Received: 17 January 2023 | Accepted: 23 February 2023

DOI: 10.1002/jmv.28623

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Effectiveness of mRNA and viral-vector vaccines in epidemic period led by different SARS-CoV-2 variants: A systematic review and meta-analysis

Jun Zhang[1] | Wenxing Yang[2] | Feijun Huang[1] | Kui Zhang[1]

[1]Department of Forensic Pathology, West China School of Basic Medical Sciences & Forensic Medicine, Sichuan University, Chengdu, China

[2]Department of Physiology, West China School of Basic Medical Sciences & Forensic Medicine, Sichuan University, Chengdu, China

Correspondence

Feijun Huang and Kui Zhang, Department of Forensic Pathology, West China School of Basic Medical Sciences & Forensic Medicine, Sichuan University, Chengdu, Sichuan 610041, China.

Email: newman-zhk@163.com and cheungque@163.com

Abstract

We assessed the effectiveness of mRNA and viral-vector vaccines in epidemic period led by different SARS-CoV-2 variants. Systematic search of PubMed, EMBASE, and CNKI (China National Knowledge Infrastructure) databases without language restriction for studies published before September 19, 2022. The review was registered with PROSPERO (CRD42022335430) and reported according to PRISMA guidelines. Forty studies met the inclusion criteria for this study, with 62 954 861 participants. The overall vaccine effectiveness (VE) to prevent COVID-19 infection was 0.76 (95% confidence interval [CI] 0.73–0.78), symptomatic infection was 0.87 (95% CI 0.83–0.91), hospital admissions was 0.82 (95% CI 0.75–0.87), and mortality was 0.76 (95% CI 0.48–0.89). Subgroup analysis were performed to characterize the effectiveness of different vaccines. When SARS-CoV-2 variants are taking account, the VE decreased along with the variation of the virus by clinical outcomes and vaccine types. The findings of this systematic review provide the best available evidence that BNT162b2, mRNA-1273, ChAdOx1, and Ad26. COV2.S seems to be approximately effective from predelta to omicron, but only modestly effective in participants aged 65 or older. When SARS-CoV-2 variants are taking account, VE decreased along with the variation of the virus for all mRNA and viral-vector vaccines.

KEYWORDS

COVID-19 vaccine, effectiveness of vaccine, meta-analysis, SARS-CoV-2 variants

1 | INTRODUCTION

The emergence and spread of SARS-CoV-2 variants of concern (VOS) has aroused global attention and public concerns.[1] The genomes of all viruses accumulate mutations over time with the genomes of RNA viruses are particularly prone to mutation. The pace of change of the SARS-CoV-2 genome has thus been estimated at 1.87×10^{-6} nucleotide substitutions per site per day,[2] thus, across the about 30 000 base pair genome of SARS-CoV-2, approximately 20 genetic changes occur per year within a lineage. The evolution of virulence depends strongly on the nature of the mutations that arise. Variants may increase transmissibility but reduce severity and death rates, or cause more severe illness due to a higher viral load. Unfortunately, the B.1.1.7 (alpha) variant, first identified in the United Kingdom, was the predominant lineage seen between January and May 2021 is both more transmissible and more virulent.[3–5] The increased transmission has been accompanied by increased virulence, with an estimated 64% higher mortality rate (95% confidence interval [CI]

Jun Zhang and Wenxing Yang contributed equally to this study.

32%–104%),[4,5] and infected individuals have a slightly higher viral load and longer infectious period.[6] The B.1.617.2 (delta) variant became the most commonly reported variant in the country starting in mid-April 2021 has a potentially higher rate of transmission than other variants.[7] Reduced vaccine effectiveness (VE) against B.1.617.2 breakthrough infections has been reported.[8] The novel B.1.1.529 (omicron) variant was first detected in mid-November 2021,[9] is involved in infections with recovered individuals.[10] The most concerning characteristic of the omicron variant is the constellation of more than 50 mutations, of them about 30 mutations are in the spike protein. At the present time, WHO is coordinating with a large number of researchers around the world to better understand omicron, including studies on performance of vaccines.[11]

During the pandemic of COVID-19, enormous hope was placed in vaccines.[12] Although full escape from vaccine-induced immunity has not yet been documented, variants displaying partial escape are already reported in B.1.617.2 and B.1.351 for some antibodies.[3,13,14] Therefore, strategies to boost vaccine responses against variants are warranted. To date, no comprehensive review is available of information about the breakthrough infections among vaccinated individuals with different SARS-CoV-2 variants. Therefore, we systematically reviewed the effectiveness of BNT162b2, mRNA-1273, ChAdOx1 and Ad26. COV2.S in epidemic period led by different SARS-CoV-2 variants.

