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INVITED ARTICLE

Efficacy of Approved Versus Unapproved Vaccines for Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Randomized Blinded Clinical Trials

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Background. Five severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines are approved in North America and/or Europe: Pfizer/BioNTech, Moderna, Janssen, Oxford-AstraZeneca, and Novavax. Other vaccines have been developed, including Sinopharm, SinoVac, QazVac, Covaxin, Soberana, Zifivax, Medicago, Clover, and Cansino, but they are not approved in high-income countries. This meta-analysis compared the efficacy of US Food and Drug Administration (FDA)/European Medicines Agency (EMA)-approved and -unapproved vaccines in randomized clinical trials (RCTs).

Methods. A systematic review of trial registries identified RCTs of SARS-CoV-2 vaccines. Risk of bias was assessed using the Cochrane tool (RoB 2). In the meta-analysis, relative risks of symptomatic infection and severe disease were compared for each vaccine versus placebo, using Cochrane-Mantel Haenszel Tests (random effects method).

Results. Twenty-two RCTs were identified and 1 was excluded for high-risk of bias. Ten RCTs evaluated 5 approved vaccines and 11 RCTs evaluated 9 unapproved vaccines. In the meta-analysis, prevention of symptomatic infection was 84% (95% confidence interval [CI], 68%–92%) for approved vaccines versus 72% (95% CI, 66%–77%) for unapproved vaccines, with no significant difference between vaccine types ($P = .12$). Prevention of severe SARS-CoV-2 infection was 94% (95% CI, 75%–98%) for approved vaccines versus 86% (95% CI, 76%–92%) for unapproved vaccines ($P = .33$). The risk of serious adverse events was similar between vaccine types ($P = .12$).

Conclusions. This meta-analysis of 21 RCTs in 390 459 participants showed no significant difference in efficacy between the FDA/EMA-approved and -unapproved vaccines for symptomatic or severe infection. Differences in study design, endpoint definitions, variants, and infection prevalence may have influenced results. New patent-free vaccines could lower costs of worldwide SARS-CoV-2 vaccination campaigns significantly.

Keywords. access to medicines; COVID-19 vaccination; vaccines.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has resulted in an excess mortality of 14.9 million people globally during 2020 and 2021 [1]. The economic and social burden associated with the coronavirus disease 2019 (COVID-19) pandemic has prompted an unprecedented fast-tracking of the vaccine development process. Although effective vaccines have been available since late 2020, access to them has been dramatically unequal between countries. Vaccine nationalism, hoarding, and unfair pricing have contributed to many preventable deaths, hampered economic recovery, and continue to increase the risk of new COVID-19 variants [2, 3]. As of May 2022, 197 COVID-19 vaccine candidates are in the clinical stages of development [4], 38 of which have already been approved or authorized for public use at either national or international levels [5].

Vaccine approvals are based on efficacy estimates traditionally derived from randomized Phase III trials. Phase III results are currently publicly available for 17 vaccines utilizing a combination of traditional and new-generation approaches [4]. These include 5 protein subunit, 4 inactivated, 4 nonreplicating viral vector, 2 mRNA, 1 viral-like particle, and 1 deoxyribonucleic acid unique vaccine formulation [4].

In these Phase III trials, each vaccine candidate is compared against placebo, and the primary efficacy outcome is the prevention of symptomatic disease [6]. Symptomatic disease is often defined according to a series of symptomatic criteria (such as those by the Food and Drug Agency [7] or the World Health Organization [WHO] [8], but may vary between

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trials), which, upon presentation, prompt definite confirmation via polymerase chain reaction (PCR) testing. Some trials, such as Oxford/AstraZeneca's vaccine Phase III trials, also look at protection against asymptomatic infection by regularly testing participants for COVID-19 [9].

However, asymptomatic or even symptomatic infections may not be the most important measures of vaccine efficacy, because prevention of hospitalization and severe disease are arguably more important for preventing an excess burden on health services.

