Effectiveness of COVID-19 vaccines against SARS-CoV-2 infection and severe outcomes in adults: a systematic review and meta-analysis of European studies published up to 22 January 2024

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Shareable abstract (@ERSpublications)
Vaccine effectiveness against SARS-CoV-2 infection and severe outcomes drops significantly 6 months after a complete primary series. Boosters restore protection, underscoring the need of timely booster doses, especially for vulnerable populations. https://bit.ly/4iI1sU6

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Abstract

Background Up-to-date evidence from European studies on long-term vaccine effectiveness (VE) of COVID-19 vaccines is lacking. This review aimed to evaluate effectiveness and durability of primary vaccine series and boosters in preventing infection and severe outcomes in the European population.

Methods We conducted systematic searches of PubMed and Embase up to 22 January 2024. We included observational studies that evaluated VE against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or severe disease (hospitalisation, intensive care unit admission or death) for primary series and boosters in Europe. We applied a random-effects meta-analysis model.

Results We included 33 studies and over 56 million participants. The overall VE of the complete primary series against infection with any SARS-CoV-2 variant was 70.7%. VE was lower for Omicron, at 26.1%, than for pre-Omicron strains, at 77.0%. Over time, VE against infection by any variant decreased from 68.9% to 38.9% after 6 months. Boosters restored VE to 76.4% and maintained at 58.4% after 3 months. The overall VE of a complete primary series for severe outcomes due to any variant was 87.4%, with 93.3% for pre-Omicron and 62.8% for Omicron strains. Protection against severe outcomes declined less than for infection. 6 months after the primary series, the vaccine still provided over 50% protection against severe outcomes caused by Omicron. Boosters restored VE to 87.9% and maintained at 78.5% after 3 months.

Conclusion VE against SARS-CoV-2 infection declines markedly with time and Omicron variants. Protection against severe outcomes was more durable and resistant to viral mutation. Boosters restored protection, emphasising the need for timely booster vaccination for vulnerable populations.

Introduction

Widespread and global vaccination programmes have played a critical role in bringing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus under control. However, neutralising antibody levels were found to decline substantially 6 months after vaccination [1]. This led to a decline in vaccine effectiveness (VE) over time, as shown in several observational studies [2, 3]. Moreover, newly emerging

Omicron variants were characterised to have viral mutations that facilitate immune escape [4]. A previous systematic review published in May 2023 showed lower VE estimates and faster waning of protection against Omicron infection [5]. Booster vaccination and later bivalent vaccines emerged as a strategy to combat this waning effectiveness [6].

Understanding the effectiveness of vaccines is critical for guiding public health policy, informing vaccination strategies and promoting public confidence in immunisation programmes. There have been several systematic reviews examining the real-world VE and durability of coronavirus disease 2019 (COVID-19) vaccine protection [5, 7–12], with some focusing solely on the Omicron variants [7, 10–12]. While these meta-analyses have provided valuable insights into the effectiveness of vaccines, the inclusion of more recent studies allows for a more up-to-date picture and the investigation of the long-term effectiveness of booster vaccination.

Moreover, existing reviews predominantly include studies from North America, Israel and Qatar, with a small number of studies from European countries [7, 8, 12]. European countries benefit from more coordinated and standardised vaccine distribution and administration approaches, ensuring consistency in immunisation programmes. The lower variability in access to vaccines could therefore reduce the variability between VE studies. Importantly, European countries also have similar healthcare systems in terms of equitable access to medical services, which may reduce severe selection bias. Another reason to include only European studies is that seasonal trends in COVID-19 cases are more pronounced than in countries such as Israel and Qatar [13, 14], which may also affect the VE estimate. A comprehensive review of synthesising VE estimates from studies conducted in European countries is needed to provide more representative VE estimates and durability of booster protection to guide the timing of booster administration.

In this meta-analysis of observational studies, we aimed to evaluate the effectiveness of the primary series of SARS-CoV-2 vaccines and subsequent boosters in preventing SARS-CoV-2 infection and severe COVID-19 outcomes from studies conducted in European countries. The potential modification of effects was explored for specific severe outcomes, namely symptomatic SARS-CoV-2 infection only *versus* all infections, pre-Omicron *versus* Omicron variants, vaccine type (mRNA *versus* viral vector), length of follow-up time, adjustment for previous infection or not and study design (cohort *versus* case–control).

Methods

This systematic review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [15]. The study protocol is publicly available on the PROSPERO website (registration number CRD42024529854).

Search strategy and selection criteria

We conducted a systematic literature search in PubMed and Embase for articles published from 1 January 2020 to 22 January 2024 with restriction to the English language. We constructed the search strategy by combining free text and medical subject headings in the following domains: disease ("SARS-CoV-2" or "coronavirus" or "COVID"), vaccine and study design. The full search strategy can be found in appendix 1.

Studies were included if they were observational studies reporting VE estimates in healthy adults (aged ⩾16 years), including both cohort and case–control studies, conducted in Europe. VE estimates needed to compare participants who have completed full primary series or boosters with unvaccinated participants. A complete primary series is defined as two doses of BNT-162b2, mRNA-1273 or ChAdOx1/AZD1222, or one dose of Ad26.COV2.S, in accordance with European Medicines Agency approval. An additional dose of the European licensed COVID-19 booster (BNT-162b2 or mRNA-1273) is considered as a booster.

The outcomes of interest were as follows: 1) any laboratory-confirmed SARS-CoV-2 infection by reverse transcription-PCR (RT-PCR), regardless of symptoms; 2) hospitalisation with or for COVID-19; 3) intensive care unit (ICU) admission with or for COVID-19; and 4) all-cause death. The outcome measure of interest was the absolute VE estimate, although any estimate that could be used to calculate VE according to the formula VE=1–adjusted odd ratio/risk ratio/hazard ratio×100% was also accepted. The full inclusion and exclusion criteria can be found in appendix 2.

After removing duplicates, two researchers (G.Z. and N.D.) independently screened articles using Rayyan (www.rayyan.ai), based on their titles and abstracts, to identify eligible studies. In the second step, the full texts were assessed according to the inclusion and exclusion criteria outlined in appendix 2 to create the final list of included articles. Any disagreements were resolved by a third reviewer (E.H.).

