American Journal of Epidemiology, 2024, 193, 1868–1881
https://doi.org/10.1093/aje/kwae142
Advance access publication date June 20, 2024
Systematic Review and Meta- and Pooled Analysis

Prior infections and effectiveness of SARS-CoV-2 vaccine in test-negative studies: a systematic review and meta-analysis

Tim K. Tsang*[,1,2], Sheena G. Sullivan[3], Xiaotong Huang[1], Can Wang[1], Yifan Wang[1], Joshua Nealon[1], Bingyi Yang[1], Kylie E. C. Ainslie[1,4], Benjamin J. Cowling*[,1,2]

[1]WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China
[2]Laboratory of Data Discovery for Health Limited, Hong Kong Science and Technology Park, New Territories, Hong Kong Special Administrative Region, China
[3]WHO Collaborating Centre for Reference and Research on Influenza, Royal Melbourne Hospital, and Doherty Department, University of Melbourne, at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
[4]Centre for Infectious Disease Control, National Institute for Public Health and Environment (RIVM), Bilthoven, the Netherlands

*Correspondence authors: Tim Tsang, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 7 Sassoon Road, Pokfulam, Hong Kong (timtsang@connect.hku.hk); Benjamin J Cowling, School of Public Health, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong (bcowling@hku.hk)

Abstract

Prior infection with SARS-CoV-2 can provide protection against infection and severe COVID-19. We aimed to determine the impact of preexisting immunity on vaccine effectiveness (VE) estimates. We systematically reviewed and meta-analyzed 66 test-negative design studies that examined VE against infection or severe disease (hospitalization, intensive care unit admission, or death) for primary vaccination series. Pooled VE among studies that included people with prior COVID-19 infection was lower against infection (77%; 95% CI, 72-81) and severe disease (86%; 95% CI, 83-89) compared with studies that excluded people with prior COVID-19 infection (pooled VE against infection: 87% [95% CI, 85-89]; pooled VE against severe disease: 93% [95% CI, 91-95]). There was a negative correlation between VE estimates against infection and severe disease, and the cumulative incidence of cases before the start of the study or incidence rates during the study period. We found clear empirical evidence that higher levels of preexisting immunity were associated with lower VE estimates. Prior infections should be treated as both a confounder and effect modificatory when the policies target the whole population or are stratified by infection history, respectively.

Key words: COVID-19; SARS-CoV-2; vaccination; vaccine effectiveness; test-negative design; preexisting immunity.

Introduction

COVID-19 vaccines reduce the risk of infection and can also ameliorate disease severity when breakthrough infection occurs.[1,2] Ongoing evaluation of COVID-19 vaccine effectiveness (VE) has largely been measured through observational studies, particularly test-negative design (TND) studies, which share some similarities with case-control studies.[3] However, there has been substantial variation among reported VE estimates,[4-7] which may be attributable to differences in study design, the vaccines used, disease incidence, and population characteristics. Importantly, preexisting population immunity due to prior infection could explain changes in COVID-19 VE over time and among populations.[8,9] Among 42 systematic reviews on VE of COVID-19 vaccines, including VE against infection, symptomatic cases, severe diseases, or fatality, none of them examined the impact of preexisting immunity on the VE estimates (Table S1). This suggests that the impact of preexisting immunity on VE estimates is rarely explored.

Infection with SARS-CoV-2 induces an immune response to protect against reinfection.[10-14] However, reinfection could occur due to waning, naturally induced immunity[15,16] or virus evolution.[17,18] Nevertheless, studies have shown that, compared with persons with no prior infection, vaccination among people with prior infection enhances neutralizing antibody activity as well as cell-mediated responses that can protect against (re)infection,[19] suggesting prior infections may modify the protection from vaccinations. In settings where a large proportion of the population has prior exposure through infection, the unvaccinated will be more protected from infection than in a naïve population, thereby diluting the apparent effectiveness of vaccination. Under these 2 scenarios, prior infection modifies the effect of vaccination (Figure S1).

Prior infection can also alter an individual's decision to be vaccinated and to present for care. For example, vaccination requirements vary for people with recent prior infection in Hong Kong.[20] Moreover, individuals with recent infection may choose not to be vaccinated if they believe they have sufficient preexisting immunity to prevent reinfection and ameliorate the severity of any reinfections that do occur.[21] Additionally, these individuals may also choose not to present for care, believing their COVID-like symptoms are due to another illness, leading to differential under-ascertainment of previously infected COVID-19 cases in surveillance data. Other individual-level factors may also affect the decision to vaccinate and engage in infection-risk behaviors,

Received: March 24, 2023. **Accepted:** June 17, 2024

such as perceived risk of severe disease after infection.[22-24] Acting in this way, prior infection may create a confounding bias along the lines of vaccination-COVID-19 association (Figure S1).

Here, we systematically review and meta-analyze published data to characterize the potential impact of preexisting population immunity on VE estimates for completed primary vaccination series against COVID-19. We also conducted meta-regression to account for the influence of key design features such as vaccine types and circulating virus strains.

Methods

Search strategy and selection criteria

This systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.[25] The review was not registered. A standardized search was done in PubMed, Embase and Web of Science, using the search terms ("test negative" OR "effectiveness") AND ("vaccine") AND ("COVID-19" OR "SARS-CoV-2"). The search was done on July 11, 2022, with no language restrictions. Additional relevant articles from the reference sections of identified articles were also reviewed. Two authors (X.H. and C.W.) independently screened the titles and full texts, and extracted data from the included studies, with disagreement resolved by consensus together with a third author (T.K.T.). Studies identified from different databases were deduplicated.

Studies that reported using a test-negative approach in which all cases and noncases were tested were included,[26,27] regardless of whether the studies assessed the role of preexisting immunity on VE estimates. We included published TND studies with participants recruited from the general population and reported VE estimates for completed primary vaccination series (2 doses for most vaccines; 1 dose for the Janssen vaccine) against at least 1 of the following endpoints: (1) positive test result, (2) symptomatic disease, (3) hospitalization, (4) intensive care unit admission, (5) severe COVID-19, and (6) death. We excluded articles if (1) the study participants were recruited from a specific sub-population, such as health care professionals; (2) studies that summarized or reanalyzed already published data; (3) studies that only reported pooled VE estimates for different vaccines; (4) the study was a preprint and, thus, was not peer-reviewed; or (5) the full text was not available.

Data were extracted from included studies using a standardized data collection form (Table S2) that collected information about the (1) study period; (2) region(s); (3) population; (4) the use of clinical criteria for enrollment; (5) whether participants with prior SARS-CoV-2 infection were included, and the corresponding proportion of participants with infections if available; and (6) method to determining vaccination status. For each study, confounder-adjusted VE estimates with CIs were extracted separately for each endpoint (eg, infection, hospitalization), vaccine, and the circulating virus. In some studies, VEs specific to time intervals after vaccination were reported. Therefore, we extracted VE estimates for the first available time interval at least 14 days after vaccination (ie, 14-30 days after vaccination), because antibodies have been shown to peak by then in naïve persons.[28] For studies that reported multiple estimates, such as by age group or type of vaccine, all subgroup-specific estimates were included, but the overall estimates were excluded.