2 | METHODS

The analysis of the overall VE, VE of different SARS-CoV-2 variants, VE of different vaccine type, and VE to prevent different clinical outcomes were evaluated regardless of vaccine dose. The VE of different vaccine types included the data of homologous vaccine injection, and the participants received heterologous vaccine regimes were classified as uncategorized. We registered this work in PROSPERO (CRD42022335430) and reported here with our findings following PRISMA guidelines.[15]

2.1 | Publication search and inclusion and exclusion criteria

We recently searched available articles in PubMed, EMBASE, and CNKI (China National Knowledge Infrastructure) databases published from the year of 2019 to 2022 on the effectiveness of mRNA, and viral-vector vaccines. Our last search was performed on September 19, 2022. The following terms were used in the search: "COVID-19 vaccine" or "BNT162b2" or "mRNA-1273" or "ChAdOx1" and "infection" or "breakthrough" and "unvaccinated". To identify the relevant publications, the references cited by the research papers were also manually screened. A total of 1043 studies were included in our review, with 971 from the database and 72 from references screening (Figure 1).

Eligible studies met all of the following criteria: (1) participates vaccinated with mRNA, or viral-vector COVID-19 vaccines regardless of vaccine dose; (2) inclusion of sufficient data or the data can be acquired from the manuscript or supplementary materials to calculate the effectiveness of the vaccines; (3) never vaccinated participates or never infected persons as controls; (4) the publication was published in English or Chinese. Excluded studies followed the criteria: (1) reviews, books, or meeting/conference abstracts; (2) duplicated studies; (3) evaluation of other vaccines except for mRNA, or viral-vector COVID-19 vaccines; (4) the manuscript or supplementary materials contains unavailable data; (5) the paper was published in other language except for English or Chinese.

2.2 | Data extraction

Two authors (Wenxing Yang and Xuehong Sun) independently reviewed and extracted the data needed. Discussion among the authors were conducted to resolve the divided opinions. The following information were recorded for each study: first author, year of publication, region, vaccine type, SARS-CoV-2 variants, adjusted estimates status, population size, and population type. All of the data are shown in Table 1.

2.3 | Statistical analysis

The odds ratio (OR) and corresponding 95% CI were used to assess the VE. To identify the VE of different vaccines, and VE to prevent different clinical outcome in epidemic periods led by different SARS-CoV-2 variants, we analyzed subgroup effects by clinical results, vaccine types, SARS-CoV-2 variants, and population types.

Obvious statistical heterogeneity exists among the included studies, according to the results from Q-test and I^2 statistic,[55] thus the random-effects model (the DerSimonian and Laird method)[56] was used to calculate the OR and 95% CIs of VE. To explore the sources of heterogeneity across the studies, we did logistic meta-regression analyses. The following characteristics of the studies were examined: publication year, region, population size. Publication bias was evaluated with funnel plot and Begg's rank correlation method.[57] The statistical analyses were performed by STATA 12.0 software (Stata Corp.).

3 | RESULTS

3.1 | Characteristics of studies

A total of 1043 abstracts were screened according to the inclusion and exclusion criteria, 77 studies were retrieved for more detailed evaluation. Twelve reviews were excluded from the 77 studies, 21 studies lacked sufficient data, two studies were related to inactivated vaccine,[58,59] and two studies were duplicated.[24,60] Finally, 40 studies out of total 1043 abstracts were finally included in our meta-analysis,[16–54,60] involving 62 954 861 participates and two kinds of

