Efficacy of SARS-CoV-2 vaccines and the dose–response relationship with three major antibodies: a systematic review and meta-analysis of randomised controlled trials

Zhi-Rong Yang, Yi-Wen Jiang*, Fu-Xiao Li, Di Liu, Teng-Fei Lin, Zi-Yi Zhao, Chang Wei, Qian-Yi Jin, Xi-Miao Li, Yuan-Xi Jia, Feng-Cai Zhu, Zu-Yao Yang, Feng Sha, Zi-Jian Feng, Jin-Ling Tang*

Summary

Background The efficacy of SARS-CoV-2 vaccines in preventing severe COVID-19 illness and death is uncertain due to the rarity of data in individual trials. How well the antibody concentrations can predict the efficacy is also uncertain. We aimed to assess the efficacy of these vaccines in preventing SARS-CoV-2 infections of different severities and the dose–response relationship between the antibody concentrations and efficacy.

Methods We did a systematic review and meta-analysis of randomised controlled trials (RCTs). We searched PubMed, Embase, Scopus, Web of Science, Cochrane Library, WHO, bioRxiv, and medRxiv for papers published between Jan 1, 2020 and Sep 12, 2022. RCTs on the efficacy of SARS-CoV-2 vaccines were eligible. Risk of bias was assessed using the Cochrane tool. A frequentist, random-effects model was used to combine efficacy for common outcomes (ie, symptomatic and asymptomatic infections) and a Bayesian random-effects model was used for rare outcomes (ie, hospital admission, severe infection, and death). Potential sources of heterogeneity were investigated. The dose–response relationships of neutralising, spike-specific IgG and receptor binding domain-specific IgG antibody titres with efficacy in preventing SARS-CoV-2 symptomatic and severe infections were examined by meta-regression. This systematic review is registered with PROSPERO, CRD42021287238.

Findings 28 RCTs (n=286 915 in vaccination groups and n=233 236 in placebo groups; median follow-up 1–6 months after last vaccination) across 32 publications were included in this review. The combined efficacy of full vaccination was 44·5% (95% CI 27·8–57·4) for preventing asymptomatic infections, 76·5% (69·8–81·7) for preventing symptomatic infections, 95·4% (95% credible interval 88·0–98·7) for preventing hospitalisation, 90·8% (85·5–95·1) for preventing severe infection, and 85·8% (68·7–94·6) for preventing death. There was heterogeneity in the efficacy of SARS-CoV-2 vaccines against asymptomatic and symptomatic infections but insufficient evidence to suggest whether the efficacy could differ according to the type of vaccine, age of the vaccinated individual, and between-dose interval (p>0·05 for all). Vaccine efficacy against symptomatic infection waned over time after full vaccination, with an average decrease of 13·6% (95% CI 5·5–22·3; p=0·0007) per month but can be enhanced by a booster. We found a significant non-linear relationship between each type of antibody and efficacy against symptomatic and severe infections (p<0·0001 for all), but there remained considerable heterogeneity in the efficacy, which cannot be explained by antibody concentrations. The risk of bias was low in most studies.

Interpretation The efficacy of SARS-CoV-2 vaccines is higher for preventing severe infection and death than for preventing milder infection. Vaccine efficacy wanes over time but can be enhanced by a booster. Higher antibody titres are associated with higher estimates of efficacy but precise predictions are difficult due to large unexplained heterogeneity. These findings provide an important knowledge base for interpretation and application of future studies on these issues.

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Introduction

SARS-CoV-2 vaccines have been rapidly developed, evaluated in randomised controlled trials (RCTs), and used worldwide.[1] Early systematic reviews of RCTs showed that the vaccines could prevent SARS-CoV-2 infections.[2–5] However, these reviews did not fully examine the efficacy of vaccines in preventing severe infections and deaths, partly due to there being none or a small number of these events in individual trials.[2] How vaccine efficacy changed over time in RCTs also remained unclear. Conversely, real-world observational studies suggested that current vaccines will be unlikely to stop the COVID-19 pandemic as they were much less effective in preventing infection than they were in preventing severe infection and death, and their effectiveness waned quickly over time.[6] If these findings

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*Contributed equally

Center for Biomedical Information Technology, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China (Z-R Yang PhD, Y-W Jiang PhD, F-X Li PhD, D Liu PhD, T-F Lin PhD, Z-Y Zhao MPH, C Wei MSc, Y-X Jia PhD, F Sha PhD, Prof J-L Tang PhD); **Department of Public Health and Primary Care, School of Clinical Medicine, University of Cambridge, Cambridge, UK** (Z-R Yang); **School of Mathematics, Sun Yat-sen University, Guangzhou, China** (Q-Y Jin BSc, X-M Li BSc); **Department of Vaccine Clinical Evaluation, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China** (Prof F-C Zhu MSc); **Division of Epidemiology, JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China** (Z-Y Yang PhD); **Division of Infectious Diseases, Chinese Center for Disease Control and Prevention, Beijing, China** (Prof Z-J Feng MMed); **Clinical Data Center, Guangzhou Women and Children's Medical Center, Guangzhou, China** (Prof J-L Tang)

Correspondence to:
Feng Sha, Center for Biomedical Information Technology, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China
feng.sha@siat.ac.cn

or

Zu-Yao Yang, Division of Epidemiology, JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, 999077, China
zyang@cuhk.edu.hk

Research in context

Evidence before this study

Since 2020, SARS-CoV-2 vaccines have been quickly developed, evaluated in randomised controlled trials (RCTs), and used worldwide. We did a comprehensive search of systematic reviews from PubMed publication published between Jan 1, 2020, and June 30, 2022, using search terms related to SARS-CoV-2, vaccines, and systematic reviews with no restrictions on language of publication. There are systematic reviews of RCTs on vaccine efficacy in preventing infections published before November, 2021. However, there remain uncertainties in the efficacy of vaccines in preventing severe infections and in the waning of efficacy, and many new trials were published after these reviews. Furthermore, in many scenarios where the efficacy is untested, antibody concentrations induced by SARS-CoV-2 vaccines are often used to predict and compare vaccine efficacy. However, the foundation of such predictions or comparisons has not been firmly established. We did this systematic review and meta-analysis to address these issues.

Added value of this study

We found moderate-quality evidence that vaccine efficacy was modest in preventing mild infection, but high in preventing severe infection and death. The efficacy of full vaccination waned quickly over time but can be enhanced by a booster. There was insufficient evidence to suggest whether the efficacy might differ according to the type of vaccine, age of the vaccinated individual, and between-dose interval. Although there was a significant non-linear dose–response relationship between the antibodies and efficacy against symptomatic and severe infection, there remained considerable heterogeneity in the efficacy which cannot be explained by antibody concentrations.