Study quality was assessed by using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool.[29] The certainty of evidence presented in an article included that the meta-analysis was graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[30]

Meta-analysis

In all identified studies, VE was defined as 100% × (1 − odds ratio [OR]). The extracted VE estimates were meta-analyzed to estimate pooled VE. The VE estimates were transformed to the ORs scale, meta-analyzed, then back-transformed to the VE scale for interpretation. The pooled OR was estimated by random-effects meta-analyses using the inverse variance method and restricted maximum likelihood estimator for heterogeneity.[31-34] Heterogeneity was assessed using Cochran's Q and the I^2 statistic.[35] We considered an I^2 value >75% to be indicative of high heterogeneity.[36] We also conducted a sensitivity analysis using fixed-effects meta-analyses.

The main study feature of interest was inclusion or exclusion of participants with prior infection. Severe disease was based on whether the estimate was limited to patients who required hospitalization, who required intensive care unit admission, and those who died. Otherwise, the estimate was classified as VE against infection, which referred to estimates of VE against test-positive or symptomatic infection (without hospitalization).

Pooled estimates were additionally disaggregated by the probable circulating virus and vaccine administered. Most studies did not report variant-specific VE estimates but did report study periods and the general prevalence of variants during that period. If this information was not reported, we used the Nextstrain[37] to determine the dominant variant in the study period in the study location. The variant with the highest proportion was considered to be the dominant variant. Therefore, estimates were grouped according to the predominant circulating virus, as follows: (1) Omicron; (2) late-Delta, which was the period with co-circulation of Delta and Omicron; (3) Delta; and (4) pre-Delta, which included ancestral strains and variants preceding Delta. The type of vaccine was categorized as follows: (1) mRNA vaccines, including vaccines produced by Moderna and Pfizer-BioNTech; (2) adenovirus vector vaccines, including vaccines produced by AstraZeneca, Janssen, and Gamaleya; and (3) inactivated virus vaccines, including vaccines produced by Sinovac Biotech and Sinopharm.

Meta-regression

To evaluate the impact of preexisting immunity on VE estimates, we used a meta-regression approach. Three proxies of prior immunity were explored: (1) inclusion vs exclusion of participants with prior infection; (2) cumulative incidence of COVID-19 since December 2019 in each of the study countries or regions before the study; and (3) the incidence rate of COVID-19 in the country or region during the study period. For this, we downloaded population denominator data and daily COVID-19 case data from the World Health Organization website.[38,39] We first used correlation analysis, including Pearson (r) and Spearman (ρ) correlation coefficients, to determine the association between preexisting immunity and VE estimates. Meta-regression models were adjusted for age group (all ages, child only, adult and elderly, elderly only), types of vaccines used, predominant circulating virus, the use of clinical criteria for enrollment, the time interval after vaccination (14-30 days after vaccination, unrestricted), and the method to determine vaccination status. A sensitivity analysis was conducted to additionally adjust for location and duration of the study.

The fitted meta-regression model estimated the ratio of ORs (ROR) for each of the prior immunity proxies explored. On the

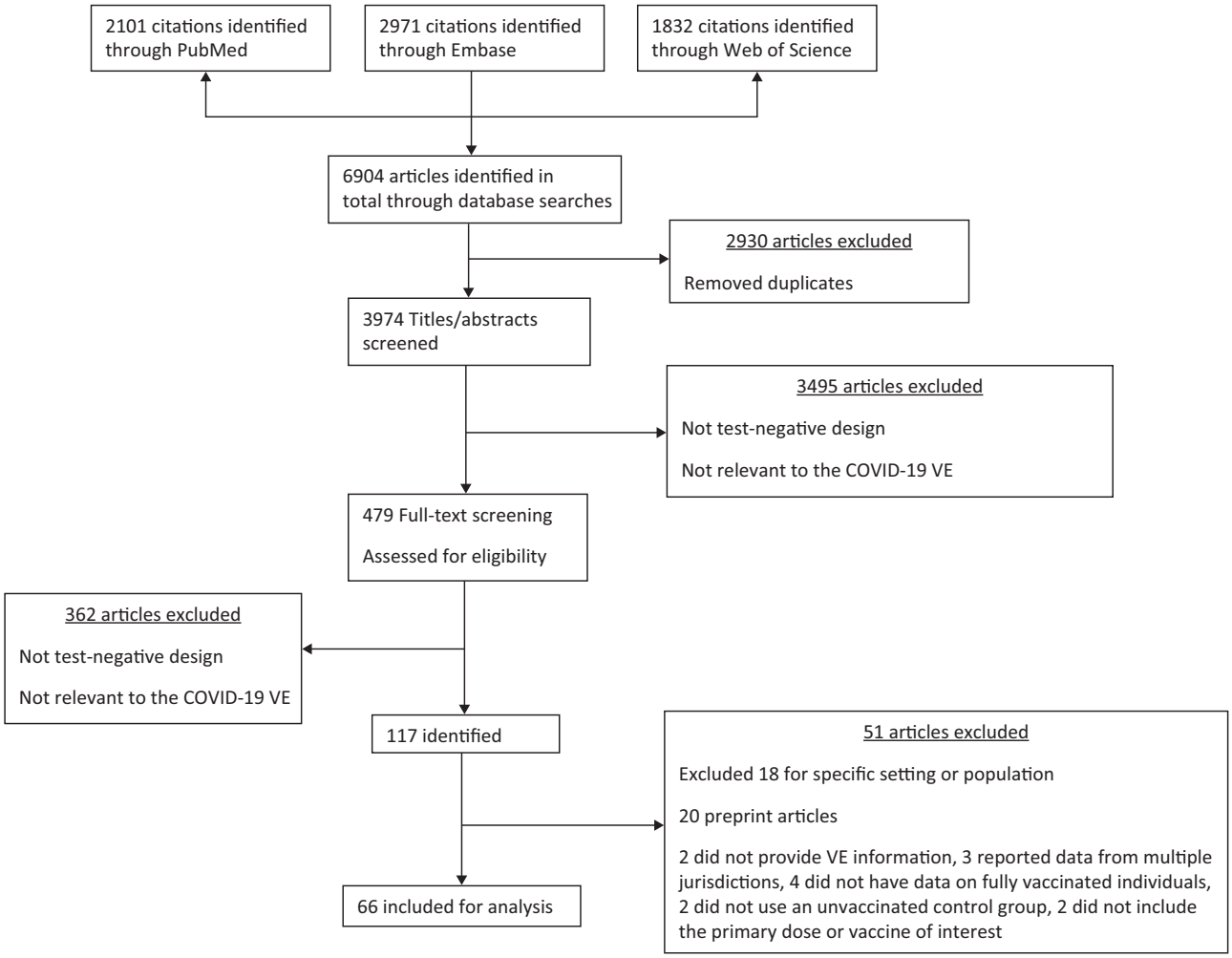

Figure 1. Selection of studies for the systematic review. VE, vaccine effectiveness.