In addition, immunogenicity trials are suggested as a predictor of future vaccine efficacy but are rarely used. For example, 2 vaccines—Valneva VLA0001 vaccine in the United Kingdom [10] and Biological E. Limited's Corbevax in India [11]—have been approved by national regulatory agencies solely based on immunogenicity results. However, the European Medicines Agency (EMA) has delayed approval of the Valneva VLA0001 vaccine and requested additional data [12].

Vaccines by large pharmaceutical companies, such as Moderna, Pfizer, AstraZeneca, Janssen, and Novavax, have been approved or authorized for emergency use in North America and Europe by the US Food and Drug Administration (FDA) and EMA, respectively [13, 14]. These vaccines (referred conjointly as "approved vaccines" from now on for simplicity) have become the standard in high-income countries. However, procurement of these approved vaccines in lower income countries has been slow due to financial, legal, and logistical barriers [15, 16]. Instead, they have often had to depend on vaccines that have not been approved by regulatory agencies and national governments in high-income countries. A full list of approved and unapproved vaccines is shown in Supplementary Table 1.

With real-world data showing a gradual decrease in vaccine efficacy over time [17, 18] and hence a potential need for regular boosters, demand for vaccines is likely to persist. As a result, global inequalities in vaccine access could continue for many years unless we find lower cost alternatives to currently approved COVID-19 vaccines. This study compared the efficacy and safety of existing FDA/EMA-unapproved vaccines to FDA/EMA-approved vaccines.

METHODS

Search Strategy and Protocol

This systematic review was registered on PROSPERO in April 2022. Our study protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-*P*) [19]. We conducted literature searches on Embase and Medline for published studies and consulted ClinicalTrials.gov and the WHO International Clinical Trial Register Platform. Recently developed living reviews on COVID-19 vaccine development evidence were also consulted, namely, the WHO COVID-19 vaccine landscape [4] and the COVID NMA vaccine tracker [20]. A search for relevant preprints in Europe PMC was also carried out due to the important role played by this type of publication in COVID-19 research. Results from the WHO COVID-19 vaccine landscape were filtered to only include vaccines in either Phase II/III, III, or IV of development. Identification numbers from conducted Phase II/III or III trials were extracted. Due to the rapidly changing field of COVID-19 vaccine development, 2 separate searches were conducted throughout the study: first in February (February 24, 2022) and then in April (April 5, 2022).

Patient Consent Statement

All of the clinical trials included in the meta-analysis were approved by local ethics committees and all patients gave informed consent.

Inclusion Criteria

The inclusion criteria were based on a PICOS assessment of the research question and are described in the Supplementary Appendix (Section 1.1). Only studies written in English were searched.

Data Extraction and Quality Assessment

Data extraction and quality assessment occurred simultaneously with full-text screening, and studies at a high risk of bias were excluded from the final statistical analysis. Reports included for full-text review were classified by vaccine type, and study characteristics were tabulated on Excel to assess for eligibility. Data extraction from reports to be included in the study was carried out manually and independently by the main author (APN) and presented in Excel in tabulated form. Data collected from each study have been described in the Supplementary Appendix (Section 1.2). The risk of bias was assessed independently by the main author (APN) using the Cochrane tool for assessing risk of bias in randomized trials (RoB 2.0) [21]. RoB 2.0 rates studies as either low risk, some concerns, or high risk of bias across 5 different domains: randomization process; deviations from the intended interventions; missing outcome data; measurement of the outcome; and selection of reported result.

Outcomes

The outcome measures of interest were vaccine efficacy against symptomatic infection (primary outcome) and severe disease (secondary outcome). The definitions for these outcomes are provided in the Supplementary Appendix (Section 1.3).

In the case of a single study reporting efficacy outcomes at different time points, the shortest time interval since the last vaccine dose was used to ensure greater homogeneity and comparability between trials. In case of multiple reports being available for a single study, the report with the longest follow-up time was selected for analysis.