Data extraction

Data were extracted for each study by a single reviewer (N.D.) and verified by a second reviewer (G.Z.). The following variables, if available, were extracted from the articles: author name, publication year, geographic location, study design, COVID-19 variant, vaccine products, the number of administered doses, inclusion criteria of population, outcome definitions, mean or median age of participants, percentage of male, the follow-up time, VE point estimates with confidence interval, and covariates adjusted for. To minimise the impact of confounding variables, we only extracted VE estimates that were adjusted for confounders using multivariable regression or propensity-score matching. For each outcome, we extracted these adjusted VE estimates according to vaccine products and variant context.

VE at various time-points since receipt of the primary series and booster doses were also extracted. However, we only extracted VE estimates for time intervals during which the vaccine schedule was followed by sufficient time to develop immunologic protection, such as 14 days after the second dose of BNT-162b2, mRNA-1273 or ChAdOx1, or 28 days after the first dose of Ad26.COV2.S, or 7 days after the booster dose.

Quality assessment and risk of bias

Two reviewers (G.Z. and N.D.) independently assessed the included studies for risk of bias using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool [16]. ROBINS-I includes seven domains. Each domain is determined to be either low risk, moderate risk, serious risk or critical risk. Any disagreements were resolved by a third reviewer, E.H.

Data synthesis and statistical analysis

For our main analysis, SARS-CoV-2 infection and severe COVID-19 outcomes were the main outcomes of interest. All RT-PCR-confirmed SARS-CoV-2 infections were included, regardless of the presence of symptoms. Severe COVID-19 outcomes included hospitalisation and/or ICU admission and/or death. We performed a secondary analysis where each of these three outcomes was examined individually. We also considered symptomatic SARS-CoV-2 infection as a secondary outcome.

In the main analysis evaluating overall VE for each outcome, all SARS-CoV-2 variants, all vaccine types and all the time intervals were considered together. Secondary analyses were conducted in which the variants were separated and the vaccines were separated by type. Strains were categorised as pre-Omicron, which includes the original strain, Alpha and Delta, and Omicron. The BNT-162b2 and mRNA-1273 vaccines were classified as mRNA vaccines.e The ChAdOx1 and Ad26.COV2.S vaccines were classified as viral vector vaccines.

In order to evaluate the potential waning of the vaccines over time, we categorised VE estimates based on the elapsed time since the last dose. For the primary series, we used the following categories: 0–3 months, 4–6 months and >6 months. If a VE estimate was not split according to time since last dose, it was classified as an overall estimate. Additionally, if a study reported estimates categorised as 0–3 months, 4–6 months and >6 months, but did not report an overall estimate, an overall estimate was calculated from these estimates using inverse variance weighting (IVW). For the booster dose estimates, follow-up time was categorised as either overall, 0–3 month or >3 months. If a study employed narrower time intervals than stated here, we used IVW to combine the estimates. If an estimate overlapped in two categories, we only included the estimate in one category if less than 25% of the time window fell outside of that interval. Otherwise, we excluded the estimate from the category. Appendix 3 gives an overview of the included studies and whether estimates were combined using IVW.

We also conducted several additional analyses. First, previous SARS-CoV-2 infection is an important confounder when assessing VE estimates. However, not all studies accounted for it. We ran the meta-analysis model on articles that either excluded or adjusted for previous SARS-CoV-2 infections and compared it with our primary analysis to see the difference. Second, the main meta-analyses were performed separately for case–control (including test-negative case–control design) only and cohort only studies to examine the effect of study design. Third, we ran the meta-analysis model only on the articles classified as “low risk”.

All extracted VE estimates were converted to log odds ratios for analysis to normalise the distribution and stabilise the variances. The pooled estimates were transformed back into percentage VE for the presentation of the results [8]. If a VE estimate or the upper bound of the confidence interval was equal to or greater than 100%, it was not possible to calculate the log odds ratios. Therefore, these values were changed to 99% or 99.9%, depending on the decimal place of the other estimates in that study [8].

Appendix 4 provides an overview of which estimates were affected by this measure. In addition, estimates with a lower bound of the confidence interval less than −100% were excluded from the analysis. Furthermore, point estimates below 0% were also excluded from the main analysis. A sensitivity analysis including these negative point estimates was conducted to test the robustness of our main analysis.

The pooled VE with its corresponding 95% confidence interval were estimated using a random-effect meta-analysis model where between-study heterogeneity is modelled by incorporating a stochastic study-specific intercept term. For estimating the between-study variance, a restricted maximum-likelihood estimate was considered, since traditional maximum likelihood tends to underestimate between-study variance. The level of between-study heterogeneity was assessed using I^2 statistic and Cochran's Q test. To ensure that studies contribute proportionally in the estimation based on their estimation precision, IVW was applied. All data analyses were performed using R statistical software (version 4.3.2) *via* the *metafor* package. The statistical significance threshold in this review was 0.05.

Results

Study characteristics

A total of 9216 records were obtained from the searched databases (5352 from Embase and 3864 from PubMed). An additional two records were identified from the reference list of previous systematic review searches. After removing duplicates, 6869 records remained to be assessed for eligibility. After excluding articles that did not fulfil our inclusion criteria, we included 33 articles in our review, which gave us a sample size of over 56 million participants. Of those, 17 studies with case–control design (of which 16 were test-negative case–control), 12 with cohort design and four with both designs. Table 1 provides an overview of the 33 articles included. The full PRISMA flow diagram of article selection, including reasons for exclusion, can be found in appendix 5.

Of the 33 articles, 39.4% (n=13) were conducted in the United Kingdom, including nine in England, three in Scotland and one in Wales. Four studies (12.1%) were conducted in Italy and three (9.1%) each in Norway and the Netherlands. Two (6.1%) each were conducted in Belgium, Germany and France, and one each in Spain, Sweden, Denmark and Portugal.

Of the 33 articles, 84.8% (n=28) had a VE estimate for at least one pre-Omicron strain, which includes the original SARS-CoV-2 strain, Alpha and Delta strain, and 45.4% (n=15) had an estimate for Omicron. In terms of vaccine products, BNT-162b2 was the most commonly studied vaccine, with 97.0% (n=32) of studies including it. ChAdOx1 was included in 84.8% (n=28) of the studies, mRNA-1273 in 72.7% (n=24) and Ad26.COV2.S in 30.3% (n=10). A VE estimate for the primary series was reported in 97.0% (n=32) of the studies, for the first booster in 57.6% (n=19) and for the second booster in 9.1% (n=3).