OR scale, values closer to 0 indicated a more effective vaccine, and values closer to 1 indicated a less effective vaccine. This was counter to the VE scale, on which values closer to 0 indicated an ineffective vaccine. Therefore, using inclusion vs exclusion of participants with prior infection as an example, if ROR > 1, then the OR estimated from studies including participants with prior infection was higher than that from studies excluding participants with prior infection. On the VE scale, this translates to lower VE for studies that included participants with prior infection than studies that excluded these participants.

We plotted the expected change in VE estimate to visualize the impact of each prior immunity proxy based on the ROR obtained from meta-regression. To illustrate the change in VE scale, we showed the change in estimate based on the ROR assuming VE for the reference group of 80% against infection and 90% against severe disease. Statistical analyses were conducted using R, version 4.0.5 (R Foundation for Statistical Computing), using the metaphor for meta-analyses and the *robvis* package for risk-of-bias visualizations.

Results

We identified 6904 studies, among which 2929 were duplicates. Title and abstract screening of the remaining articles identified 479 for full-text review, of which 66 met our inclusion criteria[4-7,40-101] (Figure 1; Tables S3-S8). Studies were set in 17 countries or regions. Most were from the United States[28] and United Kingdom.[10] Fifty-one studies provided 173 VE estimates against infection (Figure 2), and 40 studies provided 91 estimates against severe disease (Figure 3). Among all 66 studies, 40 included and 28 excluded participants with prior COVID-19 infection (including 2 studies that provided VE estimates including and excluding participants with COVID-19 infection[4,88]). A summary of study characteristics and the corresponding number of estimates, including handling of participants with prior infections, enrollment criteria, vaccine types, and circulating virus are provided in Tables S3-S7.

VE against infection and severe disease

The 173 VE point estimates against infection ranged from 14% to 98%, with I^2 = 100%, indicating considerable heterogeneity (Figures 4 and 5). Ninety-five VE estimates (55%) were higher than 80%. The 91 VE point estimates against severe disease were also considerably heterogeneous (I^2 > 97%), ranging from 20% to 100% (Figures 4 and 5). Among them, 70 (77%) were higher than 80%. For both outcomes, we observed declining VE over time from early 2021 to mid-2022 (Figure S2).

Impact of type of vaccine and circulating viruses

Our meta-analysis (Figure 5) indicated that pooled VE against infection for a primary course of mRNA vaccines was 86% (95% CI, 84-88), compared with 69% (95% CI, 64-73) for adenovirus vector

A)

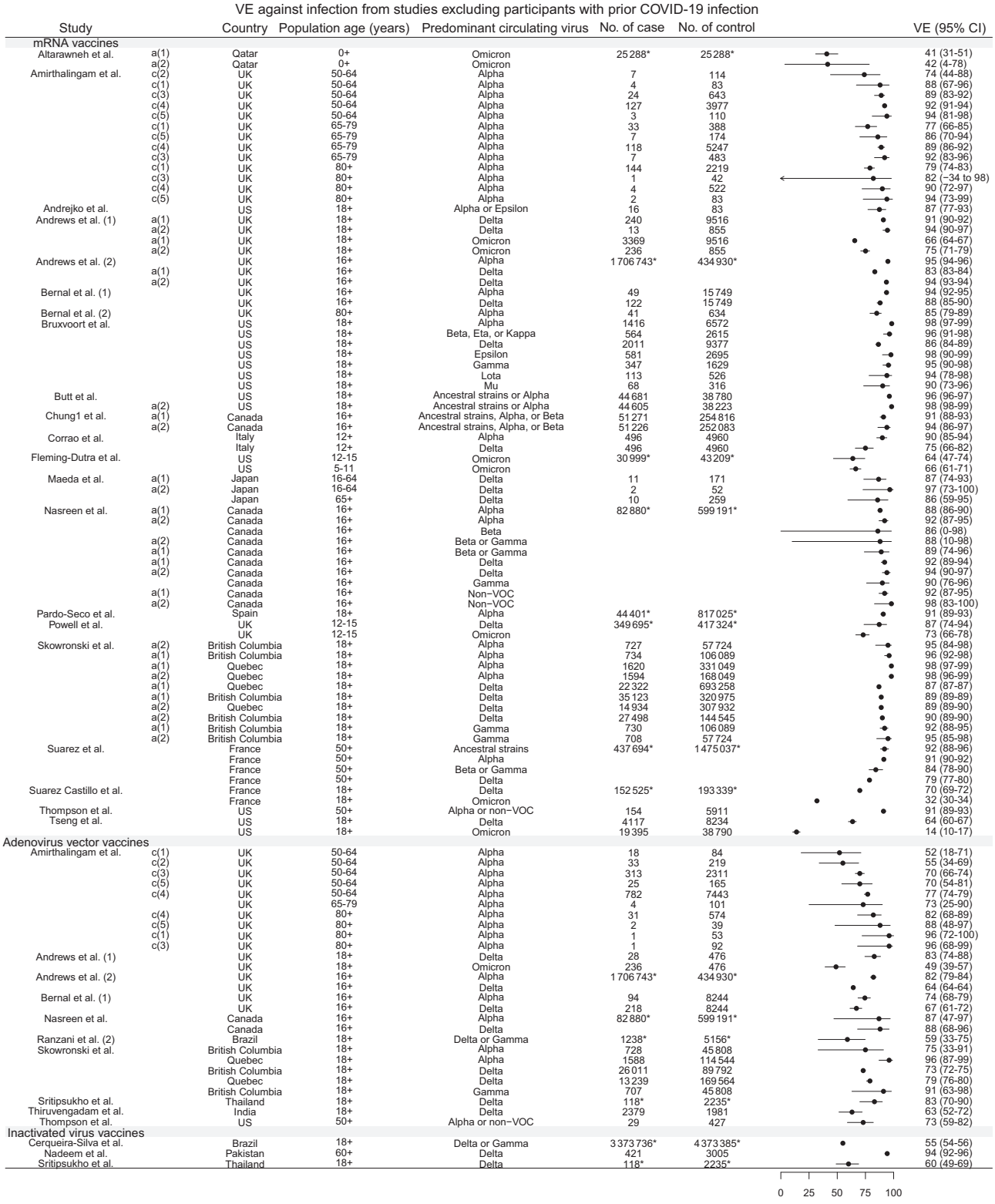

Figure 2. Continues

vaccines and 67% (95% CI, 34-84) for inactivated virus vaccines. When we examined differences in pooled VE by the circulating virus, we found that VE against infection during the Omicron period was far lower (52%; 95% CI, 45-59) than during the pre-Delta (89%; 95% CI, 87-91), Delta (78%; 95% CI, 58-88), and the late-Delta (79%; 95% CI, 74-92) periods. Similarly, VE against severe disease during the Omicron period was 64% (95% CI, 52-73), which was lower than for pre-Delta (92%; 95% CI, 89-94), Delta (87%; 95% CI, 76-93), and late-Delta (91%; 95% CI, 88-93) periods. The results were similar when further disaggregated by including or excluding prior infection (Table S9) or using fixed-effects analysis (Figure S3).