Implications of all the available evidence

Our findings suggested that SARS-CoV-2 vaccines are insufficiently efficacious in preventing infections and therefore cannot stop the pandemic alone. However, all the vaccines can be used to effectively prevent severe infection and death. Waning of vaccine efficacy makes it important to time vaccination in relation to an anticipated outbreak. Moreover, the antibody–efficacy relationship is complex and should be used with caution to predict efficacy in uncertain situations. Since the vaccines can no longer be assessed in previous predominant variants that are now extinct, this systematic review provides an irreplaceable reference for comparisons with and interpretation of future studies assessing vaccine efficacy in new scenarios, such as booster vaccine regimens, new SARS-CoV-2 vaccines, and future SARS-CoV-2 variants.

are true, the primary goal of vaccination strategies should be reset to reducing the risk of severe infection and death and the timing of vaccination should also be optimised.[7] However, real-world studies are susceptible to bias.

Furthermore, SARS-CoV-2 antibody concentrations are often used to predict or compare the efficacy of the vaccines for such important scenarios as new vaccines, booster dose, heterologous vaccination, waning efficacy, and other vaccine regimens for which efficacy trials are not immediately or will never be available.[8] The validity of such predictions or comparisons relies heavily on the assumption that there is a close dose–response relationship between antibodies and the efficacy, but this relationship has not been firmly established.[8,9] To address this issue, a preferable method is dose–response analyses within individual trials, but such analyses using paired data on antibody and efficacy collected repeatedly within the same study essentially do not exist in published trials.[10] Meta-regression analysis of data from different trials provides a possible, approximate solution to the problem.

Finally, many new trials have been published since previous systematic reviews were done that included all available efficacy trials up to November, 2021.[2–5] A collection of evidence from all currently available trials will be an important and irreplaceable reference for interpretation and application of results from future studies of SARS-CoV-2 vaccines. We therefore did this systematic review to address two issues: the efficacy of the vaccines in preventing SARS-CoV-2 infections of different degrees of severity and the dose–response relationship between antibody concentrations and efficacy.

Methods

Search strategy and selection criteria

See Online for appendix

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (appendix pp 186–92).[11] A systematic search was done in PubMed, Embase, Scopus, Web of Science, and Cochrane Library for relevant studies published between Jan 1, 2020, and Sep 12, 2022, with no restrictions on language of publication. We also searched bioRxiv, medRxiv, and the WHO COVID-19 Research Database for grey literature published during the same period. We mainly used search terms related to "SARS-CoV-2", "vaccine", and "trial" (appendix pp 7–11). The reference lists of relevant systematic reviews and included studies were manually scanned to identify additional studies.

Two groups (group one: Y-WJ, T-FL, DL, CW, and Y-XJ, group two: F-XL, X-ML, Q-YJ, and Z-YZ) of investigators screened the literature independently with discrepancies resolved by discussion with a third investigator (Z-RY, FS, Z-YY or J-LT). RCTs (of any language) that assessed the clinical efficacy of SARS-CoV-2 vaccines compared

with placebo were eligible. The clinical efficacy outcomes of interest had to be PCR-confirmed SARS-CoV-2 related and included asymptomatic infection, symptomatic infection, hospital admission, severe infection, and death. In this Article, full vaccination is defined as vaccination with a primary vaccine series, and booster is defined as additional doses following full vaccination. Studies were excluded if they: (1) had no data on vaccine efficacy, (2) were a conference abstract, or (3) were duplicate studies. For publications derived from the same study population, only those with the longest follow-up duration were included. Where data on vaccine efficacy and antibodies were not reported in the same study, we identified corresponding previous phase 2 or phase 1 trials on the immunogenicity of the same dose of the vaccine.

This systematic review is registered with PROSPERO, CRD42021287238.

Data analysis

Two investigators (Y-WJ and F-XL) extracted data independently using a pre-designed form. Disagreements were resolved by discussion with a third investigator (Z-RY). The extracted data included details on study design, participants, intervention, control, efficacy outcomes, and antibody titres of neutralising, spike-specific IgG, and receptor binding domain (RBD)-specific IgG after full vaccination. Data on T-cell response to full vaccination were also collected where available. When immunogenicity data were measured repeatedly, we used those collected at the time closest to the starting point of efficacy assessment.

The Cochrane tool (version 1) was used to evaluate the risk of bias of the included efficacy RCTs (appendix p 19).[12] For each domain of the tool, judgement can be high risk of bias, low risk of bias, or unclear risk of bias. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation framework, which considered risk of bias, indirectness, imprecision, consistency, and publication bias.[13]

A frequentist, random-effects model was used to summarise relative risks (RRs) with 95% CIs for symptomatic and asymptomatic infections. Considering the scarcity of data on hospital admission, severe infections, and deaths as well as moderate heterogeneity across RCTs, a random-effects meta-analysis using a Bayesian binomial-normal hierarchical model (appendix pp 3–4) was done as the primary analysis to estimate the pooled odds ratio (OR) for each outcome (expressed as median posterior estimate and 95% credible interval [CrI]) in R (version 4.2.1).[14] A funnel plot and Egger's test were done to assess the risk of publication bias. Vaccine efficacy was calculated as $(1–RR)\times100\%$ or $(1–OR)\times100\%$.

To explore the potential effect of risk of bias on our estimates, we did a sensitivity analysis excluding RCTs with high or unclear risk of bias in any domains of the Cochrane tool. Sensitivity analyses were done to examine the stability of Bayesian meta-analysis by varying the previous distributions (appendix p 4).[15] Sensitivity analyses were also done using other methods to account for the scarcity of data, including Peto's OR, OR from a generalised linear mixed model, risk difference, and arcsine difference.[16,17]

Heterogeneity across RCTs was assessed using I^2 statistics and Q test. For Bayesian meta-analysis, heterogeneity was assessed using posterior predictive p values for τ.[18] Subgroup analyses by types of vaccines, age, injection interval, and variants of concern were done to explore potential sources of heterogeneity where relevant data were available (appendix pp 4–5).

We plotted the change in vaccine efficacy over time for RCTs with repeated measurements of symptomatic infection for discrete time intervals after the final dose of primary vaccine series. The average change in vaccine efficacy over time was assessed using a linear mixed-effects model (appendix p 5).[6] For other outcomes, no sufficient repeated measurement data were available for this analysis.