Of the 33 articles, 15 were classified as low risk, eight as moderate risk and 10 as high risk for bias (appendix 6). No articles were classified as critical risk and therefore no articles were excluded from the meta-analysis based on the quality assessment. Common sources of potential bias were missing data and selection bias, the latter because studies did not always take care to exclude or adjust for previously infected participants.

VE against SARS-CoV-2 infection

The VE estimates against SARS-CoV-2 infection are summarised in table 2 and visualised in figure 1. These estimates include all vaccine products together. The overall VE of the complete primary series against SARS-CoV-2 infection with any variant was 70.7% (95% CI 62.4–77.1) by pooling 39 estimates from 16 studies. In the first 3 months after the last dose, the VE against any variant was 68.9% (95% CI 59.9–75.9). After 6 months, the VE decreased to 38.9% (95% CI 28.8–47.5).

When stratified by virus strain, the overall VE of a complete primary series against SARS-CoV-2 infection was 77.0% (95% CI 70.4–82.1) for all pre-Omicron strains. This was higher than the overall VE found for Omicron strains, which was 26.1% (95% CI 21.1–30.8). Both the VE against pre-Omicron and Omicron strains decreased with time since last dose. For pre-Omicron strains, VE started at 79.5% (95% CI 74.3–83.7) in the first 3 months and decreased to 53.1% (95% CI 43.0–61.4) at 6 months. For Omicron strains, VE started at 38.4% (95% CI 31.8–44.4) after the first 3 months and decreased to 17.3% (95% CI 12.3–21.9) after 6 months.

A booster dose restored VE to higher levels than the primary series for both pre-Omicron and Omicron strains, as shown in figure 1. In the first 3 months after a booster, the VE for pre-Omicron strains was 92.5% (95% CI 90.4–94.1) compared to 79.5% (95% CI 74.3–83.7) for the same follow-up period after a

TABLE 1 Summary of study characteristics of included studies (n=33) in alphabetical order by first author

Study	Publication year	Country	Study design	Age (years)	Variant	Vaccine product	Primary series or booster	Outcome measure	Covariates adjusted or stratified for
Amirthalingam [38]	2021	UK (England)	TNCC	50–89	Alpha	BNT162b2, ChAdOx1	Primary series	Symptomatic infection	Age, sex, socioeconomic status, number of comorbid risk groups, calendar time
Amodio [39]	2022	Italy	Retrospective cohort	⩾18	Alpha, Delta	BNT162b2, mRNA-1273	Primary series	Infection, severe COVID-19, COVID-19 death or intubation	Age, sex
Andeweg [40]	2022	Netherlands	TNCC	⩾18	Delta, Omicron	BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2-S	Primary series, first booster	Infection	Test date, 5-year age group, sex, region
Andrews [41]	2022	UK (England)	TNCC	⩾18	Delta, Omicron	BNT162b2, mRNA-1273, ChAdOx1	Primary series, first booster	Symptomatic infection	Age, sex, index of multiple deprivation, race or ethnic group, history of foreign travel, geographic region, period, health and social care worker status, clinical risk group status, status of being in a clinically extremely vulnerable group, previously tested positive
Andrews [42]	2022	UK (England)	TNCC	⩾16	Alpha, Delta	BNT162b2, ChAdOx1	Primary series	Symptomatic infection, hospitalisation, death	Age, sex, index of multiple deprivation, race or ethnic group, care home residence status, geographic region, period, health and social care worker status, status of being in a clinical risk group, status of being in a clinically extremely vulnerable group
Andrews [43]	2022	UK (England)	TNCC	⩾18	Delta	BNT162b2, ChAdOx1	Primary series, first booster	Symptomatic infection, hospitalisation, death	Age, sex, index of multiple deprivation, ethnic group, care-home residence status, geographic region, period, health and social care worker status, clinical risk group status, clinically extremely vulnerable, severely immunosuppressed, previously testing positive
Braeye [44]	2023	Belgium	TNCC	⩾18	Delta, Omicron	BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2-S	Primary series, first booster	Symptomatic infection, hospitalisation	Age, sex, prior infection, time since vaccination, residence, calendar week of sampling
Cerqueira-Silva [45]	2023	UK (Scotland)	TNCC	⩾18	Omicron	BNT162b2, ChAdOx1	Primary series, first booster, second booster	Symptomatic infection, hospitalisation and death	Age, sex, index of multiple deprivation, number and types of comorbidities, geographic area, previous infection, calendar week of sampling, number of previous RT-PCR as proxy for healthcare worker, residential settlement type, household size

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TABLE 1 Continued

Study	Publication year	Country	Study design	Age (years)	Variant	Vaccine product	Primary series or booster	Outcome measure	Covariates adjusted or stratified for
Erazo [46]	2022	Belgium	Retrospective cohort	All	Unknown	BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2-S	Primary series, first booster	Hospitalisation	None
Flacco [47]	2021	Italy	Retrospective cohort	⩾18	Unknown	BNT162b2, mRNA-1273, ChAdOx1	Primary series	Infection, hospitalisation and death	Age, gender, hypertension, diabetes, major cardiovascular disease, chronic obstructive pulmonary diseases, kidney diseases, cancer
Gram [48]	2022	Denmark	Retrospective cohort	⩾18	Delta, Omicron	BNT162b2, mRNA-1273	First booster	Hospitalisation	Age, sex, geographic region, diabetes, adiposity, haematological and other cancers, neurological disease, kidney diseases, cardiovascular diseases, chronic pulmonary diseases, respiratory diseases, immune deficiency conditions
Katikireddi [49]	2021	UK (Scotland)	TNCC and retrospective cohort	⩾18	Delta	ChAdOx1	Primary series	Symptomatic infection, hospitalisation and death	Age, sex, deprivation, comorbidities, number of at-risk groups, smoking status, blood pressure, body mass index, health board, interval between doses, temporal trend
Kerr [50]	2022	UK (Scotland)	TNCC and retrospective cohort	⩾18	Delta	BNT162b2, mRNA-1273, ChAdOx1	Primary series	Symptomatic infection, hospitalisation	Age, sex, socioeconomic status, number of comorbid risk groups, calendar time
Kirsebom [51]	2022	UK (England)	TNCC	⩾18	Omicron	BNT162b2, mRNA-1273, ChAdOx1	Primary series, first booster	Symptomatic infection, hospitalisation	Age, sex, index of multiple deprivation, ethnic group, history of travel, geographic region, week of test, health and social care worker status, clinical risk group status, clinically extremely vulnerable, previously testing positive
Kirsebom [52]	2022	UK (England)	TNCC	⩾40	Delta, Omicron	BNT162b2, ChAdOx1	Primary series, first booster	Symptomatic infection, hospitalisation	Age, sex, index of multiple deprivations, ethnic group, geographic region, week of test, health and social care worker status, clinical risk group status, clinically extremely vulnerable, severely immunosuppressed, previously testing positive
Kirsebom [53]	2023	UK (England)	TNCC	⩾18	Omicron	BNT162b2, mRNA-1273, ChAdOx1	Primary series, first booster, second booster	Hospitalisation	Week of test, gender, age, risk group, residing in a care home, health or social care worker status, region, index of multiple deprivation quintile, ethnicity, probable variant that caused the most recent previous infection