B)

VE against infection from studies including participants with prior COVID-19 infection

Study		Country	Population age (years)	Predominant circulating virus	No. of case	No. of control	VE (95% CI)
mRNA vaccines							
Abu-Raddad et al. (1)		Qatar	0+	Beta or Delta	87 509	148 349	85 (84-87)
Abu-Raddad et al. (2)		Qatar	0+	Alpha	16 404	16 404	90 (86-92)
		Qatar	0+	Beta	19 575	19 575	75 (70-79)
Andrews et al (3)		UK	18-49	Delta	156 429	204 534	65 (65-66)
		UK	50+	Delta	39 217	48 995	61 (60-62)
Britton et al.	a(1)	US	20+	Ancestral strains, Alpha, or Gamma	390 762*	423 621*	90 (89-91)
	a(2)	US	20+	Ancestral strains, Alpha, or Gamma			95 (95-96)
	a(1)	US	20+	Delta			84 (83-84)
	a(2)	US	20+	Delta			90 (89-90)
Bruxvoort et al.		US	18+	Alpha	1422	7110	98 (97-99)
		US	18+	Beta, Eta, or Kappa	568	2840	96 (91-98)
		US	18+	Delta	2027	10 135	87 (84-89)
		US	18+	Epsilon	583	2915	98 (90-99)
		US	18+	Gamma	349	1745	96 (91-98)
		US	18+	Lota	114	570	96 (82-99)
		US	18+	Mu	69	345	90 (74-96)
Chemaitelly et al. (1)		Qatar	12+	Alpha, Beta, or Delta	113 830	113 830	32 (28-36)
Chemaitelly et al. (2)		Qatar	0+	Beta	44 737	44 737	96 (91-98)
Chemaitelly et al. (3)	a(2)	Qatar	0+	Omicron	12 061	7202	43 (15-62)
	a(1)	Qatar	0+	Omicron	13 208	7908	48 (41-54)
Chung et al. (2)	a(1)	US	12+	Ancestral strains, Alpha, or Gamma	614*	1615*	66 (56-73)
	a(2)	US	12+	Ancestral strains, Alpha, or Gamma			81 (73-86)
Drawz et al.	a(1)	US	19+	Delta	51 779	239 244	45 (44-47)
	a(2)	US	19+	Delta	47 835	235 636	65 (64-66)
Ferdinands et al.		US	18+	Delta	8136	77 235	80 (79-81)
		US	18+	Omicron	8351	11 471	41 (38-43)
Fleming-Dutra et al.		US	12-15	Omicron	53	144	60 (44-71)
		US	5-11	Omicron	363	909	60 (55-65)
Grannis et al.	a(1)	US	18+	Delta	314	3632	77 (74-80)
	a(2)	US	18+	Delta	98	2558	92 (89-93)
Husin et al.		Malaysia	12-17	Delta	50 240	125 640	66 (64-67)
Kim et al.		US	16+	Alpha	216	480	91 (83-95)
Kirsebom et al.		UK	18+	Omicron(BA.1)	59 405	76 835	35 (33-36)
		UK	18+	Omicron(BA.2)	35 955	76 835	45 (43-47)
Mallow et al.	a(1)	US	18+	Ancestral strains, Alpha, Delta, or Gamma	1252*	11 951*	74 (66-80)
	a(2)	US	18+	Ancestral strains, Alpha, Delta, or Gamma			78 (68-85)
Sheikh et al.		UK	15+	Alpha	104	53 471	92 (90-93)
		UK	15+	Delta	208	53 471	79 (75-82)
Tabak et al.	a(1)	US	18+	Delta or Gamma			92 (92-93)
	a(2)	US	18+	Delta or Gamma			96 (96-97)
Tang et al.	a(1)	Qatar	0+	Beta	3728	17 153	74 (70-78)
	a(2)	Qatar	0+	Beta	3287	14 766	81 (69-88)
	a(1)	Qatar	0+	Delta	3846	15 977	51 (45-55)
	a(2)	Qatar	0+	Delta	2947	12 151	72 (66-77)
Tartof et al.		US	18+	Delta	7361*	3762*	61 (55-66)
		US	18+	Omicron			47 (40-54)
Whitaker et al.		UK	16-64	Alpha	3755*	8418*	49 (−62-84)
		UK	65+	Alpha			85 (78-90)
Winkelman et al.	a(1)	US	19+	Delta	52 742	374 666	53 (52-54)
	a(2)	US	19+	Delta	47 373	332 942	66 (65-67)
Adenovirus vector vaccines							
Andrews et al. (3)		UK	18-49	Delta	172 928	186 375	45 (44-46)
		UK	50+	Delta	75 861	66 130	39 (37-41)
Britton et al.		US	20+	Ancestral strains, Alpha, or Gamma	390 762*	423 621*	58 (53-63)
		US	20+	Delta			38 (35-42)
Grannis et al.		US	18+	Delta	100	657	65 (56-72)
Hitchings et al.		Brazil	60+	Gamma	81 997*	56 676*	78 (69-84)
Rearte et al.	a(4)	Argentina	60+	Alpha, Gamma, or Lambda	440 467*	842 461*	64 (63-65)
	a(3)	Argentina	60+	Alpha, Gamma, or Lambda			68 (67-69)
Sheikh et al.		UK	15+	Alpha	100	32 488	73 (66-78)
		UK	15+	Delta	231	32 488	60 (53-66)
Tabak et al.		US	18+	Delta or Gamma			51 (45-55)
Whitaker et al.		UK	16-64	Alpha	3755*	8418*	68 (−1 to 90)
		UK	65+	Alpha			82 (60-92)
Winkelman et al.		US	19+	Delta	44 063	260 609	33 (30-37)
Inactivated virus vaccines							
Li et al.		China	18-59	Delta	54	226	59 (16-82)
Ranzani et al. (1)		Brazil	70+	Gamma	39 716*	59 858*	47 (39-54)
Rearte et al.		Argentina	60+	Alpha, Gamma, or Lambda	440 467*	842 461*	44 (42-45)

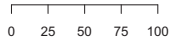

Figure 2. Estimates of vaccine effectiveness (VE) against infection from identified studies that excluded (A) or included (B) participants with COVID-19 infection history. Multiple estimates could be due various factors. These are labeled as follows: for vaccine, a(1) for Pfizer, a(2) for Moderna, a(3) for ChAdOx1, or a(4) for rAd26-rAd5 (Sputnik V); as for the control, b(1) for syndrome-negative), and (b2) for test-negative control; and for different duration between first and second dose: (c1) for 19-29 days, (c2) for 30-44 days, (c3) for 45-64 days, (c4) for 65-84 days, and (c5) for ≥85 days. VOC, variant of concern.