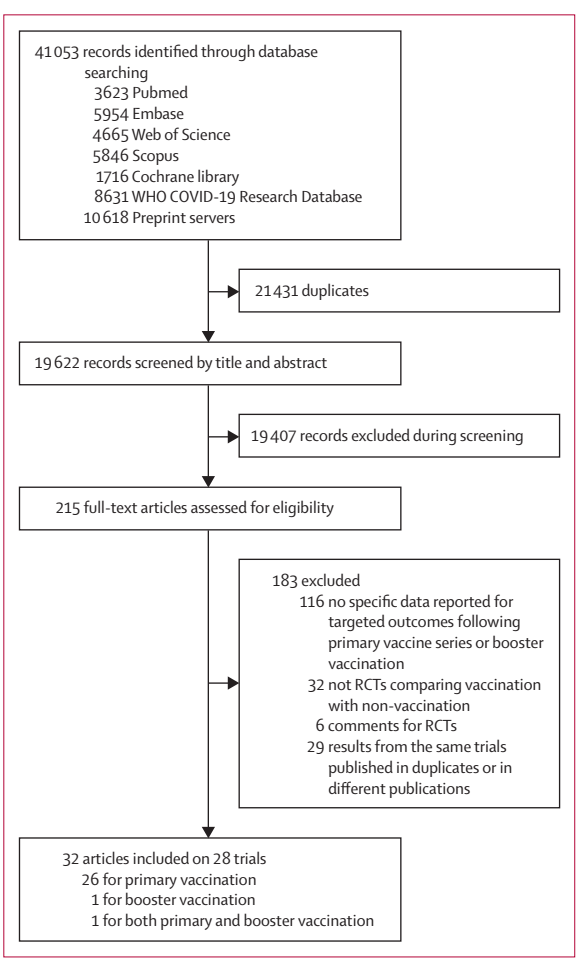
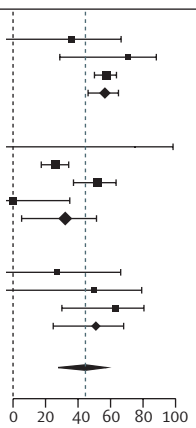


Figure 1: **Study selection**
RCTs=randomised controlled trials.

For the antibody–efficacy relationship, we plotted the efficacy of each type of antibody in preventing symptomatic infections and severe infections. As antibody assays varied in different studies, antibody titres were transformed to standardised mean difference for comparison. We did a random-effects meta-regression on

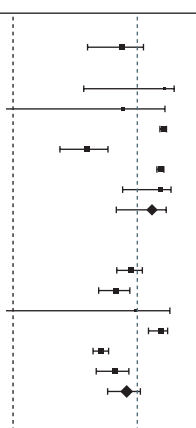
A Asymptomatic infection

	Vaccine name	Days after full vaccination	Vaccination (n/N)	Control (n/N)	Efficacy (95% CI)
mRNA vaccine					
Ali (2021)[20]	mRNA-1273	14	21/2139	16/1042	36·1 (−22·0 to 66·5)
Creech (2022)[22]	mRNA-1273	14	9/2644	10/853	71·0 (28·8 to 88·2)
El Sahly (2021)[25]	mRNA-1273	14	214/14 287	498/14 164	57·4 (50·1 to 63·6)
Subtotal			**244/19 070**	**524/16 059**	**56·5 (46·2 to 64·9)**
I^2=8·9%, heterogeneity p=0·33					
Viral vector vaccine					
Kulkarni (2021)[37]	SII-ChAdOx1	14	1/1162	1/287	75·3 (−293·7 to 98·5)
Sadoff (2022)[43]	Ad26.COV2.S	28	498/19 113	669/18 924	26·3 (17·4 to 34·3)
Sobieszczyk (2021)[45]	AZD1222	15	104/17 662	105/8550	52·1 (37·2 to 63·4)
Voysey (2021)[49]	AZD1222	14	41/2692	42/2751	0·2 (−52·9 to 34·9)
Subtotal			**644/40 629**	**817/30 512**	**32·1 (5·3 to 51·4)**
I^2=73·9%, heterogeneity p=0·0093					
Inactivated virus vaccine					
Al Kaabi (2021)[19]	WIV04	14	16/12 727	11/6361	27·3 (−56·6 to 66·2)
Al Kaabi (2021)[19]	HB02	14	10/12 713	10/6361	50·0 (−20·1 to 79·2)
Ella (2021)[26]	BBV152	14	13/3248	33/3041	63·1 (30·1 to 80·5)
Subtotal			**39/28 688**	**54/15 763**	**51·0 (24·7 to 68·1)**
I^2=0·0%, heterogeneity p=0·41					
Overall			**927/88 387**	**1395/62 334**	**44·5 (27·8 to 57·4)**
I^2=79·6%, heterogeneity p<0·0001					



B Symptomatic infection

	Vaccine name	Days after full vaccination	Vaccination (n/N)	Control (n/N)	Efficacy (95% CI)
DNA vaccine					
Khobragade (2022)[35]	ZyCoV-D	28	20/12 350	61/12 320	67·3 (45·8 to 80·2)
mRNA vaccine					
Ali (2021)[20]	mRNA-1273	14	1/2139	7/1042	93·0 (43·5 to 99·1)
Creech (2022)[22]	mRNA-1273	14	3/2644	3/853	67·7 (−59·5 to 93·5)
El Sahly (2021)[25]	mRNA-1273	14	55/14 287	744/14 164	92·7 (90·4 to 94·4)
Kremsner (2022)[36]	CVnCoV	15	83/12 851	145/12 211	45·6 (28·8 to 58·4)
Thomas (2021)[47]	BNT162b2	7	77/20 998	850/21 096	90·9 (88·5 to 92·8)
Walter (2022)[50]	BNT162b2	7	3/1305	16/663	90·5 (67·4 to 97·2)
Subtotal			**222/54 224**	**1765/50 029**	**85·5 (63·5 to 94·2)**
I^2=96·3%, heterogeneity p<0·0001					
Viral vector vaccine					
Falsey (2021)[29]	AZD1222	15	73/17 662	130/8550	72·8 (63·8 to 79·6)
Halperin (2022)[31]	Ad5-nCoV	14	77/14 591	211/14 586	63·5 (52·7 to 71·9)
Kulkarni (2021)[37]	SII-ChAdOx1	14	2/1162	2/287	75·3 (−74·6 to 96·5)
Logunov (2021)[38]	Gam-COVID-Vac	7	13/14 094	47/4601	91·0 (83·3 to 95·1)
Sadoff (2022)[43]	Ad26.COV2.S	14	495/19 400	1082/19 398	54·3 (49·2 to 58·8)
Voysey (2021)[49]	AZD1222	14	74/7201	197/7179	62·6 (51·2 to 71·3)
Subtotal			**734/74 110**	**1669/54 601**	**69·9 (58·2 to 78·4)**
I^2=86·5%, heterogeneity p<0·0001					
Inactivated virus vaccine					
Al Kaabi (2021)[19]	WIV04	14	26/12 743	48/6369	72·9 (56·4 to 83·2)
Al Kaabi (2021)[19]	HB02	14	21/12 726	47/6368	77·6 (62·6 to 86·6)
Ella (2021)[26]	BBV152	14	24/8471	106/8502	77·3 (64·6 to 85·4)
Fadlyana (2021)[28]	CoronaVac	14	7/798	18/804	60·8 (6·7 to 83·5)
Palacios (2021)[41]	CoronaVac	14	67/3637	133/3587	50·3 (33·6 to 62·8)
Tanriover (2021)[46]	CoronaVac	14	9/6559	32/3470	85·1 (68·9 to 92·9)
Subtotal			**154/44 934**	**384/29 100**	**72·1 (58·9 to 81·1)**
I^2=72·0%, heterogeneity p=0·0032					
Recombinant protein vaccine					
Bravo (2022)[21]	SCB-2019	14	52/5935	155/5806	67·2 (55·2 to 76·0)
Dai (2022)[23]	ZF2001	7	158/12 625	580/12 568	72·9 (67·7 to 77·2)
Dunkle (2022)[24]	NVX-CoV2373	7	14/17 312	63/8140	89·6 (81·4 to 94·1)
Hager (2022)[30]	CoVLP+AS03	7	33/10 115	121/10 106	72·8 (60·0 to 81·4)
Heath (2021)[33]	NVX-CoV2373	7	10/7020	96/7019	89·6 (80·0 to 94·6)
Hernández-Bernal (2022)[34]	Abdala	14	11/19 689	142/19 674	92·3 (85·7 to 95·8)
Nguyen (2022)[40]	Nanocovax	14	93/8642	89/4052	51·0 (34·6 to 63·3)
Shinde (2021)[44]	NVX-CoV2373	7	15/1357	29/1327	49·4 (6·1 to 72·8)
Toledo-Romani (2023)[48]	SOBERANA 02	14	38/12 578	136/12 879	71·4 (59·0 to 80·0)
Subtotal			**424/95 273**	**1411/81 571**	**76·3 (67·0 to 82·9)**
I^2=85·7%, heterogeneity p<0·0001					
Overall			**1554/280 891**	**5290/227 621**	**76·5 (69·8 to 81·7)**
I^2=93·0%, heterogeneity p<0·0001					