Continued

TABLE 1 Continued

Study	Publication year	Country	Study design	Age (years)	Variant	Vaccine product	Primary series or booster	Outcome measure	Covariates adjusted or stratified for
Kislaya [31]	2023	Portugal	Retrospective cohort	⩾18	Omicron	BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2-S	Primary series, first booster	Hospitalisation	Age group, sex, region of residency, week of swab collection
Langlete [54]	2023	Norway	Retrospective cohort	18–66	Delta, Omicron	BNT162b2, mRNA-1273, ChAdOx1	Primary series, first booster	Infection	Sex, country of birth, county of residence, crowded living situation, underlying comorbidities
Lopez Bernal [55]	2021	UK (England)	TNCC	⩾16	Alpha, Delta	BNT162b2, ChAdOx1	Primary series	Symptomatic infection	Age, sex, index of multiple deprivation, race or ethnic group, care home residence status, history of foreign travel, geographic region, period, health and social care worker status, status of belonging in a clinically extremely vulnerable group, history of SARS-CoV-2 infection
Martellucci [56]	2022	Italy	Retrospective cohort	All	Alpha, Delta	BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2-S	Primary series	Infection, hospitalisation, death	Age, gender, hypertension, diabetes, major cardio- and cerebrovascular events, COPD, kidney diseases, cancer
Niessen [30]	2022	Netherlands	TNCC	⩾18	Alpha	BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2-S	Primary series	Hospitalisation	Week of symptom onset, age group, sex, comorbidity, nursing home residency
Nordström [57]	2022	Sweden	Retrospective cohort	All	Delta	BNT162b2, mRNA-1273, ChAdOx1	Primary series	Infection	Age, baseline date, sex, homemaker service, place of birth, education, comorbidities
Pardo-Seco [58]	2022	Spain	TNCC	⩾18	Unknown	BNT162b2	Primary series	Infection	Sex, age, time period between SARS-CoV-2 test and the start of study
Perry [59]	2022	UK (Wales)	Retrospective cohort	⩾50	Alpha, Delta	BNT162b2, ChAdOx1	Primary series	Infection, hospitalisation	Age, shielding list status and health and care worker status, previous positive SARS-CoV-2 test, number of SARS-CoV-2 tests prior to the cohort start, QCOVID score, health board of residence, sex, ethnic group, socioeconomic quintile of deprivation, urban/rural location of residence, previous vaccination against shingles or pneumococcal disease, vaccination against influenza, number of days with a GP consultation recorded in the year prior to 1 February 2020

Continued

TABLE 1 Continued

Study	Publication year	Country	Study design	Age (years)	Variant	Vaccine product	Primary series or booster	Outcome measure	Covariates adjusted or stratified for
Russo [60]	2022	Italy	Retrospective cohort	⩾19	Delta, Omicron	BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2-S	Primary series, first booster	Hospitalisation, ICU admission, death	Age, gender, socioeconomic status, nationality, number of comorbidities
Seppälä [61]	2021	Norway	Retrospective cohort	⩾18	Alpha, Delta	BNT162b2, mRNA-1273	Primary series	Infection	Age, sex, country of birth, county of residence, underlying comorbidities
Starrfelt [62]	2022	Norway	Retrospective cohort	⩾18	Delta	BNT162b2, mRNA-1273, ChAdOx1,	Primary series, first booster	Infection, hospitalisation, ICU admission, death	10-year age bands, sex, comorbidities, county of residence, country of birth, crowded living conditions
Stoliaroff-Pepin [63]	2022	Germany	TNCC	18–90	Alpha, Delta	BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2-S	Primary series, first booster	Hospitalisation	Age, pre-existing comorbidities, education
Stoliaroff-Pepin [64]	2023	Germany	Case–control	18–90	Omicron	BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2-S	Primary series, first booster, second booster	Hospitalisation	Age, sex, socioeconomic status, pre-existing comorbidities, risk of infection, region, phase of pandemic
Stowe [65]	2022	UK (England)	TNCC	⩾18	Delta, Omicron	BNT162b2, mRNA-1273, ChAdOx1	Primary series, first booster	Symptomatic infection, hospitalisation	Sex, index of multiple deprivation, ethnic group, geographic region, period, health and social care worker status, clinical risk group status, clinically extremely vulnerable, severely immunosuppressed, previously testing positive
Suarez Castillo [66]	2022	France	TNCC and retrospective cohort	⩾18	Delta, Omicron	BNT162b2, mRNA-1273, ChAdOx1	Primary series, first booster	Symptomatic infection, hospitalisation, ICU admission, death	Age, sex, residence, week of testing, presence of a comorbidity
Tamandjou Tchuem [67]	2023	France	TNCC and retrospective cohort	⩾50	Delta, Omicron	BNT162b2, mRNA-1273	Primary series, first booster	Symptomatic infection, hospitalisation, ICU admission and death	Age, sex, type of residence, presence of at least one low or medium-risk comorbidity, healthcare professional status
van Ewijk [68]	2022	Netherlands	TNCC	⩾18	Delta	BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2-S	Primary series	Infection	Age, sex, calendar week, education level, comorbidities, household size, number of close contacts inside and outside, face mask wearing habits, visiting busy locations inside and outside, contact with a SARS-CoV-2 positive person

GP: general practitioner; ICU: intensive care unit; RT-PCR: reverse transcriptase PCR; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TNCC: test-negative case–control.