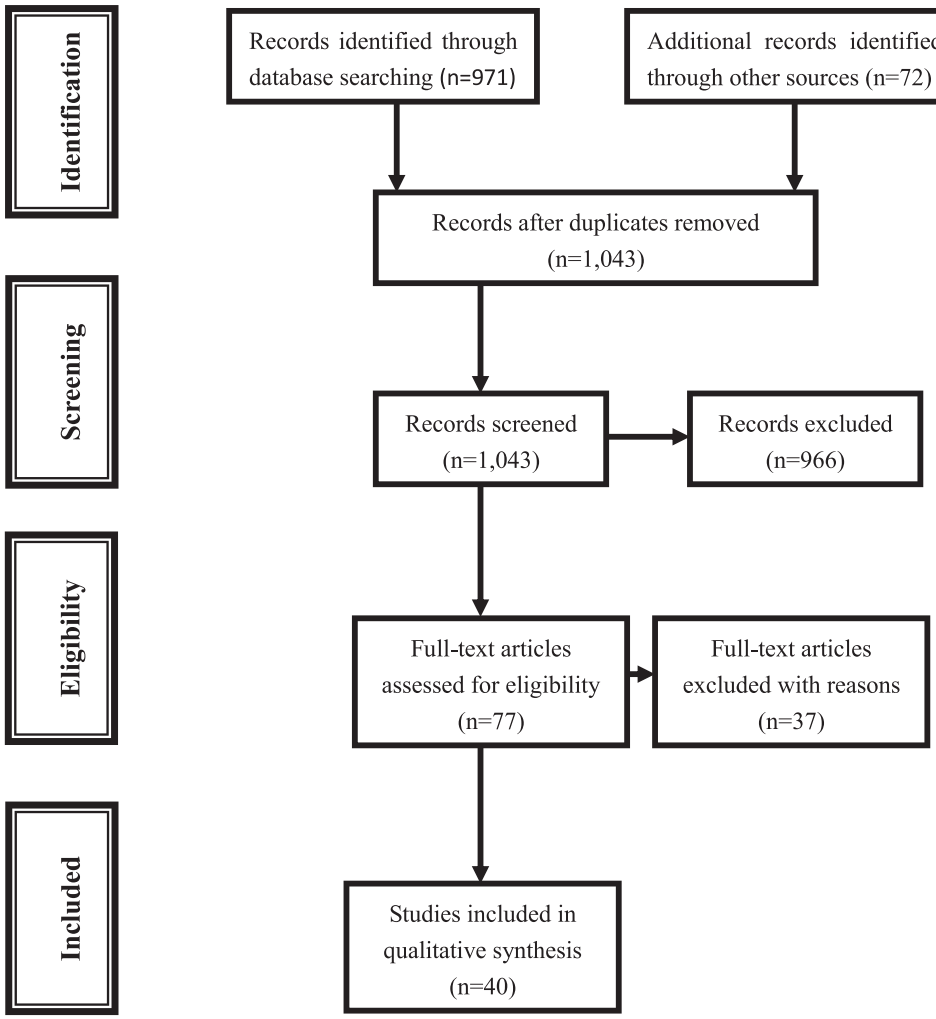

FIGURE 1 Flowchart for identification of studies.

COVID-19 mRNA vaccines, namely BNT162b2 and mRNA-1273; two kinds of viral vector vaccines, namely ChAdOx1 and Ad26.COV2.S. The included studies spanned from the phase of predelta to omicron, detailed information of these studies is listed in Table 1.

3.2 | Quantitative synthesis

As shown in Table 2, the overall VE to prevent COVID-19 was 0.76 (95% CI 0.73–0.78); when SARS-CoV-2 variants are taking account, the VE decreased from 0.84 (95% CI 0.79–0.87) of predelta pandemic period to 0.41 (95% CI 0.22–0.55) of omicron pandemic period. For the participants aged 65 or older, the overall VE to prevent COVID-19 was 0.68 (95% CI 0.56–0.76), while VE decreased from 0.71 (95% CI 0.58–0.79) of predelta period to 0.37 (95% CI −0.30 to 0.69) of omicron period (Table 2 and Figure 2A,B). The overall VE to prevent COVID-19-associated symptomatic infection was 0.87 (95% CI 0.83–0.91), while VE decreased from 0.90 (95% CI 0.83–0.94) of predelta period to 0.82 (95% CI 0.72–0.89) of delta period (Table 2 and Figure 2A,C). The overall VE to prevent COVID-19-associated hospital admissions was 0.82 (95% CI 0.75–0.87), while VE decreased from 0.85 (95% CI 0.76–0.90) of predelta period to 0.58 (95% CI 0.14–0.79) of omicron period (Table 2 and Figure 2A,D). The overall VE to prevent COVID-19-associated death was 0.76 (95% CI 0.48–0.89), while VE decreased from 0.82 (95% CI 0.68–0.89) of predelta period to 0.44 (95% CI −0.08 to 0.71) of omicron period.