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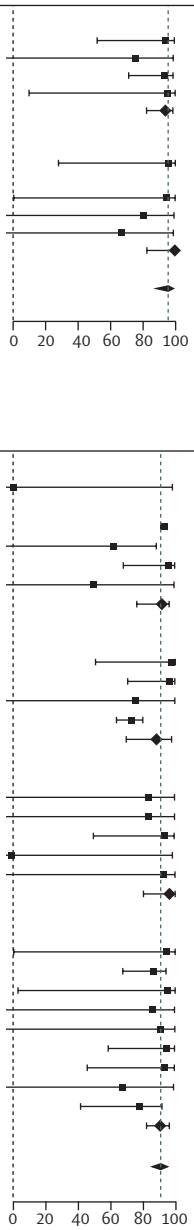
C Admission to hospital

	Vaccine name	Days after full vaccination	Vaccination (n/N)	Control (n/N)	Efficacy (95% CrI)
Viral vector vaccine					
Falsey (2021)[29]	AZD1222	15	1/17662	8/8550	94·0 (51·7 to 99·2)
Kulkarni (2021)[37]	SII-ChAdOx1	14	1/1162	1/287	75·4 (−295 to 98·5)
Sadoff (2021)[42]	Ad26.COV2.S	14	2/19514	29/19544	93·1 (71·1 to 98·4)
Voysey (2021)[49]	AZD1222	14	0/11794	9/11776	94·7 (9·8 to 99·7)
Subtotal			**4/50132**	**47/40157**	**93·7 (82·1 to 98·3)**
I^2=6·2%, heterogeneity p=0·88					
Inactivated virus vaccine					
Tanriover (2021)[46]	CoronaVac	14	0/6559	6/3470	95·9 (27·9 to 99·8)
Recombinant protein vaccine					
Bravo (2022)[21]	SCB-2019	14	0/5935	8/5806	94·3 (0·4 to 99·7)
Hager (2022)[30]	CoVLP+AS03	7	0/12074	2/12067	80·0 (−316·3 to 99)
Heath (2021)[33]	NVX-CoV2373	7	0/7020	1/7019	66·7 (−718·2 to 98·6)
Subtotal			**0/25029**	**11/24892**	**99·5 (82·3 to 100·0)**
I^2=11·7%, heterogeneity p=0·69					
Overall			**4/81720**	**64/68519**	**95·4 (88·0 to 98·7)**
I^2=4·0%, heterogeneity p=0·95					

D Severe infection

	Vaccine name	Days after full vaccination	Vaccination (n/N)	Control (n/N)	Efficacy (95% CrI)
DNA vaccine					
Khobragade (2022)[35]	ZyCoV-D	28	0/12350	0/12320	0·2 (−4927·8 to 98·0)
mRNA vaccine					
El Sahly (2021)[25]	mRNA-1273	14	55/14287	744/14164	93·0 (90·8 to 94·7)
Kremsner (2022)[36]	CVnCoV	15	4/12851	10/12211	62·0 (−21·2 to 88·1)
Thomas (2021)[47]	BNT162b2	7	1/23040	23/23037	95·7 (67·8 to 99·4)
Walter (2022)[50]	BNT162b2	7	0/1305	0/663	49·2 (−2464·2 to 99·0)
Subtotal			**60/51483**	**777/50075**	**91·5 (76·1 to 96·0)**
I^2=43·4%, heterogeneity p=0·010					
Viral vector vaccine					
Falsey (2021)[29]	AZD1222	15	0/17662	8/8550	97·2 (50·7 to 99·8)
Halperin (2022)[31]	Ad5-nCoV	14	1/14591	25/14586	96·0 (70·5 to 99·5)
Kulkarni (2021)[37]	SII-ChAdOx1	14	0/1162	0/287	75·3 (−1149·0 to 99·5)
Sadoff (2022)[43]	Ad26.COV2.S	14	56/19400	205/19398	72·9 (63·6 to 79·8)
Subtotal			**57/52815**	**238/42821**	**88·2 (69·6 to 97·5)**
I^2=16·8%, heterogeneity p=0·055					
Inactivated virus vaccine					
Al Kaabi (2021)[19]	WIV04	14	0/12743	1/6369	83·3 (−309·0 to 99·3)
Al Kaabi (2021)[19]	HB02	14	0/12726	1/6368	83·3 (−309·5 to 99·3)
Ella (2021)[26]	BBV152	14	1/8471	15/8502	93·3 (49·4 to 99·1)
Fadlyana (2021)[28]	CoronaVac	14	0/798	0/804	−0·8 (−4983·8 to 98·0)
Palacios (2021)[41]	CoronaVac	14	0/4953	6/4870	92·5 (−34·1 to 99·6)
Subtotal			**1/39691**	**23/26913**	**96·2 (80·2 to 99·7)**
I^2=3·9%, heterogeneity p=0·76					
Recombinant protein vaccine					
Bravo (2022)[21]	SCB-2019	14	0/5935	8/5806	94·3 (0·4 to 99·7)
Dai (2022)[23]	ZF2001	7	6/12625	43/12568	86·2 (67·5 to 94·1)
Dunkle (2022)[24]	NVX-CoV2373	7	0/17312	4/8140	94·8 (3·0 to 99·7)
Hager (2022)[30]	CoVLP+AS03	7	0/12074	3/12067	85·7 (−176·4 to 99·3)
Heath (2021)[33]	NVX-CoV2373	7	0/7020	5/7019	90·9 (−64·3 to 99·5)
Hernández-Bernal (2022)[34]	Abdala	14	1/19689	18/19674	94·5 (58·5 to 99·3)
Nguyen (2022)[40]	Nanocovax	14	1/8642	7/4052	93·3 (45·6 to 99·2)
Shinde (2021)[44]	NVX-CoV2373	7	0/1357	1/1327	67·4 (−700·3 to 98·7)
Toledo-Romani (2023)[48]	SOBERANA 02	14	5/12578	23/12879	77·8 (41·5 to 91·6)
Subtotal			**13/97232**	**112/83532**	**90·5 (82·1 to 96·1)**
I^2=6·4%, heterogeneity p=0·77					
Overall			**131/253571**	**1150/215661**	**90·8 (85·5 to 95·1)**
I^2=47·6%, heterogeneity p=0·0030					



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the log-transformed RR for symptomatic infection and on the log-transformed OR for severe infections (appendix p 5). We did a sensitivity analysis by only including RCTs reporting both antibody and efficacy data.