Data Synthesis and Statistical Analysis

Between-study heterogeneity was quantified using the I^2 statistical parameter, an estimate of the percentage of observed variation attributable to between-study heterogeneity. Heterogeneity was considered significant when I^2 >50%. For each outcome, we conducted a meta-analysis with the random-effects Mantel-Haenszel model. We used incidence values of symptomatic and severe COVID-19 in vaccine and placebo arms to calculate pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs). The use of a random-effects model was justified by the high between-study heterogeneity identified, whereas the choice of ORs as the summary statistic was justified by the overall small number of cases identified in each treatment arm. Studies measuring more than 1 clinical outcome of interest were included in both analyses.

Subgroup analyses were performed to compare vaccine efficacy and safety outcomes between approved vaccines (defined as those approved or authorized by the FDA or the EMA) and unapproved vaccines (those not yet approved or authorized by the FDA or the EMA). A funnel plot including all studies was produced to assess for publication bias for the outcomes of symptomatic and severe infection (Supplementary Figure 3A and B). All statistical analyses were conducted on RevMan 5 (Version 5.4.1).

Certainty of the Evidence

We assessed certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Certainty about each outcome was ranked as very low, low, moderate, or high, based on an assessment of 5 different domains—risk of bias, inconsistency, indirectness, publication bias, and imprecision—based on definitions from the GRADE handbook [22].

RESULTS

A total of 568 clinical trials were identified by searching clinical trial registers. After screening, 238 trials satisfied the inclusion criteria. Associated published reports were identified for 58 randomized trials. Parallel searches of literature databases identified 309 publications.

After excluding 178 duplicates and screening 190 titles and abstracts and 34 full texts (2 of which were identified after the literature search cutoff date of April 5, 2022), 22 unique randomized clinical trials from 19 publications [23–41] assessing the efficacy of 16 COVID-19 vaccines were identified (Figure 1).

Most reports excluded during full-text review were preliminary reports or substudies of published final reports. Two studies evaluating the efficacy of Gamaleya Institute Sputnik V [42] and Zydus Cadila ZyCoV-D [43] vaccines were excluded due to a lack of prespecified symptomatic diagnostic criteria for COVID-19 infection, as required per protocol. One report evaluating efficacy of the CVnCoV vaccine [44] was excluded due to the discontinuation of the vaccine development process by the pharmaceutical company. Three other reports were excluded due to the wrong study design.

Of the 2 trials identified after April 5th, 1 was a peer-reviewed publication initially identified as a preprint [45]. The other trial looked at a new vaccine [31] and after careful deliberation was included in the final analysis to ensure our study was as comprehensive as possible.

All 22 trials included for review reported both rates of symptomatic infection and severe disease. Ten trials (45.5%) looked at approved vaccines (Table 1) and 12 trials (54.5%) looked at unapproved vaccines (Table 2). This included trials on 5 FDA/EM-approved vaccines and 9 FDA/EMA-unapproved vaccines (Supplementary Figure 4).

Two of the trials on the Oxford/AstraZeneca vaccine were Phase I and Phase I/II, respectively. However, results were reported conjointly [26] with results from 1 Phase II and 1 Phase II/III trial and therefore had to be included in the review.

Of the 22 trials included, 17 (77.3%) were published in peer-reviewed journals and 4 (18.2%) were preprints. All preprints reported results about unapproved vaccines [23, 34, 37, 38].

As shown in Supplementary Figure 1, trials on approved vaccines started on average 3.8 months sooner than those on unapproved vaccines. The duration of studies was similar between subgroups. All studies assessed vaccine efficacy in adults in good or stable health, except 1 study that included participants from the age of 12.

Supplementary Tables 2 and 3 summarize outcome data for each study. Figure 2 shows pooled efficacy estimates for each vaccine. One trial for the NanoCovax vaccine [23] was excluded from the efficacy analysis after being identified as high risk of bias. Study characteristics for this trial are available in the Supplementary Appendix, along with further characteristics of included studies (Supplementary Table 4A and B).

Risk of Bias

One study [23] was excluded from the analysis after being identified as high risk of bias. Of the remaining studies, 1 was identified as low risk of bias and 19 had some concerns for bias (Supplementary Figure 2). The most common sources of bias were the inappropriate use of a per-protocol analysis and the lack of a publicly available protocol.