We performed subgroup analysis to characterize the effectiveness of different mRNA, and viral-vector vaccines in epidemic periods led by different SARS-CoV-2 variants (Table 2 and Figure 3). The overall VE was 0.78 (95% CI 0.72–0.82) for BNT162b2, 0.89 (95% CI 0.84–0.92) for mRNA-1273, 0.60 (95% CI 0.50–0.67) for ChAdOx1, 0.58 (95% CI 0.38–0.72) for Ad26.COV2.S, and 0.65 (95% CI 0.59–0.70) for uncategorized mRNA, and viral-vector vaccines, respectively (Table 2). In General, VE decreased along with the variation of the virus (Figure 3). VE decreased from 0.83 (95% CI 0.75–0.88) of predelta period to 0.43 (95% CI 0.08–0.64) of omicron period for BNT162b2, 0.94 (95% CI 0.88–0.97) of predelta period to 0.79 (95% CI 0.66–0.88) of delta period for mRNA-1273, and 0.74 (95% CI 0.56–0.85) of predelta period to 0.37 (95% CI 0.17–0.53) of delta period for ChAdOx1, respectively.

TABLE 1 Characteristics of literatures included in the meta-analysis.

Reference	Year	Region	Vaccine type	SARS-CoV-2 variants	Adjusted estimates	Population size	Population type
Glampson et al.[16]	2021	UK	Any mRNA, or viral-vector vaccines	Predelta	Yes	2 183 939	Adults
Lauring et al.[17]	2022	USA	Any mRNA, or viral-vector vaccines	Predelta, Delta, Omicron	Yes	11 690	Adults, Aged 65 years or older
León et al.[18]	2022	USA	Any mRNA, or viral-vector vaccines	Delta	No	1 108 600	Adults
Thompson et al.[19]	2022	USA	Any mRNA, or viral-vector vaccines	Delta, omicron	No	222 772	Adults
Fowlkes et al.[20]	2021	USA	Any mRNA, or viral-vector vaccines	Predelta, Delta	No	4136	Adults
Amodio et al.[21]	2022	Italy	Any mRNA, or viral-vector vaccines	Predelta, Delta	No	3 966 976	Adults
Thompson et al.[22]	2021	USA	Any mRNA, or viral-vector vaccines	Predelta	Yes	3950	Adults
Oliver et al.[23]	2022	Canada	Any mRNA, or viral-vector vaccines	Predelta	No	13 759	Adults
Angel et al.[24]	2021	Israel	BNT162b2	Predelta	No	6710	Adults
Bianchi et al.[25]	2021	Italy	BNT162b2	Predelta	No	2034	Adults, Aged 60 years or older
Self et al.[26]	2021	USA	Ad26. COV2.S, BNT162b2, mRNA-1273	Intermediate	No	3689	Adults
Puranik et al.[27]	2021	USA	BNT162b2, mRNA-1273	Predelta, Delta	No	645 109	Adults
Hall et al.[28]	2021	UK	BNT162b2	Predelta	Yes	23 324	Adults
Katz et al.[29]	2022	Israel	BNT162b2	Predelta	No	1567	Adults
Eyre et al.[30]	2022	UK	BNT162b2, ChAdOx1	Predelta, Delta	Yes	146 243	Adults
Fowlkes et al.[31]	2022	USA	BNT162b2	Delta, Omicron	No	1364	Aged 5–15 Years
Del Cura-Bilbao et al.[32]	2022	Spain	BNT162b2, ChAdOx1, mRNA-1273	Predelta	No	964 258	Adults
Alali et al.[33]	2021	Kuwait	BNT162b2, ChAdOx1	Predelta	No	3246	Adults
Muhsen et al.[34]	2021	Israel	BNT162b2	Predelta	Yes	15 535	Adults
Singer et al.[35]	2021	Israel	BNT162b2	Predelta	No	350	Adults
Klein et al.[36]	2022	USA	BNT162b2	Delta, Omicron, Preomicron	No	39 217	Aged 5–17 Years
Eick-Cost et al.[37]	2022	USA	BNT162b2, mRNA-1273	Predelta, Delta	No	441 379	Adults
Paris et al.[38]	2021	France	BNT162b2, ChAdOx1, mRNA-1273	Predelta	No	8165	Adults
Nanduri et al.[39]	2021	USA	BNT162b2, mRNA-1273	Predelta, Intermediate, Delta	No	136 160	Adults
Dagan et al.[40]	2021	Israel	BNT162b2	Predelta	No	21 722	Adults
Pawlowski et al.[41]	2021	USA	BNT162b2, mRNA-1273	Predelta	Yes	136 532	Adults
Björk et al.[42]	2022	Sweden	BNT162b2	Predelta	No	805 741	Adults
Grannis et al.[43]	2021	USA	BNT162b2, Ad26 COV2.S, mRNA-1273	Delta	Yes	32 867	Adults, Aged 75 years or older
Flacco et al.[44]	2021	Italy	BNT162b2, ChAdOx1, mRNA-1273	Predelta	Yes	245 226	Adults