TABLE 2 Vaccine effectiveness (VE) of COVID-19 vaccines against SARS-CoV-2 infection

Primary series					
Follow-up time	**Variant**	**k[#]**	**VE (95% CI)**	**I^2 (%)[¶]**	**Q[+]**
Overall	All	16 (39)	70.7 (62.4–77.1)	99.98	58 939.5
Overall	Pre-Omicron	15 (31)	77.0 (70.4–82.1)	99.94	8246.3
Overall	Omicron	5 (8)	26.1 (21.1–30.8)	99.40	1104.2
0–3 months	All	12 (26)	68.9 (59.9–75.9)	99.96	51 104.1
0–3 months	Pre-Omicron	11 (16)	79.5 (74.3–83.7)	99.93	25 306.1
0–3 months	Omicron	6 (10)	38.4 (31.8–44.4)	98.81	297.3
4–6 months	All	9 (22)	53.1 (40.2–63.2)	99.98	60 566.6
4–6 months	Pre-Omicron	9 (14)	65.6 (55.2–73.5)	99.96	10 617.5
4–6 months	Omicron	5 (8)	19.8 (12.9–26.2)	99.44	327.7
>6 months	All	10 (26)	38.9 (28.8–47.5)	99.87	16 124.8
>6 months	Pre-Omicron	8 (14)	53.1 (43.0–61.4)	99.85	4851.1
>6 months	Omicron	7 (12)	17.3 (12.3–21.9)	97.79	453.4
First or second booster					
Follow-up time	**Variant**	**K[#]**	**VE (95% CI)**	**I^2 (%)[¶]**	**Q[+]**
Overall	All	10 (25)	76.4 (67.0–83.1)	99.99	103 279.0
Overall	Pre-Omicron	7 (9)	91.8 (88.9–94.0)	99.81	1283.5
Overall	Omicron	9 (16)	57.5 (55.0–59.9)	99.65	8846.9
0–3 months	All	10 (43)	80.4 (74.1–85.2)	99.98	74 578.4
0–3 months	Pre-Omicron	7 (19)	92.5 (90.4–94.1)	99.69	2494.4
0–3 months	Omicron	9 (24)	59.1 (55.2–62.6)	99.82	10 199.9
>3 months	All	7 (16)	58.4 (38.9–71.6)	99.95	6944.9
>3 months	Pre-Omicron	2 (3)	91.0 (86.6–93.9)	97.61	45.3
>3 months	Omicron	7 (13)	40.8 (35.4–45.7)	99.08	2138.7

[#]: Number of studies pooled (number of observations pooled). [¶]: Percentage of variance in a meta-analysis that is explained by differences between the included studies rather than by sampling error. [+]: Weighted sum of squared differences between the observed effect and the weighted average effect.

primary series. More than 3 months after booster vaccination, VE against pre-Omicron strains remained stable at 91.0% (95% CI 86.6–93.9). A decrease in initial VE and a more pronounced decline over time was observed for the Omicron strain, starting at 59.1% (95% CI 55.2–62.6) in the first 3 months and decreasing to 40.8% (95% CI 35.4–45.7) at 3 months.

The primary analysis considered all types of RT-PCR confirmed SARS-CoV-2 infections, regardless of symptoms. When focusing only on symptomatic SARS-CoV-2 infections, there is no significant difference between studies that looked only at symptomatic infections and studies that looked at all infections (appendix 7).

When split by mRNA or viral vector vaccine, there was no significant difference between the mRNA and viral vector vaccines in most cases. However, there appears to be a trend for the viral vector vaccines to have a lower VE against SARS-CoV-2 infection than the mRNA vaccines, both against pre-Omicron and Omicron strains (appendix 8).

VE against severe outcomes

The VE estimates against severe outcomes of COVID-19 are summarised in table 3 and visualised in figure 2. The definition of severe outcomes includes hospitalisation, ICU admission, death and any composite of these three outcomes. Similar to the estimates for SARS-CoV-2 infection, these estimates include all four vaccine products together. The overall VE of the complete primary series against severe outcomes caused by any variant was found to be 87.4% (95% CI 81.4–91.4) by pooling 32 estimates from 15 different studies. In the first 3 months after completion of the primary series, the VE against severe outcomes was 89.8% (95% CI 84.7–93.2). After 6 months, the VE decreased to 76.3% (95% CI 68.3–82.3).

There was a decrease in VE against severe outcomes of COVID-19 over time for both the pre-Omicron and Omicron strains. For the pre-Omicron strains, the VE was 93.2% (95% CI 89.1–95.8) in the first

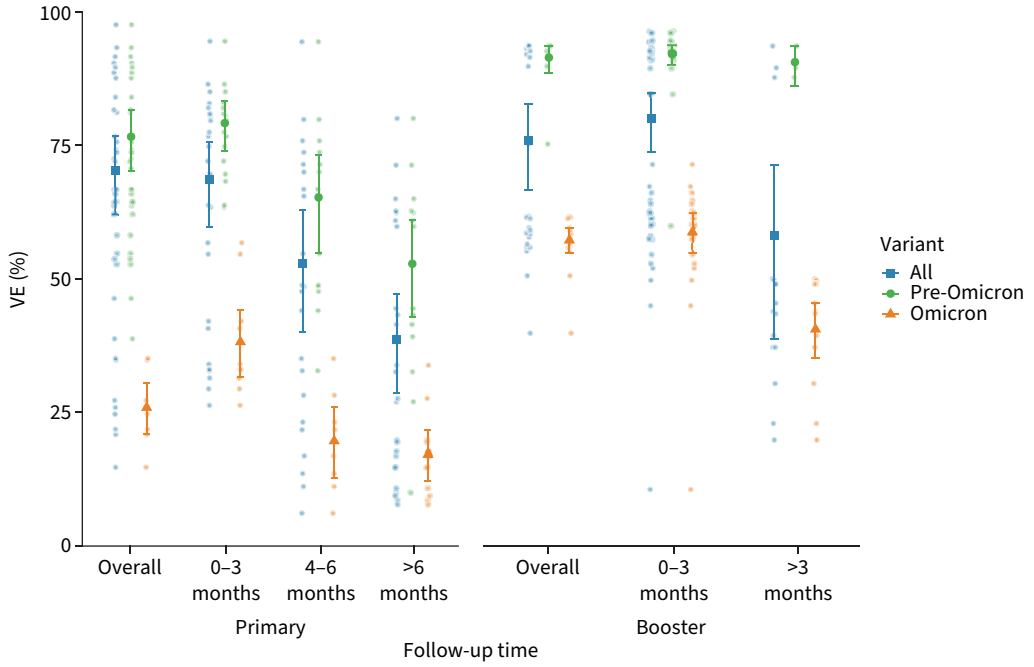

FIGURE 1 Vaccine effectiveness (VE) of primary series or booster against severe acute respiratory syndrome coronavirus 2 infection. The main data points represent the result of the meta-analysis along with the error bars representing the 95% confidence interval. The lighter data points represent the individual VE estimates pooled in the meta-analysis.