Role of prior infection on VE estimates

In general, VE estimates derived from study participants with lower preexisting immunity were higher. The pooled VE against infection for studies that excluded participants with prior COVID-19 infection was higher (87%; 95% CI, 84-89) than from studies that included these participants (76%: 95% CI, 71-81). Similarly, pooled

A)

VE against severe disease from studies excluding participants with prior COVID-19 infection

Study		Country	Population age (years)	Predominant circulating virus	No. of case	No. of control	VE (95% CI)
mRNA vaccines							
Andrews et. al (2)		UK	16+	Alpha	1706743*	434930*	98 (91-100)
		UK	16+	Delta			97 (96-97)
Nasreen et al.	a(2)	Canada	16+	Alpha	82880*	599191*	95 (92-97)
	a(1)	Canada	16+	Alpha			96 (94-97)
		Canada	16+	Beta			92 (39-99)
		Canada	16+	Beta or Gamma			95 (64-99)
	a(1)	Canada	16+	Delta			98 (96-99)
	a(2)	Canada	16+	Delta			98 (93-100)
		Canada	16+	Gamma			94 (59-99)
		Canada	16+	Non−VOC			97 (88-99)
Niessen et al.		Netherlands	18+	Alpha	338	175	94 (80-98)
Skowronski et al.	a(2)	Quebec, Canada	18+	Alpha	78	168049	91 (70-97)
		British Columbia, Canada	18+	Alpha	71	106089	96 (83-99)
	a(1)	Quebec, Canada	18+	Alpha	77	331049	99 (94-100)
	a(2)	British Columbia, Canada	18+	Delta	2492	144545	97 (97-98)
	a(1)	Quebec, Canada	18+	Delta	1106	586032	97 (97-98)
	a(2)	Quebec, Canada	18+	Delta	923	236262	97 (96-98)
	a(1)	British Columbia, Canada	18+	Delta	2719	320975	98 (97-98)
		British Columbia, Canada	18+	Gamma	54	106089	95 (82-98)
Suarez et al.		France	50+	Ancestral strains	437694*	1475037*	96 (92-100)
		France	50+	Alpha			94 (92-96)
		France	50+	Beta or Gamma			98 (96-101)
		France	50+	Delta			89 (87-91)
Tenforde et al. (2)	a(1), b(1)	US	18+	Alpha	593*	619*	84 (71-91)
	a(1), b(2)	US	18+	Alpha			85 (74-91)
	a(2), b(2)	US	18+	Alpha			89 (79-94)
	a(2), b(1)	US	18+	Alpha			90 (81-95)
Thompson et al.		US	50+	Alpha or non−VOC	258	14616	89 (87-91)
Tseng et al.		US	18+	Delta	83	166	99 (93-100)
		US	18+	Omicron	21	42	84 (23-97)
Adenovirus vector vaccines							
Andrews et al. (2)		UK	16+	Alpha	1706743*	434930*	95 (87-98)
		UK	16+	Delta			92 (92-93)
Nasreen et al.		Canada	16+	Alpha	82880*	599191*	92 (41-99)
		Canada	16+	Delta			90 (67-97)
Skowronski et al.		British Columbia, Canada	18+	Delta	2435	89792	95 (93-97)
		Quebec, Canada	18+	Delta	894	106164	95 (93-97)
Thiruvengadam et al.		India	18+	Delta	84	2295	82 (10-99)
Thompson et al.		US	50+	Alpha or non−VOC	30	677	68 (50-79)
Inactivated virus vaccines							
Cerqueira-Silva et al.		Brazil	18+	Delta or Gamma	3373736*	4373385*	82 (81-83)
Nadeem et al.		Pakistan	60+	Delta	129	292	60 (8-83)

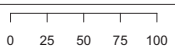

Figure 3. Continues

VE against severe disease from studies that excluded participants with prior COVID-19 infection (94%; 95% CI, 92-95) was higher than from studies that included these participants (86%: 95% CI, 82-88), with considerable heterogeneity among the estimates (I^2 > 99%).

In meta-regression adjusting for vaccine type, circulating virus, and enrollment criteria (Table S10; Figure 6, Figure S4), the OR against infection from studies that included participants with prior COVID-19 infection was 1.62-fold higher (95% CI, 1.32-1.98) than the OR from studies that excluded these participants (ie, with generally lower preexisting immunity). Therefore, if the VE against infection in a study that originally excluded participants with prior COVID-19 infection was 80%, the expected estimate was 68% (95% CI, 60-74) had they included those participants. Similarly, the OR against severe disease from studies that included participants with prior COVID-19 infection was 2.34-fold higher (95% CI, 1.60-3.40) than from studies that excluded these participants. Assuming a baseline VE against severe disease of 90%, the expected VE when participants with prior infection were included would be 77% (95% CI, 66-84). When using the proportion of individuals with prior infections, the results were similar to those obtained when the variable used was whether or not the study included participants with prior infections (Table S10). The results were similar with adjustment for location and duration of study (Table S11).

Impact of population incidence in the study locations

There was a modest negative correlation between prestudy cumulative incidence of cases (Figure 4) as a proxy of preexisting population immunity (Figure S5), and VE against infection ($r = -0.42$ [95% CI, −0.54 to −0.30]; $\rho = -0.32$ [95% CI, −0.45 to −0.18]) and severe disease ($r = -0.41$, 95% CI, −0.56 to −0.22; $\rho = -0.49$ [95% CI, −0.64 to −0.30]). There was also a modest negative correlation between the during-study incidence rates of cases with VE against infection ($r = -0.38$ [95% CI, −0.50 to −0.24]; $\rho = -0.48$ [95% CI, −0.59 to −0.34]) and severe disease ($r = -0.50$ [95% CI, −0.64 to −0.33]; $\rho = -0.42$ [95% CI, −0.58 to −0.23]).

The Pearson and Spearman correlation coefficients were modestly negative between prestudy cumulative incidence of cases (Figure S5), and VE against infection (Figure 4D) and severe disease (Figure 4E). Similarly, we estimated a negative correlation between during-study incidence rates of cases (Figure S5), and VE against infection (Figure 4I) and severe disease (Figure 4J).