TABLE 1 (Continued)

Reference	Year	Region	Vaccine type	SARS-CoV-2 variants	Adjusted estimates	Population size	Population type
Porru et al.[45]	2022	Italy	BNT162b2	Predelta	Yes	9811	Adults
Thompson et al.[46]	2021	USA	BNT162b2, mRNA-1273	Predelta	No	3975	Adults
Nordström et al.[47]	2022	Sweden	BNT162b2, ChAdOx1, mRNA-1273	Intermediate	Yes	1 685 948	Adults
Jones et al.[48]	2021	UK	BNT162b2	Predelta	No	8819	Adults
Eyre et al.[30]	2022	UK	ChAdOx1	Predelta, Delta	Yes	146 243	Adults
Gram et al.[49]	2021	Denmark	ChAdOx1	Predelta	No	5 542 079	Adults
Katikireddi et al.[50]	2022	Scotland	ChAdOx1	Delta	No	1 972 454	Adults
Katikireddi et al.[50]	2022	Brazil	ChAdOx1	Delta	No	42 558 839	Adults
Shrotri et al.[51]	2021	UK	BNT162b2, ChAdOx1	Predelta	No	10 412	Aged 65 years or older
Lopez Bernal et al.[52]	2021	UK	BNT162b2, ChAdOx1	Predelta	No	174 731	Aged 70 years or older
Gomes et al.[53]	2021	Germany	BNT162b2	Predelta	Yes	708 187	Aged 80 years or older
Goldin et al.[54]	2022	Israel	BNT162b2	Predelta	No	43 596	Aged 65 years or older

Logistic meta-regression analyses revealed publication year, region, population size did not substantially affect the heterogeneity, and subgroup analysis were performed.

We investigated the influence of each included study on the overall result of current meta-analysis by a series of analyses omitting one study at a time, from which we got similar results, indicating that our results are statistically reliable. The Begg's test was performed to evaluate the publication bias of selected literatures. No evidence of publication bias in our study is observed ($p = 0.76$ for any mRNA vaccine, $p = 0.085$ for BNT162b2, $p = 0.371$ for ChAdOx1, and $p = 0.198$ for mRNA-1273, as shown in Supporting Information: figure).

4 | DISCUSSION

The findings of this systematic review of 40 studies about the mRNA and viral-vector vaccines provide the best available evidence that BNT162b2, mRNA-1273, ChAdOx1 and Ad26.COV2.S seems to be approximately effective from predelta to omicron, but only modestly effective in participants aged 65 or older. When SARS-CoV-2 variants are taking account, VE decreased along with the variation of the virus for all mRNA and viral-vector vaccines.