3 months and decreased to 86.6% (95% CI 82.1–90.0) at 6 months. For the Omicron strain, the VE was 73.9% (95% CI 55.8–84.5) in the first 3 months and 52.9% (95% CI 42.6–61.3) at 6 months. Vaccination against Omicron strains was less effective in preventing severe outcomes than vaccination against pre-Omicron strains at any follow-up time.

In the first 3 months after a booster dose, VE was 96.5% (95% CI 93.7–98.0) for pre-Omicron strains and 83.0% (95% CI 76.9–87.5) for Omicron. This showed a slight increase compared to the VE estimates for a primary series with the same follow-up time. After 3 months, the VE for pre-Omicron strains was still high at 93.6% (95% CI 86.1–97.0) with a negligible decrease. The decrease in booster VE over time was more pronounced for Omicron, with a VE of 72.8% (95% CI 62.9–80.1) at 3 months.

Overall and at each follow-up period, VE was consistently higher for severe outcomes than for SARS-CoV-2 infection. For example, the overall VE after completion of the primary series was 87.4% (95% CI 81.4–91.4) for severe outcomes compared with 70.7% (95% CI 62.4–77.1) for SARS-CoV-2 infection. The decline in VE over time was also less steep for severe outcomes than for SARS-CoV-2 infection.

Results for severe outcomes by vaccine type, mRNA or viral vector are presented in appendix 8. Pooled VE estimates for hospitalisation, ICU admission and death are presented separately in appendix 9.

Additional sensitivity analyses

For assessing the robustness of our findings, we performed three additional analyses. First, we stratified the analysis by cohort and case–control design. For infection, it is difficult to draw firm conclusions about the difference between these designs because of the small number of cohort studies for some follow-up periods. For severe outcomes, cohort studies reported higher overall VE estimates for primary series and boosters. The results are reported in appendix 10.

In our primary analysis, we excluded VE point estimates that were below 0, as these were not considered informative. To ensure that this did not have a disproportionate effect on our results, a sensitivity analysis was conducted that included these negative estimates. After excluding these sub-zero estimates, we did not observe much difference in the point estimates and the trend of decline over time. The results of this sensitivity analysis are presented in appendix 11.

TABLE 3 Vaccine effectiveness (VE) of COVID-19 vaccines against severe outcomes

Primary series					
Follow-up time	**Variant**	**k[#]**	**VE (95% CI)**	**I^2 (%)[¶]**	**Q[+]**
Overall	All	15 (32)	87.4 (81.4–91.4)	99.34	4839.7
Overall	Pre-Omicron	11 (19)	93.3 (90.0–95.4)	98.68	943.6
Overall	Omicron	6 (10)	62.8 (50.4–72.1)	93.59	64.3
0–3 months	All	10 (28)	89.8 (84.7–93.2)	98.89	1590.2
0–3 months	Pre-Omicron	8 (17)	93.2 (89.1–95.8)	98.95	958.1
0–3 months	Omicron	4 (8)	73.9 (55.8–84.5)	80.02	34.5
4–6 months	All	8 (24)	82.9 (77.3–87.1)	98.63	1725.1
4–6 months	Pre-Omicron	6 (14)	88.2 (84.0–91.3)	98.19	1059.8
4–6 months	Omicron	3 (7)	70.0 (60.0–77.5)	72.07	26.8
>6 months	All	10 (32)	76.3 (68.3–82.3)	98.59	3662.6
>6 months	Pre-Omicron	6 (16)	86.6 (82.1–90.0)	97.46	479.4
>6 months	Omicron	7 (13)	52.9 (42.6–61.3)	90.11	74.4
First or second booster					
Follow-up time	**Variant**	**k[#]**	**VE (95% CI)**	**I^2 (%)[¶]**	**Q[+]**
Overall	All	14 (35)	87.9 (83.8–91.0)	99.82	3596.6
Overall	Pre-Omicron	5 (10)	94.7 (90.8–96.9)	95.34	108.3
Overall	Omicron	11 (22)	83.2 (77.3–87.5)	99.82	2218.2
0–3 months	All	10 (33)	92.3 (88.3–94.9)	99.87	7012.0
0–3 months	Pre-Omicron	7 (16)	96.5 (93.7–98.0)	98.78	1024.0
0–3 months	Omicron	8 (17)	83.0 (76.9–87.5)	99.74	1694.7
>3 months	All	8 (19)	78.5 (69.3–85.0)	99.51	649.0
>3 months	Pre-Omicron	2 (4)	93.6 (86.1–97.0)	44.70	5.3
>3 months	Omicron	7 (15)	72.8 (62.9–80.1)	99.38	575.5

[#]: Number of studies pooled (number of observations pooled). [¶]: Percentage of variance in a meta-analysis that is explained by differences between the included studies rather than by sampling error. [+]: Weighted sum of squared differences between the observed effect and the weighted average effect.

In addition, not all studies included the effect of previous SARS-CoV-2 infection in their methodology. This could affect the results because previous infections confer natural immunity to SARS-CoV-2 that protects them from future infections or severe outcomes, which could affect VE estimates. Therefore, we repeated the analyses excluding studies that did not exclude or adjust for individuals with prior infections. No obvious differences were found. The results of this sensitivity analysis are presented in appendix 12.

When the meta-analysis model was run only on the low-risk articles, the heterogeneity represented by I^2 did not generally decrease. Leaving out the nonlow-risk articles, we generally have slightly higher VE estimates than those obtained from the primary analysis. However, for boosters against severe outcomes, the sensitivity analysis resulted in a much lower estimate. The results of this sensitivity analysis are presented in appendix 13.