Symptomatic Infection

Twenty-one RCTs in 18 publications including 374 456 participants reported incidence of symptomatic infection, all of which were included in the meta-analysis. Similar definitions for COVID-19 infection were used across all trials, with the most common definition involving the presence of either 1 specific symptom or 2 nonspecific symptoms. Detailed descriptions of endpoint definitions for each trial are included in the

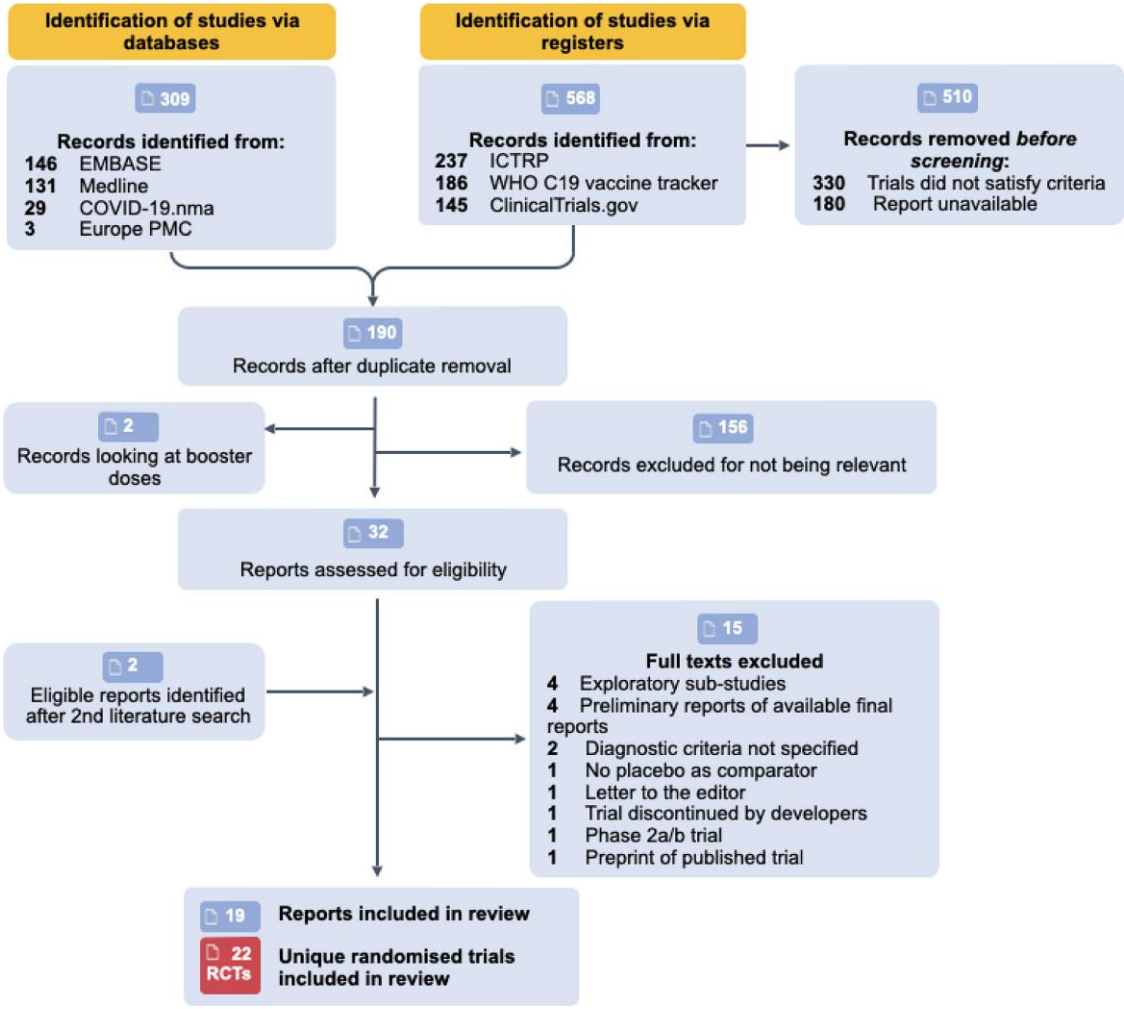

Figure 1. Study selection.