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 41053 papers retrieved, 28 eligible efficacy RCTs published in 32 publications were included in this review (figure 1; appendix pp 20–100).[19–50] A total of 286915 participants in vaccination groups and 233236 in placebo groups were involved, with a median follow-up ranging from 1 month to 6 months after last vaccination in individual RCTs. 27 eligible RCTs assessed the efficacy of full vaccination for DNA, mRNA, viral vector, inactivated

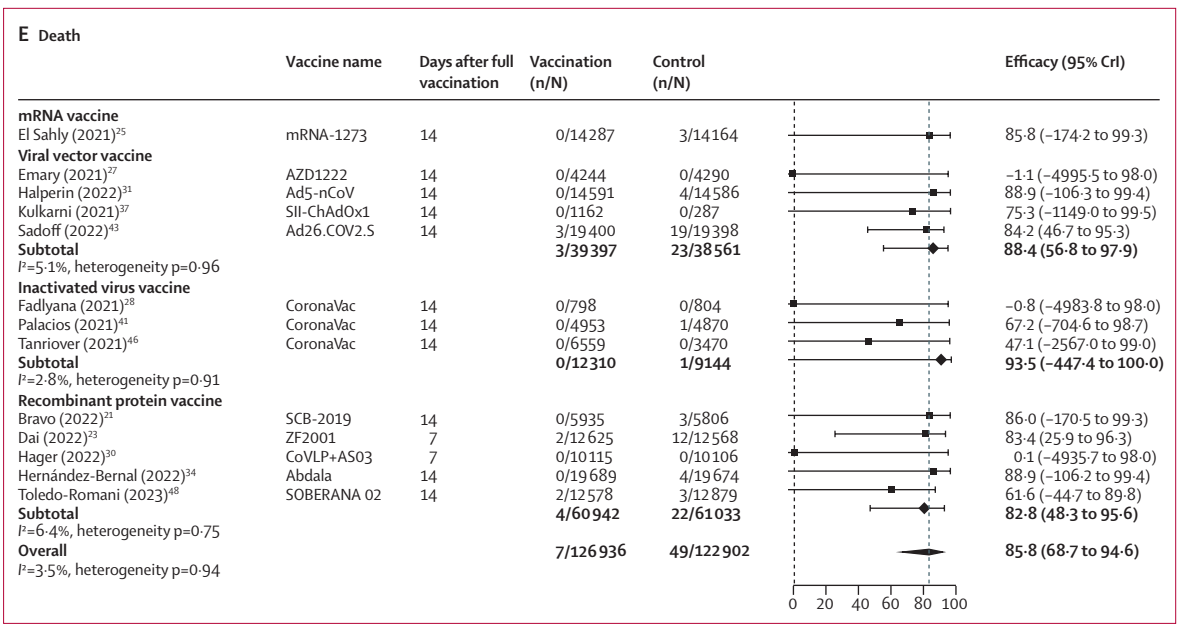

Figure 2: **Forest plot for efficacy of full vaccination of SARS-CoV-2 vaccines on preventing infections according to severity of infection and type of vaccine**
Vaccine efficacy for individual studies was calculated with continuity correction by adding 0·5 to zero-count cells. CrI=credible interval.

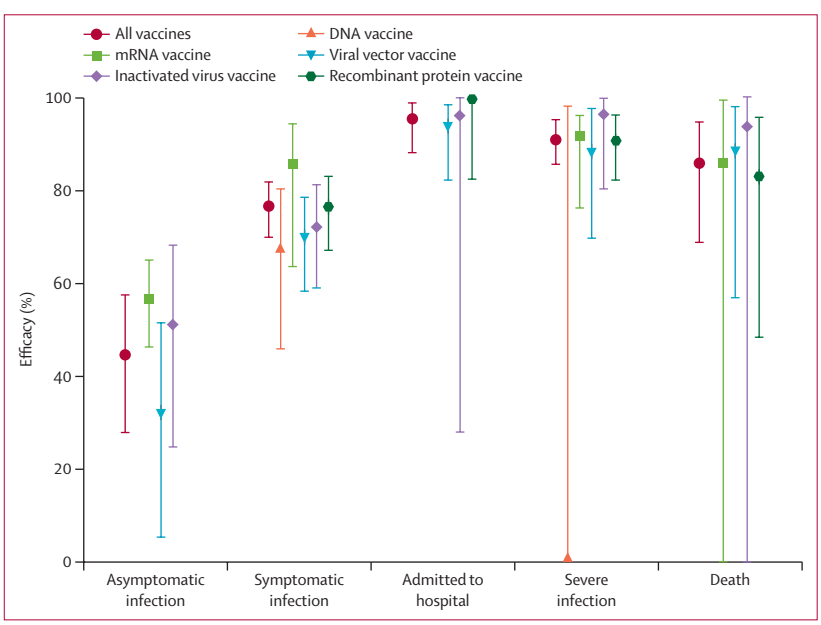

Figure 3: **Differences in efficacy of different SARS-CoV-2 full vaccinations on preventing infections of different severity, according to vaccine type**
Error bars show 95% CI for asymptomatic and symptomatic infection and 95% credible interval for hospital admission, severe infection, and death. Data on asymptomatic infection were not available for DNA vaccine and recombinant protein vaccine; data on hospitalisation were not available for DNA vaccine and mRNA vaccine; data on deaths were not available for DNA vaccine.

virus, and recombinant protein vaccines. Two RCTs compared booster vaccination with no vaccination.

The risk of bias was low in most studies (appendix p 182). The main concern about risk of bias was insufficient blinding of participants and personnel. Quality of evidence was moderate for all outcomes (appendix p 175).

Nine RCTs evaluated vaccine efficacy against asymptomatic infection.[19,20,22,25,26,37,43,45,49] The combined efficacy was 44·5% (95% CI 27·8–57·4) with high heterogeneity (I^2=79·6%, p<0·0001): 56·5% (95% CI 46·2–64·9) for mRNA vaccines, 32·1% (5·3–51·4) for viral vector vaccines, and 51·0% (24·7–68·1) for inactivated vaccines (figures 2, 3).