The mRNA vaccines are composed of the Spike S1 protein-encoding mRNA, and the viral vector vaccines have incorporated DNA sequences encoding the SARS-CoV-2 Spike S1 protein into adenoviruses. Actually, they all target Spike only in nature.[61] Immunological memory to viruses includes antibodies, memory B cells, memory $CD4^+$ T cells, and memory $CD8^+$ T cells.[61] Immune memory is the source of protective immunity from infection.[62,63] The ability of SARS-CoV-2 to escape humoral immune responses in the near term is unclear. SARS-CoV-2 mutations could affect individual neutralizing antibody epitopes. However, no single viral mutation on SARS-CoV-2 Spike targeted by neutralizing antibodies is expected to avoid neutralization by the broad range of SARS-CoV-2 neutralizing antibodies.[64–66] As for T cell immunity consisting of $CD4^+$ and $CD8^+$ T cell responses, a very broad array of SARSCoV-2 epitopes make it highly unlikely to escape.[67,68] Thus, although it is important to track SARS-CoV-2 evolution, the virus is unlikely to escape from the majority of humoral and cellular immune memory in COVID-19 vaccine recipients soon.[61] Our present study with accumulated data indicated that BNT162b2, mRNA-1273, ChAdOx1 and Ad26.COV2.S seems to be approximately effective from predelta to omicron. The human immune system is inherently diverse from person to person.[68] Age is the largest risk factor, thus older individuals are less likely to make a coordinated adaptive immune response to SARS-CoV-2.[69] A T cell response to any new viral infection depends on the repertoire of naive T cells. Notably, it is well characterized that the abundance of naive T cells declines substantially with age.[70,71] Consequently, our results suggested only modestly effective in participates aged 65 or older.

In the past few years, several SARS-CoV-2 VOCs containing multiple mutations have been reported: alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and omicron (B.1.1.529). There has been great trepidation that COVID-19 vaccine fails to induce immune memory and fails to induce protective immunity as the evaluation of SARS-CoV-2.

TABLE 2 Effectiveness of mRNA, or viral-vector vaccines against different SARS-CoV-2 variants.

Vaccine type		Pre delta				Intermediate				Delta			
		N[a]	Population	VE (95%CI)	P[b]	N[a]	Population	VE (95%CI)	P[b]	N[a]	Population	VE (95%CI)	P[b]
Any vaccine	Infection	40	15,352,435	0.84 (0.79, 0.87)	<0.001	8	1,825,797	0.74 (0.62, 0.82)	<0.001	20	51,287,806	0.68 (0.63, 0.72)	<0.001
	Symptomatic	13	2,514,895	0.90 (0.83, 0.94)	<0.001					6	2,255,762	0.82 (0.72, 0.89)	<0.001
	Hospital	11	10,757,874	0.85 (0.76, 0.90)	<0.001	3	3,689	0.81 (0.68, 0.89)	<0.001	11	6,429,393	0.84 (0.72, 0.90)	<0.001
	Death	6	4,281,595	0.82 (0.68, 0.89)	0.001					2	3,978,666	0.70 (−3.12, 0.98)	<0.001
	≥65 yrs	8	950,650	0.71 (0.58, 0.79)	<0.001					2	44,557	0.63 (0.15, 0.84)	0.001
BNT162b2		20	3,625,906	0.83 (0.75, 0.88)	0.001	3	1,825,797	0.76 (0.56, 0.87)	0.001	7	1,442,339	0.70 (0.60, 0.77)	0.001
mRNA-1273		8	2,580,804	0.94 (0.88, 0.97)	<0.001	3	1,825,797	0.82 (0.68, 0.91)	<0.001	4	1,255,515	0.79 (0.66, 0.88)	<0.001
ChAdOx1		6	6,909,217	0.74 (0.56, 0.85)	<0.001	1	1,685,948	0.44 (0.35, 0.51)		3	44,677,536	0.37 (0.17, 0.53)	<0.001
Ad26.COV2.S													
uncategorized													