Discussion

This systematic review and meta-analysis investigated the effectiveness of the primary series of SARS-CoV-2 vaccines and subsequent boosters in preventing SARS-CoV-2 infection and severe COVID-19 outcomes in European countries. We found that the overall VE after completion of the primary series against SARS-CoV-2 infection by any variant was 70.7%. When examining pre-Omicron and Omicron strains, VE was initially lower and declined more rapidly over time for the Omicron variants, from 38.4% to 17.3% after 6 months. Boosters restore the protection to an even higher level than the primary series. For the pre-Omicron strain, vaccine protection is still substantial 3 months after the booster, while for the Omicron strain, protection begins to wane 3 months later. For severe COVID-19 outcomes, the overall VE after completion of the primary series was 87.4%. In all analysed subgroups, VE against severe COVID-19 outcomes was higher than that against SARS-CoV-2 infection. Even 6 months after the primary series, the vaccine still provided more than 50% protection against the severe outcomes caused by the Omicron strain. In addition, the decline in VE against severe outcomes from the Omicron strain is less pronounced than that observed with infection, meaning that protection against severe outcomes is more robust in the face of evolving viral mutations and immune escape.

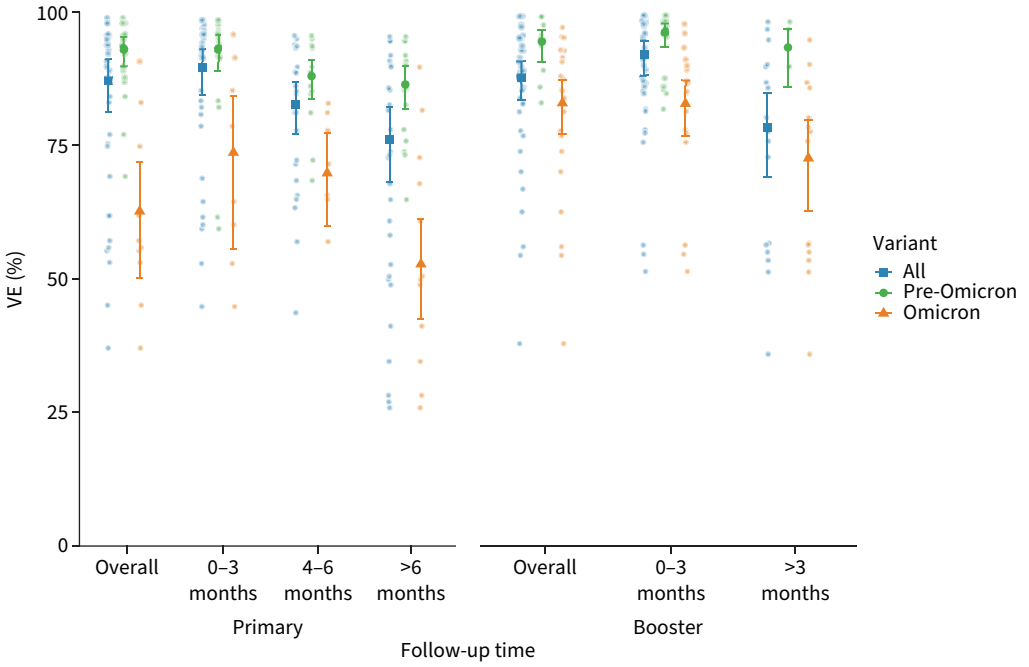

FIGURE 2 Vaccine effectiveness (VE) of primary series or booster against severe COVID-19 outcomes. Severe outcomes included hospitalisation, intensive care unit admission and death. The main data points represent the result of the meta-analysis along with the error bars representing the 95% confidence interval. The lighter data points represent the individual VE estimates pooled in the meta-analysis.

VE against all outcomes decreased dramatically over time after completion of the primary series, but the booster vaccination restored vaccine protection. This finding is consistent with the dynamics of antibody titres following SARS-CoV-2 vaccination, showing that the initial high antibody levels appear to decline over time [17–19]. A booster serves as a re-exposure to the virus, which creates new antibodies as well as additional and improved memory B-cells responses to fight off future infections. It has even been found that booster exposure also improves the ability of the memory B-cells to recognise unknown variants such as the Omicron strain [18, 20]. This partially explains why, with the same follow-up time, VE was even higher after a booster than after a primary series alone. The rebound of VE after a booster is consistent with the findings of the systematic review by Song *et al*. [7] and Mohammed *et al*. [12].

Vaccines provided better protection against pre-Omicron strains than Omicron strains. There was a large difference in VE, overall and at each follow-up time, against the Omicron strains compared to the pre-Omicron strains, which included the original strain, Alpha and Delta. This suggests that the reduced effectiveness of vaccination against the Omicron variant is due to the variant itself rather than the waning protection of the vaccines. Compared to earlier strains, Omicron has more mutation sites in the spike protein, of which 15 mutation sites are located in the receptor binding domain (RBD) [21]. Mutations in the spike protein and RBD have been shown to affect antibody neutralisation and thus reduce vaccine-induced immunity [22]. This explains why vaccination with the original strain is less effective against the Omicron variant, regardless of follow-up time.

We also found that vaccine protection against severe COVID-19 was more durable and less sensitive to viral mutation than against SARS-CoV-2 infection. Two types of protective immune responses occur after vaccination. Memory B-cells are responsible for producing neutralising antibodies to prevent virus entry, while memory T-cells play a role in controlling SARS-CoV-2 infection by removing infected cells and thereby preventing more severe outcomes of COVID-19 [23]. Based on previous reports, the Omicron variant has a strong ability to evade B-cell-mediated humoral immunity, while T-cell epitopes are relatively unchanged [24]. Furthermore, Khoury *et al*. [25] found that protection against SARS-CoV-2 infection required higher levels of neutralising antibodies than protection against severe outcomes. This explains why, over time, as antibody levels decline, the effectiveness of vaccine against severe outcomes declines less than against infection. A previous systematic review by Wu *et al*. [8] also found that the decline in VE over time was more pronounced for SARS-CoV-2 infection than for severe outcomes.

When comparing the VE estimates from our review with other global systematic reviews on observational studies, we observed a higher overall VE against Omicron infection at 6 months in Wu *et al*. [8] (50% *versus* 39%), but a lower VE in Mohammed *et al*. [12] (4% *versus* 39%). For the booster, our VE against Omicron infection at 3 months was higher than both studies (58% *versus* 43% and 57%). Their studies were conducted earlier, at a time when some boosters were only administered to the priority group such as elderly, and they did not exclude these studies. As a result, their booster VE estimates may be less representative of the general population. In contrast, our review excluded studies focused exclusively on the elderly to better isolate the true effect of booster vaccination.

