YY and IL conceived the study. SS, ZM, and ML collected the data. SS, ZM, ML, and YY reviewed the data. SS analyzed data under the supervision of YY, ZM, and IL. SS, ZM, and YY drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023. 1195908/full#supplementary-material

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