Vaccine type		Pre omicron				Omicron				Overall			
		N[a]	Population	VE (95%CI)	P[b]	N[a]	Population	VE (95%CI)	P[b]	N[a]	Population	VE (95%CI)	P[b]
Any vaccine	Infection					5	275,043	0.41 (0.22, 0.55)	<0.001	73	62,954,861	0.76 (0.73,0.78)	<0.001
	Symptomatic									19	2,514,895	0.87 (0.83, 0.91)	<0.001
	Hospital	1	39,217	0.70 (0.58, 0.78)		2	234,462	0.58 (0.14, 0.79)	0.001	28	12,165,019	0.82 (0.75, 0.87)	<0.001
	Death					1	11,690	0.44 (−0.08, 0.71)		9	4,281,595	0.76 (0.48, 0.89)	<0.001
	≥65 yrs					1	11,690	0.37 (−0.30, 0.69)		11	983,517	0.68 (0.56, 0.76)	<0.001
BNT162b2						3	40,581	0.43 (0.08, 0.64)	0.001	33	5,365,667	0.78 (0.72, 0.82)	<0.001
mRNA-1273										15	4,303,308	0.89 (0.84, 0.92)	<0.001
ChAdOx1										10	53,126,458	0.60 (0.50, 0.67)	<0.001
Ad26.COV2.S										2	36,556	0.58 (0.38, 0.72)	0.065
uncategorized										13	7,515,822	0.65 (0.59, 0.70)	<0.001

[a]Number of comparisons.

[b]P value of Q-test for heterogeneity test.

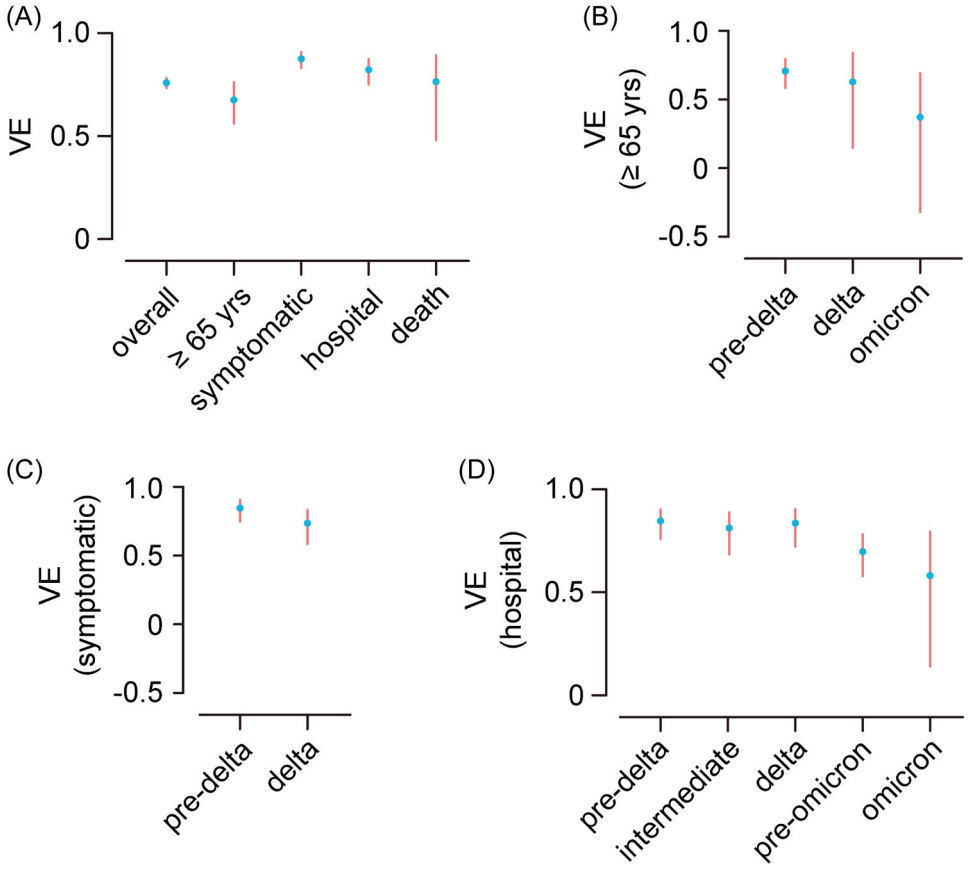

FIGURE 2 Vaccine effectiveness (VE) in different population of patients and different COVID-19 epidemic periods. (A) VE in different population of COVID-19 patients. (B) VE of COVID-19 patients aged 65 or older in different variants epidemic periods. (C) VE of COVID-19 patients with symptomatic infection in predelta and delta epidemic periods. (D) VE of patients with hospital admissions in different variants epidemic periods.