27 RCTs investigated vaccine efficacy against symptomatic infection.[19–26,28–31,33–38,40,41,43,44,46–50] The combined efficacy was 76·5% (95% CI 69·8–81·7) with high heterogeneity (I^2=93·0%, p<0·0001): 67·3% (95% CI 45·8–80·2) for the DNA vaccine, 85·5% (63·5–94·2) for mRNA vaccines, 69·9% (58·2–78·4) for viral vector vaccines, 72·1% (58·9–81·1) for inactivated vaccines, and 76·3% (67·0–82·9) for recombinant protein vaccines (figures 2, 3). Vaccine efficacy for preventing symptomatic infection was 78·2% (64·0–86·8) for alpha (B.1.1.7) variants of concern, 33·4% (7·1–52·2) for beta (B.1.351) variants of concern, 73·1% (31·5–89·4) for gamma (P.1) variants of concern, and 67·0% (50·0–78·2) for delta (B.1.617.2) variants of concern. There was significant waning of efficacy over time (p=0·0007), with an average decrease of 13·6% (95% CI 5·5–22·3) per month after full vaccination (figure 4).

Eight RCTs assessed vaccine efficacy against COVID-19 related hospital admission.[21,29,30,33,37,42,46,49] The combined efficacy was 95·4% (95% CrI 88·0–98·7) with modest heterogeneity (I^2=4·0%, p=0·95). All types of vaccines showed high efficacy against hospital admission (figures 2, 3).

22 RCTs reported the efficacy of different vaccines against severe infection.[19,21,23–26,28–31,40,41,43,44,47,48,50] The combined efficacy was 90·8% (95% CrI 85·5–95·1) with moderate heterogeneity (I^2=47·6%, p=0·0030): 91·5% (95% CrI 76·1–96·0) for mRNA vaccines, 88·2% (69·6–97·5) for viral vector vaccines, 96·2% (80·2–99·7) for inactivated virus vaccines, and 90·5% (82·1–96·1) for recombinant protein vaccines (figures 2, 3). Only one RCT was available for the DNA vaccine, with no severe infections in both groups. In general, a moderate efficacy in preventing symptomatic infections was related to a higher efficacy in preventing severe infections (appendix p 184).

13 RCTs assessed the efficacy of vaccination against COVID-19 related death.[21,23,25,27,28,30,31,34,37,41,43,46,48] The combined efficacy was 85·8% (95% CrI 68·7 to 94·6) with modest heterogeneity (I^2=3·5%, p=0·94): 85·8% (95% CrI –174·2 to 99·3) for mRNA vaccines, 88·4% (56·8 to 97·9) for viral vector vaccines, 93·5% (–447·4 to 100·0) for inactivated vaccines, and 82·8% (48·3 to 95·6) for recombinant protein vaccines (figures 2, 3).

Characteristics of studies about antibody measurements are in the appendix (pp 101–171). We found a non-linear dose–response relationship between each type of antibody and efficacy against both symptomatic and severe infections (all p values for coefficients were <0·0001) but there remained large unexplained variations in the relationship (figure 5).[51] As T-cell immunity measures differed substantially across trials, it was not feasible to assess the T-cell immunity–efficacy relationship in this Article (appendix pp 172–74).

The funnel plot and Egger's test showed no clear evidence of publication bias (appendix p 183). There was insufficient evidence to suggest whether efficacy against SARS-CoV-2 differed according to type of vaccine, age of the vaccinated, and between-dose interval (all p>0·05; appendix pp 177–79). A series of sensitivity analyses showed similar results to the main findings (appendix pp 180–81).

Two RCTs assessed the efficacy of a booster with Ad26.COV2.S (Johnson & Johnson; 75·6%, 95% CI 55·5–87·5) or SOBERANA-02 Plus (Instituto Finlay de acunas, Havana; 92·0%, 80·4–96·7) vaccines against symptomatic infection, with scarce or no data on other outcomes (appendix pp 12–18).[32,48]

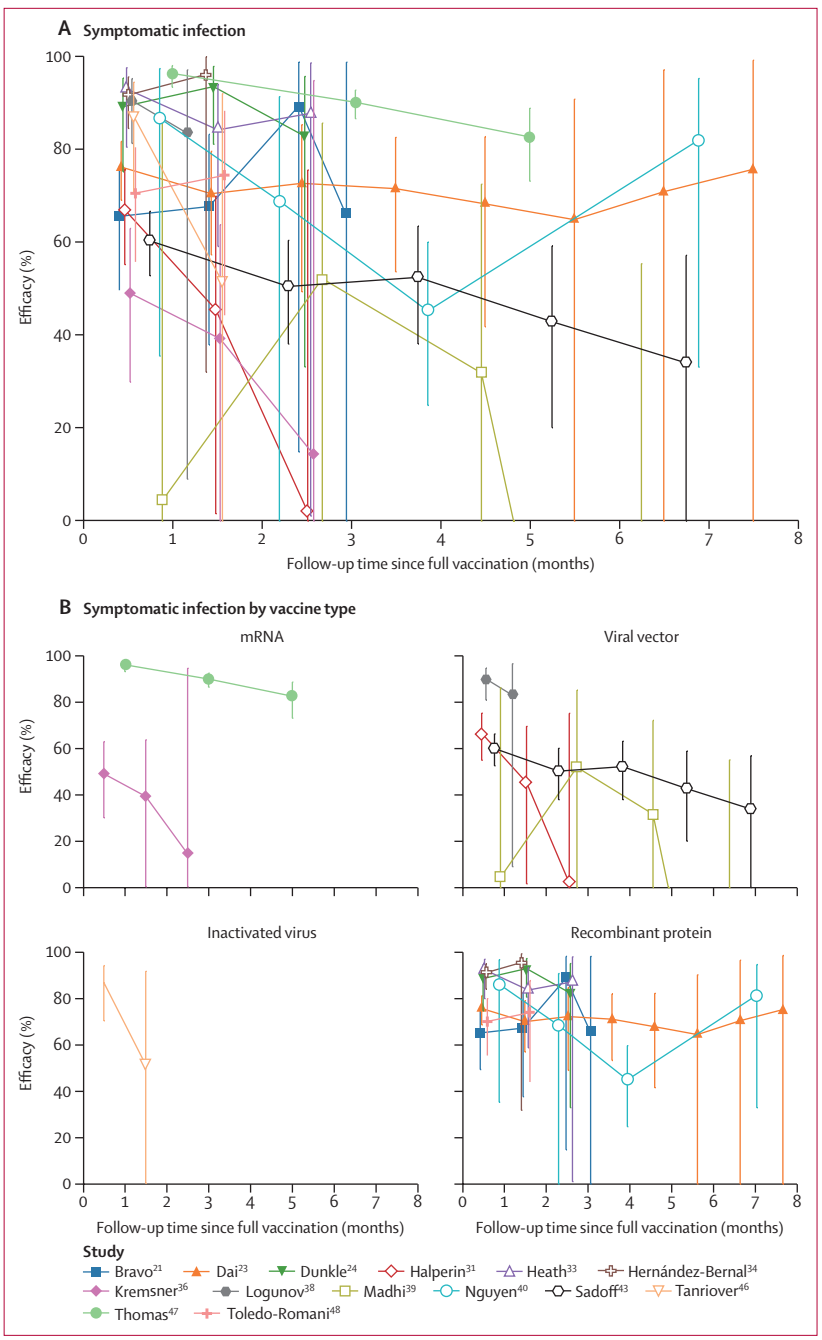

Figure 4: **Change of vaccine efficacy in preventing symptomatic infection after full vaccination**
Error bars show 95% CI.