In meta-regression, adjusting for vaccine type, circulating virus, and enrollment criteria (Table S10; Figure 6, Figure S4), the ROR against infection associated with twice prestudy cumulative

B)

VE against severe disease from studies including participants with prior COVID-19 infection

Study		Country	Population age (years)	Predominant circulating virus	No. of case	No. of control	VE (95% CI)
mRNA vaccines							
Abu-Raddad et al. (1)		Qatar	0+	Beta or Delta	3072	11773	97 (92-99)
Abu-Raddad et al. (2)		Qatar	0+	Alpha	401	401	100 (82-100)
		Qatar	0+	Beta	300	300	100 (74-100)
Andrews et al. (3)		UK	50+	Delta	234	37733	90 (86-93)
Bruxvoort et al.		US	18+	Delta	141	705	98 (93-99)
Chemaitelly et al. (1)		Qatar	12+	Alpha, Beta, or Delta	4134	4134	65 (55-73)
Chemaitelly et al. (2)		Qatar	0+	Alpha or Beta	3394	3394	90 (19-99)
Collie et al.		South Africa	15+	Delta	8569	124868	93 (90-94)
		South Africa	15+	Omicron	19070	59103	70 (62-76)
Drawz et al.	a(1)	US	19+	Delta	57658*	307299*	67 (65-69)
	a(2)	US	19+	Delta			73 (71-75)
Embi et al.	a(1)	US	18+	Delta	10604	46171	88 (86-89)
	a(2)	US	18+	Delta	10210	41791	93 (92-94)
Ferdinands et al.		US	18+	Delta	3315	35392	85 (84-85)
		US	18+	Omicron	979	2640	55 (50-60)
Grannis et al.	a(1)	US	18+	Delta	135	4108	80 (73-85)
	a(2)	US	18+	Delta	70	2905	95 (92-97)
Kirsebom et al.		UK	18+	Omicron(BA.1)	299	763	76 (59-86)
		UK	18+	Omicron(BA.2)	68	763	86 (53-96)
Lauring et al.		US	18+	Alpha	1072	1738	85 (82-88)
		US	18+	Delta	3890	3509	85 (83-87)
		US	18+	Omicron	479	247	65 (51-75)
Lewis et al.		US	18+	Alpha, Delta, or Gamma	1669*	1950*	96 (93-98)
Ngyen et al.		France	16+	Ancestral strains, Alpha, or Gamma	463*	390*	96 (84-99)
Olson et al. (1)		US	12-18	Delta	179	285	93 (83-97)
Olson et al. (2)		US	12-18	Delta	444	351	95 (91-97)
Price et al.		US	12-18	Delta	486	442	91 (86-94)
		US	12-18	Omicron	175	196	20 (−25 to 49)
Self et al.	a(1)	US	18+	Alpha or Delta	1591	1509	88 (85-91)
	a(2)	US	18+	Alpha or Delta	1517	1321	93 (91-95)
Tang et al.		Qatar	0+	Beta	159	698	93 (82-97)
	a(1)	Qatar	0+	Delta	117	453	94 (86-98)
	a(2)	Qatar	0+	Delta	104	376	96 (71-100)
Tartof et al.		US	18+	Delta	7361*	3762*	76 (69-82)
		US	18+	Omicron			62 (53-69)
Tenforde et al.		US	65+	Ancestral strains or Alpha	187*	230*	94 (49-99)
Tenforde et al. (3)	a(1)	US	18+	Delta	4906*	5172*	79 (74-83)
	a(2)	US	18+	Delta			87 (83-90)
Winkelman et al.	a(1)	US	19+	Delta	59770*	479363*	81 (79-82)
	a(2)	US	19+	Delta			81 (79-82)
Zambrano et al.		US	12-18	Delta	102	90	92 (77-97)
Adenovirus vector vaccines							
Andrews et al. (3)		UK	50+	Delta	298	33111	83 (77-87)
Grannis et al.		US	18+	Delta	30	428	60 (31-77)
Hitchings et al.		Brazil	60+	Gamma	81997*	56676*	88 (78-93)
Lewis et al. (2)		US	18+	Alpha or Delta	3979*	2229*	72 (64-77)
Rearte et al.	a(3)	Argentina	60+	Alpha, Gamma, or Lambda	440467*	842461*	80 (78-82)
	a(4)	Argentina	60+	Alpha, Gamma, or Lambda			81 (79-82)
Self et al.		US	18+	Alpha or Delta	1500	975	71 (56-81)
Winkelman et al.		US	19+	Delta	59770*	479363*	78 (75-81)
Inactivated virus vaccines							
Ranzani et al. (1)		Brazil	70+	Gamma	39716*	59858*	56 (46-63)
Rearte et al.		Argentina	60+	Alpha, Gamma, or Lambda	440467*	842461*	73 (71-75)

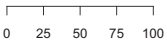

Figure 3. Estimates of vaccine effectiveness (VE) against severe disease from identified studies that excluded (A) or included (B) participants with COVID-19 infection history. Multiple estimates could be due to various factors. These are labeled as follows: for vaccine, a(1) for Pfizer, a(2) for Moderna, a(3) for ChAdOx1, or a(4) for rAd26-rAd5 (Sputnik V); as for the control, b(1) for syndrome-negative), and (b2) for test-negative control; and for different duration between first and second dose: (c1) for 19-29 days, (c2) for 30-44 days, (c3) for 45-64 days, (c4) for 65-84 days, and (c5) for ≥85 days. VOC, variant of concern.

incidence of cases was 1.13 (95% CI, 1.05-1.23). Therefore, if the baseline VE against infection from a study was 80%, then the corresponding VE for a setting with twice prestudy cumulative incidence of cases would represent a 2-percentage point reduction in VE (VE = 77%; 95% CI, 75-79 for the initial doubling). The ROR against severe disease for each doubling of prestudy cumulative incidence of cases (higher preexisting immunity) was 1.53 (95% CI, 1.31-1.77). Assuming a baseline VE against severe diseases of 90%, the corresponding VE for a setting with twice the prestudy cumulative incidence of cases would represent a 5 percentage point drop in VE (VE = 85%; 95% CI, 82-87 for a doubling).

Similarly, we estimated that the ROR against infection for each doubling of during-study incidence rate of cases was 1.16 (95% CI, 1.07-1.26). If the baseline VE against infection from a study was 80%, then the corresponding VE from a study with twice during-study incidence rate of cases would be 77% (95% CI, 75-79). We also estimated that the ROR against severe disease associated with twice during-study incidence rate of cases was 1.22 (95% CI, 1.04-1.43). Therefore, assuming a baseline VE of 90% against severe disease, the corresponding VE for a study with twice during-study incidence rate of cases would be 88% (95% CI, 86-89.6).