In our review, we found a pooled VE of 71% against SARS-CoV-2 infection, whereas systematic reviews of randomised clinical trials reported higher pooled vaccine efficacy of 83% [26] and 77% [27]. Our lower VE estimate reflects the vaccine protection in a real-world setting with longer follow-up periods, as most clinical trials had a maximum follow-up of 4 months, with few extending beyond 6 months. Among the studies with longer follow-up, Thomas *et al*. [28] and El Sahly *et al*. [29] reported mRNA vaccine efficacy of 91–93% against laboratory-confirmed SARS-CoV-2 infection and 97–98% against severe disease. However, these clinical trials only included cases of the original and alpha variants and did not include the latter variants such as Delta and Omicron.

In one of the sensitivity analyses, we included only studies with a low risk of bias in the meta-analysis model and found generally higher VE estimates compared to the primary analysis. This is largely because nonlow-risk studies often have bias due to missing data, which in some cases was not handled properly. For example, some studies classified people with missing vaccination information as unvaccinated [30, 31]. This may underestimate the VE estimate because these people may have been vaccinated somewhere and with vaccine-induced immunity. Future research should use more rigorous methods, such as multiple imputation or advanced methods such as artificial intelligence [32], to deal with missing data and avoid bias.

To the best of our knowledge, this is the first meta-analysis to specifically examine the effectiveness of primary series and booster of COVID-19 vaccines in Europe. Healthcare systems and vaccination policies vary around the world, whereas European countries are more similar. By including only studies conducted in European countries, the observed variation in vaccination policies may be less. Another strength of this review is the inclusion of more recent studies published since 2023, which allowed us to include more studies with longer follow-up after boosters.

Our study has several limitations. First, due to lack of power for the individual outcomes, we combined hospitalisation, ICU admission and death into a combined category of severe outcomes. Although analyses were performed for the individual outcomes, too few studies examined ICU admission and death to draw firm conclusions differentiating the three outcomes. A further complicating factor was the definitions used by each study for these outcomes. While some studies took care to distinguish between hospitalisation with COVID-19 and hospitalisation due to COVID-19, others did not. Hospitalisation with COVID-19 is a composite outcome that includes both incidental cases where the patient is hospitalised for other reasons and true COVID-19 cases that require hospitalisation. In contrast, hospitalisation due to COVID-19 is a more reliable measure to represent the severe outcomes caused by COVID-19.

The second limitation is the limited generalisability of this meta-analysis, especially outside Europe. The decision was made to include only the four main vaccines licensed in Europe. In addition, strict rules were applied regarding the diagnosis of COVID-19 only by RT-PCR testing. This led to the exclusion of several articles and thus reduced the power of our meta-analysis. However, on the other hand, this means that there is a higher level of confidence in the diagnosis of infections, as rapid antigen tests have been shown to be less accurate, especially regarding Omicron [33].

Third, the I^2 estimates of the pooled VE estimates were very high in most cases. There is a substantial amount of overall variation that cannot be explained by sampling error alone, such as variation in populations, geographic region, outcome definition, covariates adjusted for, dosing intervals and more. The high heterogeneity also limits the generalisability of this meta-analysis.

Fourth, we included only English-language studies, which may have excluded some relevant non-English studies published. However, in the article selection flowchart (appendix 5), none of the studies were excluded solely on the basis of language. They were excluded for other reasons, such as focusing on healthcare workers, outside of Europe, *etc*. The effect of excluding foreign language studies may be marginal.

We note that none of the included articles considered other preventive measures concomitant with vaccination, such as concomitant medication use, when assessing VE, probably due to lack of access to prescription records. However, we believe that these preventive measures play an important role in estimating VE [34]. Moreover, vaccine hesitancy and racial disparities may impact the estimation of VE, as they introduce bias in population coverage and uptake of vaccines [35, 36]. Future studies should address these potential biases and confounding more rigorously.

Additional analyses for Omicron subvariants such as BA.4 and BA.5 could not be performed due to a lack of subvariant studies. The Omicron strain continues to mutate and evolve, further reducing the neutralising capacity of existing antibodies and thus reducing the effectiveness of the vaccines. In addition, evaluating the long-term effectiveness of second and third booster doses is becoming more difficult as most countries have dismantled their large-scale COVID-19 testing facilities. Many European countries continue to offer bivalent booster does to vulnerable populations in the fall and winter. With the significant reduction in mortality from Omicron infection [37], the focus of the VE study should shift to protection against more relevant outcomes such as re-infection or post-COVID symptoms.

Conclusion

COVID-19 vaccines provide effective protection against SARS-CoV-2 infection and severe outcomes such as hospitalisation, ICU admission and all-cause death. Vaccine protection against severe COVID-19 was more durable and less affected by viral mutation compared to protection against SARS-CoV-2 infection. The Omicron variant significantly reduced VE. Although VE declined substantially over time, boosters can restore vaccine protection against all variants, including Omicron, for at least several months, underscoring the importance of boosters, especially for vulnerable populations. Further VE studies should also consider the impact of other preventive measures, such as concomitant medication use, on VE estimates and focus on other outcomes such as reinfection or post-COVID symptoms.

Points for clinical practice

COVID-19 VE against infection declines substantially over time, especially for Omicron variants. Booster doses are essential for restoring and maintaining protection, particularly for vulnerable populations. While VE against severe outcomes (such as hospitalisation, ICU admission or death) remains more resistant to viral mutation, booster doses also play a crucial role in maintaining protection against severe disease. Regular booster vaccination should be considered for continued protection, especially as variants evolve. Considering the seasonality of COVID-19, the timing of booster vaccination is also essential.

Provenance: Submitted article, peer reviewed.

Data availability: The datasets supporting the conclusions of this article are included within the article and its additional files. Informed consent was not required as no personal information was used in our article. The R code for data analysis can be shared by emailing the corresponding author.

Author contributions: G. Zhou is the guarantor of the content of the manuscript, including the data and analysis of this systematic review. G. Zhou, N. Dael, and E. Hak had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis. G. Zhou and N. Dael contributed to literature search, data acquisition, meta-analysis, and data interpretation. All authors contributed to the protocol and manuscript preparation. All authors were responsible for conceptualisation, design of work, analysis, interpretation, manuscript preparation, editing, and review of manuscript.

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