Discussion

In this systematic review and meta-analysis, we found moderate-quality evidence that SARS-CoV-2 vaccines could reduce the risk of SARS-CoV-2 infections and effectively prevent most severe infections and deaths. The magnitude of vaccine efficacy could vary in different populations as suggested by the moderate-to-high heterogeneity across RCTs. Efficacy against symptomatic infection waned over time after full vaccination was completed but can be enhanced by a booster. We found a non-linear antibody–efficacy relationship but there remained large heterogeneity in the efficacy that cannot be explained by the antibody concentrations.

Mild infections are the main source of SARS-CoV-2 transmission. Successful prevention of mild infections is crucial for containing the pandemic. However, the efficacy of vaccination in preventing asymptomatic infections was suboptimal and could well be lower than 50%, suggesting that the vaccines alone are unlikely to be able to stop the

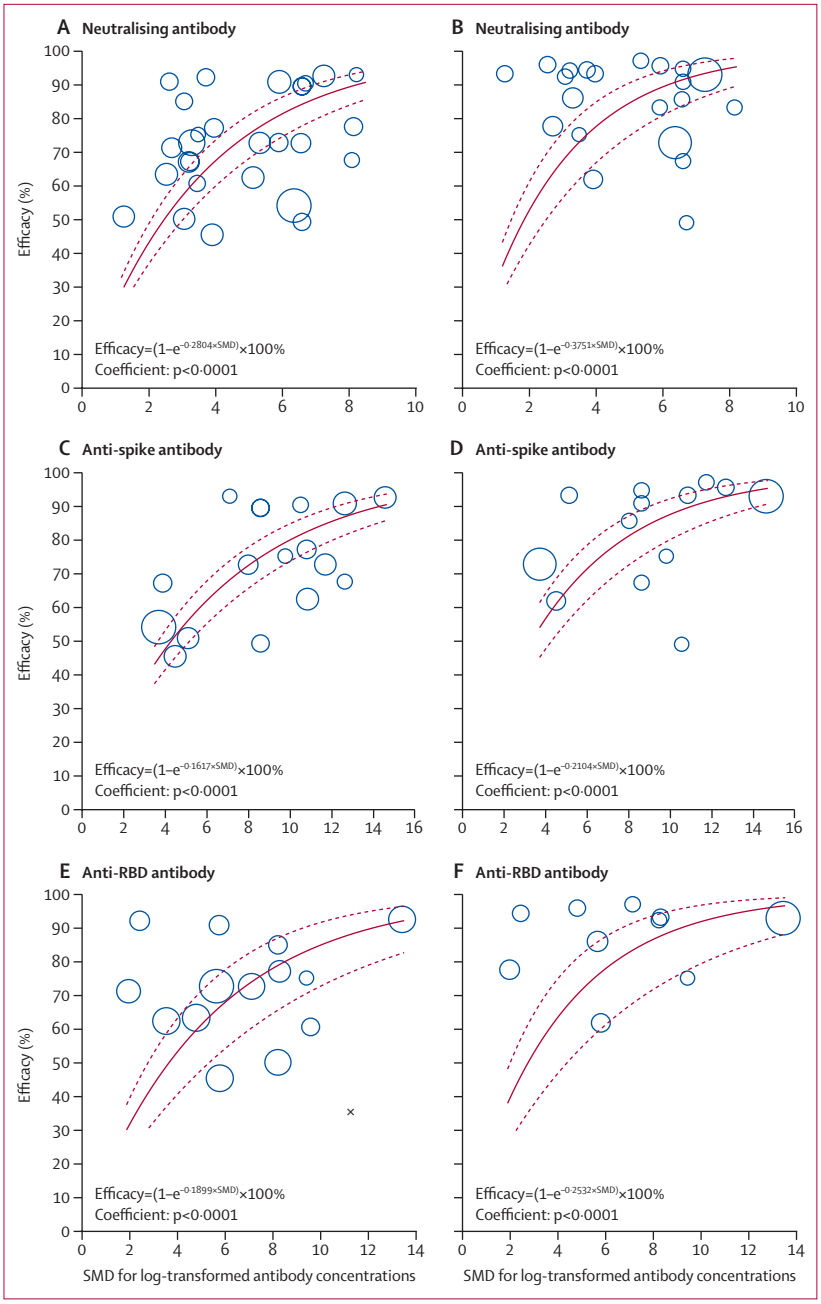

Figure 5: **Dose–response relationship of three SARS-CoV-2 antibodies with efficacy of full vaccination for preventing symptomatic infections (A–C) and severe infections (D–F)**
An example of prediction. Thiruvengadam and colleagues[51] showed that the neutralising antibody titres 61 days after the second vaccine dose of ChAdOx1 nCoV-19 (adenovirus-vectored vaccine) were 599·4 (95% CI 376·9–953·2), which converts to an SMD of 3·96. Using the formula efficacy=(1–e$^{-0·2804×SMD}$)×100%, an efficacy of 67·1% for preventing symptomatic infection is obtained, which is close to the efficacy estimate of 63·1% given in the study. Where n_1 is the number of trials providing both efficacy and antibody data and n_2 is the number of trials providing efficacy data only, with corresponding antibody data reported in previous phase trials: (A) n_1=13, n_2=14; (B) n_1=9, n_2=8; (C) n_1=6, n_2=8; (D) n_1=9, n_2=13; (E) n_1=6, n_2=8; (F) n_1=5, n_2=6. RBD=receptor binding domain. SMD=standardised mean difference.

pandemic. In addition, vaccine efficacy against symptomatic infections seemed lower than that estimated in other meta-analyses[4,9] of earlier RCTs done in the wild-type strain predominant period (about 95% for mRNA vaccines and 80% for virus vector vaccines). The evolution of SARS-CoV-2 variants might be a cause for the compromised efficacy,[5] but confirming this based on indirect comparisons from different RCTs will be difficult due to the large unexplained heterogeneity and incomplete coverage of people who are infected for whole-genome sequencing in RCTs.