Risk of bias

Most studies included in the meta-analysis were judged to be at moderate risk of bias (analyses of VE against infection: 41 [80%] of 51 studies; analyses of VE against severity: 33 [83%] of 40 studies; Figures S6-S7). Eight studies (16%) included in the analyses of VE against infection and 5 studies (13%) in analyses of VE against severity were judged to be at a serious risk of bias. The main sources of bias were potential confounding, bias in the classification of interventions due to self-reported vaccination status, and bias due to missing data (Figures S6-S7). We conducted a sensitivity analysis that removed estimates from studies classified as having serious or critical bias (Figure S8; Table S12), and the impact of prior infections was still similar to one estimated in the main analysis.

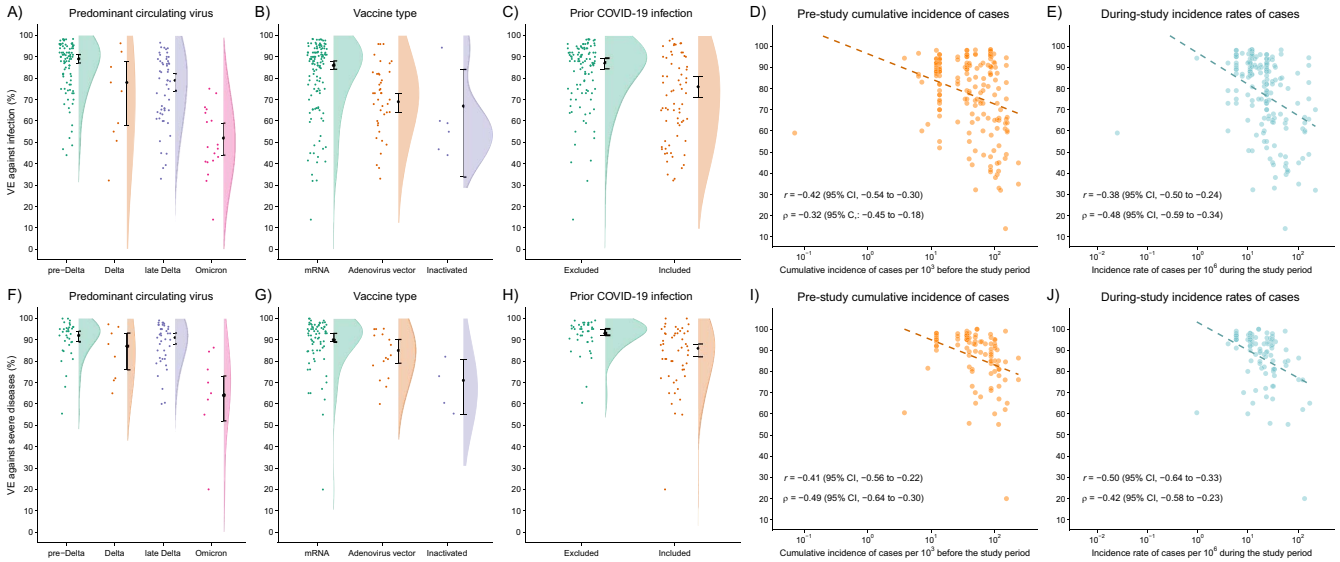

Figure 4. Vaccine effectiveness (VE) point estimates from identified studies based on prior infection (A), predominant circulating virus (B) and vaccine type (C). Each point represents the VE point estimate. Estimates are jittered to enable visualization. Black points represent the pooled VE estimate from meta-analysis, with black lines representing the 95% CI around the pooled estimate. The shaded area is the violin plot, showing the smoothed density of the VE point estimates. VE estimates against infection and severity disease (D) vs the cumulative incidence of cases before the study (in log scale) (I) in the study regions are shown; VE estimates against infection and severity disease (E) vs the incidence rate of cases during study (in log scale) (J) in the study regions are shown. Pearson (r) and spearman (ρ) correlation coefficients are provided.

Discussion

In this study, we summarized VE estimates from TND studies to understand the impact of prior infections on VE estimates. We found that higher preexisting immunity in the source population, indicated by including participants with prior COVID-19 infection, higher prestudy cumulative incidence of cases, and higher during-study incidence rate of cases, was associated with lower VE.

Prior infection could be a confounder, effect modifier, or both. As a confounder, it could affect a person's decision to vaccinate and modify their risk behaviors as well as provide protection against reinfection.[12,13,21] Hence, the VE obtained from individuals with or without prior infection would be similar if the influence of the confounding could be controlled in analysis. On the other hand, if prior infection were only an effect modifier (ie, only associated with the risk of (re)infection and not the propensity to be vaccinated), vaccination in settings with higher preexisting immunity would appear to have a relatively modest effect on further increasing protection at the population level, because VE would be lower among previously infected participants, compared with VE among uninfected participants.[12,13] This scenario differs from hybrid immunity,[102,103] which refers to the scenario in which a combination of naturally acquired and vaccine-induced immunity provides stronger protection against SARS-CoV-2 infection than vaccine-derived immunity alone (estimated only on the basis of vaccinated participants).

Factors		No. of estimates	VE range	VE (95% CI)	I^2 (%)
VE against infection					
Including participants with prior COVID-19 infection	Excluded	106	14-98	87 (84-89)	100
	Included	67	32-98	76 (71-81)	100
Vaccine type	mRNA vaccines	126	14-98	86 (84-88)	100
	Adenovirus vector vaccines	41	33-96	69 (64-73)	100
	Inactivated virus vaccines	6	44-94	67 (34-84)	100
Predominant circulating virus	pre-Delta	92	44-98	89 (87-91)	99
	Delta	9	32-96	78 (58-88)	100
	late-Delta	54	33-97	79 (74-82)	100
	Omicron	18	14-75	52 (44-59)	99
VE against severe disease					
Including participants with prior COVID-19 infection	Excluded	40	60-99	94 (92-95)	97
	Included	51	20-100	86 (82-88)	99
Vaccine type	mRNA vaccines	71	20-100	91 (89-93)	99
	Adenovirus vector vaccines	16	60-95	85 (79-90)	98
	Inactivated virus vaccines	4	56-82	71 (55-81)	99
Predominant circulating virus	pre-Delta	35	56-100	92 (89-94)	97
	Delta	8	65-97	87 (76-93)	98
	late-Delta	40	60-99	91 (88-93)	99
	Omicron	8	20-86	64 (52-73)	84

Figure 5. Pooled vaccine effectiveness (VE) estimates against infection and severe disease by circulating virus, vaccine types, and the inclusion or exclusion of participants with prior COVID-19 infection from random-effect meta-analysis.