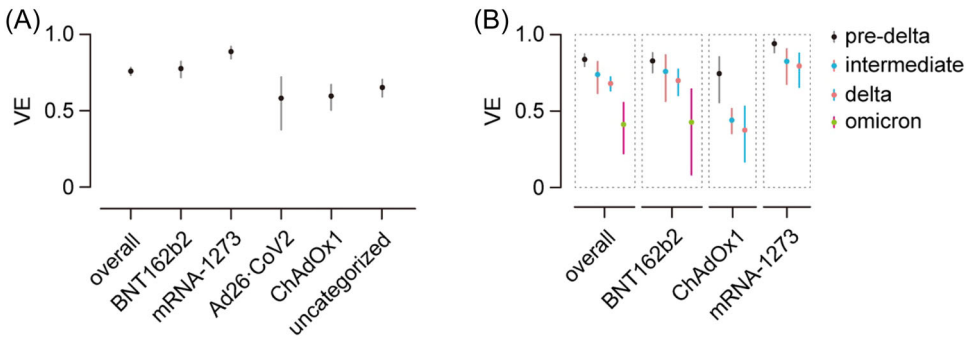

FIGURE 3 Vaccine effectiveness (VE) of different mRNA, or viral-vector vaccines in different COVID-19 epidemic period. (A) general VE of different mRNA, or viral-vector vaccines. (B) VE of different mRNA, or viral-vector vaccines in different variant epidemic period.

Infection with the Delta variant was associated with more frequent recovery of infectious virus compared to the Alpha variant,[72–75] both BNT162b2 and mRNA-1273 vaccine displayed lower effectiveness in preventing infection,[76,77] but vaccination can provide robust effectiveness in preventing Delta hospitalization and mortality.[75,76] Genetically, omicron is more antigenically distant from the original SARS-CoV-2 vaccine strain than the previously most distant strains, beta and delta. Accordingly, substantial decreased neutralization titer and even spaced neutralizing antibodies at all were discovered in postvaccinated recipients.[78,79] Fast-spreading COVID variant can elude immune responses,[80] with the heavily mutated Omicron variant puts scientists on alert.[81] A booster dose for those who are fully vaccinated[82,83] or heterologous second dosing[84,85] was advised to increase transient systemic reactogenicity. However, fully vaccinated individuals after receipt of booster vaccine doses were less effective against symptomatic omicron infection.[86,87] Our findings provide available evidence that VE of mRNA and viral-vector vaccines decreased along with the variation of the virus. Therefore, the future research for updated SARS-CoV-2

vaccine and attention to infection control procedures is needed in the postvaccination era.

The primary limitation of our study is that we analyzed the VE of mRNA and viral-vector vaccines by comparison the breakthrough infection between the vaccinated individuals with the spaced vaccination. However, due to the limited available data, we failed to perform subgroup analysis of the VE of mRNA and viral-vector vaccines among the fully vaccination or partly vaccination individuals. Furthermore, information is limited about the effect of vaccines on omicron, that make the results need further confirmation.

Our comprehensive systematic review provides the best available information that mRNA and viral-vector vaccines provide the best available evidence that BNT162b2, mRNA-1273, ChAdOx1 and Ad26.COV2.S seems to be continuously effective from predelta to omicron, but only modestly effective in participants aged 65 or older. When SARS-CoV-2 variants are taking account, VE decreased along with the variation of the virus for all mRNA and viral-vector vaccines. Fast-spreading COVID variant can elude immune responses, booster vaccine doses and other vaccination strategy seems to be not effective for the long-term control of the pandemic of COVID-19, future research for updated SARS-CoV-2 vaccine may provide better protection against subsequent variants.

AUTHOR CONTRIBUTIONS

Conceptualization: Kui Zhang and Feijun Huang. *Data curation and project administration*: Wenxing Yang and Jun Zhang. *Software and writing—review and editing*: Jun Zhang. *Writing—original draft*: Wenxing Yang and Kui Zhang.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study. The authors confirm that the data supporting the findings of this study are available within the article.

ORCID

Kui Zhang http://orcid.org/0000-0003-2769-1940

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhang J, Yang W, Huang F, Zhang K. Effectiveness of mRNA and viral-vector vaccines in epidemic period led by different SARS-CoV-2 variants: a systematic review and meta-analysis. *J Med Virol*. 2023;95:e28623. doi:10.1002/jmv.28623