Given the moderate and variable efficacy of vaccines in preventing mild infections, the primary goal of SARs-CoV-2 vaccination strategies should be reset to reducing the risk of severe COVID-19 illness and deaths. Although mild infection has become more common and fatality is much lower during the omicron pandemic, the number of severe infections can still be large if many people are infected in a short period.[52] Surges in severe infections could also stress hospital systems, negatively affecting health care, which in turn could further increase the risk of death from COVID-19.[53] Vaccination is therefore still crucial as it can prevent about 90% of severe COVID-19 illness and deaths. These findings are also reconfirmed in large real-world observational studies.[54–56]

In line with a meta-analysis of observational studies,[6] we found that overall vaccine efficacy decreased in the first 6 months after full vaccination was completed in RCTs. However, the peaking time and waning rate might vary by different vaccines and booster vaccination might compensate for the waning of efficacy, which was also supported by observational studies.[57,58] For severe infections, data from RCTs were insufficient to establish the change in the efficacy over time, but observational studies suggested that the effectiveness against severe COVID-19 remained high by 6 months after full vaccination.[6] Given the evidence for waning efficacy, it is important to time vaccination in relation to an anticipated outbreak.

Although observational studies found that the protection against symptomatic and severe infections differed by types of vaccines,[59] currently available RCTs provided no strong evidence to support this difference. In fact, we found significant heterogeneity in vaccine efficacy across individual RCTs and the heterogeneity was high even in RCTs on the same type of vaccines. This heterogeneity suggests that the variability in vaccine efficacy was more likely a result of a total effect of differences in trial design, population characteristics, sample size, outcome detection, duration after vaccination, and other factors, than the types of vaccines themselves.

SARs-CoV-2 antibodies elicited by vaccines are commonly used to predict or compare the magnitude of vaccine efficacy. The validity of such predictions has, however, not been firmly established. Indeed, our exploratory analysis found that a higher concentration of neutralising, anti-spike, or anti-RBD antibody titres, regardless of the working mechanisms of the vaccines, was associated with a higher efficacy, particularly for preventing severe infections. However, the efficacy was

not proportional to concentrations of antibodies. These findings agreed with the dose–response relationships shown within the only study available at the time of review.[10]

Although the antibody–efficacy association might truly exist,[10,60,61] precise prediction of vaccine efficacy using the association seems difficult as there remains large variability in the efficacy, which cannot be explained by the antibody concentrations. The antibody–efficacy association might differ by population characteristics, assays, types of vaccines, and time after vaccination. Even within the same study, however, large unexplained variations were also found in the antibody–efficacy association.[10] Therefore, any efforts to use antibody concentrations to predict efficacy should be cautious, particularly when antibodies and efficacy are measured from different populations. Better prediction could be achieved if other potential factors in the prediction model are accounted for, rather than antibody concentrations alone.

T-cell immunity was also proposed as a factor in predicting vaccine efficacy.[62] However, the dose relationship between T-cell concentrations and efficacy has yet to be established and this relationship is difficult to assess on current available trial data given non-standardised measures of T-cell immunity (appendix pp 168–70). Before more reliable evidence on the T-cell immunity–efficacy relationship becomes available, simply labelling strong (or weak) T-cell response found in a group of people as high (or low) efficacy should also be cautioned against.

To our knowledge, this is the most comprehensive investigation of all currently available vaccine efficacy trials and paired immunogenicity–efficacy data to assess the vaccine efficacy and the antibody–efficacy association. Due to data on severe SARs-CoV-2 infections being extremely rare in individual trials, our meta-analysis provided considerably more robust evidence on the efficacy against severe infections than individual trials have. The findings on the antibody–efficacy relationship are also highly valuable as the paired data collected repeatedly over time within a trial are unlikely to become available in the near future or at all.

There are some limitations in our review. First, considerable heterogeneity exists in the efficacy of vaccination for preventing symptomatic infections and moderate heterogeneity for preventing severe infections. Most of the heterogeneity is probably a result of trial-design factors and makes comparing the efficacy of different types of vaccines evaluated in separate trials difficult, although current trial evidence is insufficient to support such differences. Second, many limitations in our study originated from individual trials, for example insufficient data on the SARS-CoV-2 variants, inconsistent definitions of infection severity, the paucity of information on environmental factors, and partial coverage of study population for nucleic acid testing. These factors could also contribute to the unexplained heterogeneity and potentially resulted in biases in vaccine efficacy estimates. Finally, ecological bias might exist in our meta-regression using aggregated study-level data as there could be other factors that can affect both the antibody concentration and efficacy, such as types of vaccines and predominant variants of SARS-CoV-2. However, due to the low number of studies within each category of these factors, we were not able to do a meta-regression stratified by these factors. Individual participant data are needed to better assess this relationship; however, these data are unlikely to be made available.

This Article has some important implications for future research. First, the large evidence base summarised in our review provides an irreplaceable reference for comparisons with and interpretation of new trials in the development of new vaccines and booster regimens, including those against omicron variants. For example, a moderate efficacy in preventing symptomatic infections seems to be related to a higher efficacy in preventing severe infections. Waning of efficacy also probably exists for new vaccines against new variants of the virus. Immunogenicity in people vaccinated with a booster or a new vaccine might not accurately predict vaccine efficacy.

Second, this study suggested that uncertainties remain over vaccine efficacy beyond 6 months of the last vaccination and efficacy against omicron infections. The efficacy according to type of vaccines, age of the vaccinated, between-dose interval, and variant of the virus remained unsatisfactorily answered due to the small number of trials available and large unexplained between-trial heterogeneity. Although a booster can enhance efficacy, the best timing and the best regimen for a booster remain to be investigated.

Third, this study has also identified some important gaps, which could guide the design of future trials on SARS-CoV-2 vaccines. To enable valid comparison of the results from different trials, assays and timing for immunogenicity measurement should be standardised. The relationships of vaccine efficacy with humoral and cellular immune responses should be further confirmed. To reduce detection bias, surveillance testing for SARS-CoV-2 infection should cover all the study population. Since vaccine efficacy might vary for different SARS-CoV-2 variants, genome sequencing should be done to confirm the variants, particularly for trials done through different periods of predominant variants. Future trials need to increase the power if they aim to assess comparative efficacy between vaccine regimens or between different participant subgroups. Since it is not always feasible to conduct such large-scale RCTs, real-world studies as an alternative could be done to timely address some of the important questions for decision making.

Contributors

J-LT, FS, Z-YY, and Z-RY conceived the research question and designed the study. Z-RY and Y-WJ did the literature search. Z-RY, Y-WJ, F-XL,

DL, T-FL, Z-YZ, CW, Q-YJ, X-ML, Y-XJ, and FS screened articles. Z-RY, Y-WJ, F-XL, DL and T-FL read the full texts for eligibility. Z-RY, Y-WJ, and F-XL extracted data from the original trials. DL and T-FL evaluated the risk of bias. Y-WJ and Z-RY did the analyses and evaluated the quality of evidence. J-LT, FS, Z-YY, Z-RY, Y-WJ, F-CZ, and Z-JF contributed to the interpretation of the results. Z-RY and Y-WJ wrote the first draft of the manuscript. J-LT, FS, and Z-YY critically revised the manuscript. All authors acknowledge full responsibility for the analyses and interpretation of the report. All authors have read and approved the final manuscript. J-LT is the guarantor. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

We declare no competing interests.

Data sharing

All data included were derived from publicly available documents cited in the references. Extracted data are all presented in this manuscript and appendix.

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