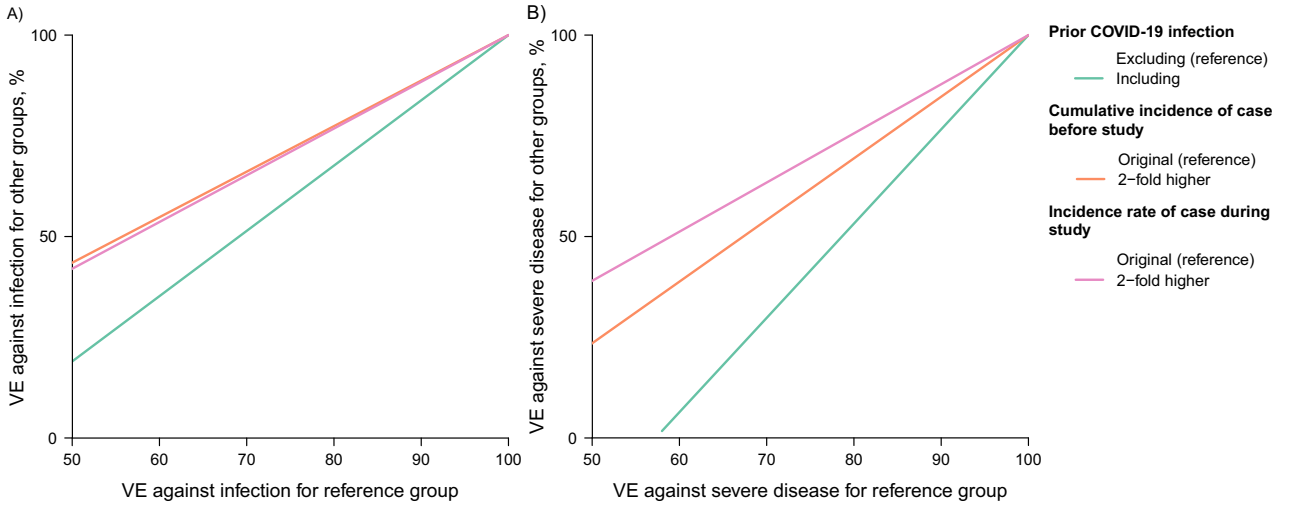

Figure 6. Predicted vaccine effectiveness (VE) for a group of individuals based on the estimated ratio of odds ratios estimated from meta-regression, and the VE for the individuals in the reference group. Predicted VE against infection (A) and severe disease (B) are shown. Prior COVID-19 infection, cumulative incidence of cases before the study, and the incidence rate of cases during study are considered. Models adjusted for age group, type of vaccine, predominant circulating virus, and enrolment criteria, corresponding to the estimate in model 1.

In reality, prior infection is probably both a confounder and effect modifier and, therefore, studies should consider both an appropriate confounding control, such as through covariate adjustment or stratification, as well as inclusion of interaction terms to explore the potential effect modification. The impact of prior infection could be even larger than observed in our study, because not all prior infections may be documented and, therefore, some participants may have been unknowingly infected and misclassified as infection-naïve. As the pandemic progresses, the proportion of undocumented previous infections could grow. This is likely to be particularly problematic for prior Omicron infections because that variant has lower severity than previous strains.[104,105]

When VE was estimated on the basis of studies excluding participants with prior infection, these VE estimates should be interpreted as the VE for a hypothetical population with no preexisting immunity. As of 2023, these estimates have limited practical value because most locations have experienced substantial epidemics. Epidemic forecasting models used to inform public health control policies should separate individuals into different compartments based on infection history to improve the precision of their forecasts. Therefore, groups estimating VE estimates to inform policy should stratify by infection history so their work will be more broadly useful for policy.[106,107]

Although 55% of VE estimates against infection and 76% of estimates against severe disease were higher than 80%, heterogeneity was considerable, based on high I^2 values. Consistent with previous reviews, high heterogeneity could be attributed to differences in effectiveness among vaccine types or the predominant circulating virus in each study.[8,108] However, we continued to observe high heterogeneity when estimating pooled VE against specific vaccine types and the predominant virus. Our meta-regression identified some sources of the heterogeneity, such as preexisting immunity. Further investigation is needed to identify other causes to ensure valid VE estimates are available for ongoing optimization of vaccination strategies.[109]

Our review focused on VE of primary vaccination series to answer the research question of whether prior infection may have an impact on VE estimates. Further analysis would be required to determine whether similar issues apply to estimation of VE for booster doses, which are complicated by dosing schedules that mix vaccine types, the number of doses received, greater antigenic differences between the vaccines received and the dominant circulating virus, changes in vaccine formulation including bivalent formulations, and the accumulation of immunity through both vaccination and infection over time.

Our study had some limitations. First, most studies were conducted with adults, so our results may not be generalizable to children. Second, TND studies included in our review were observational. Some confounders were adjusted for in these studies, including age, sex, being a health care worker, or preexisting conditions. Despite our bias assessment to evaluate whether studies adequately addressed confounding and considered other potential sources of bias, such as measurement errors and selection bias, we cannot rule out other unidentified sources of bias. Third, the predominant variant was determined by Nextstrain[37] for some studies, which can be inaccurate. Fourth, multiple group-specific estimates reported from studies were included in the analysis (Table S5). If a study reported estimates for multiple factors, such as age group–specific VE estimates and vaccine type–specific estimates, there could be correlations among VE estimates from the same study. Finally, we used incidences of COVID-19 in study countries as a proxy for preexisting immunity. However, we acknowledge that national statistics may not apply to individual study sites.

In conclusion, we observed reduced VE associated with higher preexisting immunity in the population, which is likely to act both as a confounder and effect modifier of the vaccine's effect. Exclusion of participants with prior infection could artificially inflate VE estimates and affect their generalizability to the wider population. If the goal of a study is to inform policy that applies to the whole population, participants with prior infection should be included and their status included as a covariate for confounder control. However, if decision-makers desire different vaccination policies dependent on infection history, then studies need to stratify or include interaction terms, rather than exclude participants with prior infection. In studies in which prior infection cannot be adjusted for, researchers could consider using external adjustment[110] to assess the potential effect of this confounder on their estimates. Optimal design of VE studies remains a research

priority. In particular, more work is needed to understand how prior infection influences VE for booster doses and as vaccine formulations change.

Supplementary material

Supplementary material is available at *American Journal of Epidemiology* online.

Funding

This project was supported by the National Institute of General Medical Sciences (grant R01 GM139926), and the Theme-based Research Scheme (project T11-712/19-N) of the Research Grants Council of the Hong Kong SAR Government. B.J.C. is supported by a Research Grants Council Senior Research Fellowship (grant HKU SRFS2021-7S03) and the AIR@innoHK program of the Innovation and Technology Commission of the Hong Kong SAR Government. The WHO Collaborating Centre for Reference and Research on Influenza is supported by the Australian Government Department of Health and Aged Care.

Conflict of interest

B.J.C. reports honoraria from AstraZeneca, Fosun Pharma, GSK, Haleon, Moderna, Pfizer, Roche, and Sanofi Pasteur. J.N. was previously employed by and owns stocks in Sanofi. S.G.S. reports honoraria from CSL Seqirus, Novavax, and Pfizer. The other authors declare no conflicts.

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