Supplementary Appendix (Table 5A and B). Polymerase chain reaction confirmation of symptomatic cases was required in all trials.

As shown in Figure 3, all trials favored vaccine over placebo. Efficacy values are calculated as ORs in the meta-analysis and presented as a percentage reduction in the body of text to aid clarity. Subgroup analysis showed a vaccine efficacy of 84% (95% CI, 68%–92%) for approved vaccines and 72% (95% CI, 66%–77%) for unapproved vaccines. Subgroup differences were not statistically significant ($P = .12$).

Table 1. Summary Table of Approved and Unapproved Vaccine Included in the Review

Developers	Vaccine Name (Type)	Vaccine Schedule	*N* (Number of Trials) [Ref.]	Location of Trials	Average Follow-up (Months)
			Approved Vaccines		
Janssen	Ad26.COV2.S (VVnr)	0	39 321 (1) [24]	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA	4
Moderna	mRNA-1273 (RNA)	0–28	30 415 (1) [30]	USA	5
Novavax	NVX-CoV2373 (PS)	0–21	43 621 (2) [27, 28]	USA, Mexico, UK	3
Oxford/Astra Zeneca	Vaxzevria/ChAdOx1-S (VVnr)	Variable[a]	44 087 (5) [25, 26]	UK, Brazil, South Africa, USA, Chile, Peru	2.5
Pfizer/BioNTech	BNT162b2 (RNA)	0–21	44 060 (1) [29]	USA	6

Abbreviations: mRNA, mRNA vaccine; PS, protein subunit; VVnr, nonreplicating viral vector.

[a]Two vaccine doses given in all trials. 3 out of 5 trials administered second vaccine after a 28 day interval. Minimum interval between doses amongst all 5 trials was of 4 weeks and maximum time interval was of 12 weeks.

Table 2. Summary Table of Unapproved Vaccines Included in the Review

Developers	Vaccine Name (Type)	Vaccine Schedule	*N* (Number of Trials)	Location of Trials	Average Follow-up (Months)
			Unapproved Vaccines		
Anhui Zhifei Longcom Biopharma.	ZF2001 (PS)	0–30–60	25 193 (1) [31]	Uzbekistan, Indonesia, Pakistan, Ecuador, China[a]	6
Bharat Biotech International Limited	BBV152 (IV)	0–21	16 973 (1) [39]	India	3
CanSino Biological Inc.	Ad5-nCoV (VVnr)	0	29 177 (1) [41]	Argentina, Chile, Mexico, Pakistan, Russia	1.5
Clover Biopharmaceuticals	SCB-2019 (PS)	0–28	12 361 (1) [32]	Belgium, Brazil, Colombia, Philippines, and South Africa	2
Instituto Finlay de Vacunas	FINLAY-FR-2-25 (PS)	0–14	28 774 (1) [38]	Cuba	1.66
Medicago	CoVLP+ S03 (VLP)	0–21	20 090 (1) [33]	Argentina, Brazil, Canada, Mexico, UK, USA	2
RIBSP	QazVac (IV)	0–28	2835 (1) [37]	Kazakhstan	6
Sinopharm	BBiBP-CorV (IV)	0–21	40 382 (1) [40]	UAE and Bahrain	1.33
Sinovac	CoronaVac (IV)	0–14	21 454 (3) [34–36]	Turkey, Indonesia, Brazil	1.66
Nanogen	Nanocovax (PS)	0–28	13 007 (1) [23]	Vietnam	6

Abbreviations: IV, inactivated virus; PS, protein subunit; RIBSP, Research Institute for Biological Safety Problems; VLP, viral-like particle; VVnr, nonreplicating viral vector.
[a]China participants only included in analysis of safety data.

Overall, when considering the substantial between-study heterogeneity identified, quality of evidence was downgraded by 1 level due to inconsistency. Therefore, certainty of evidence was rated as moderate (Supplementary Table 6).

Severe Disease

Twenty-one RCTs in 18 publications including 380 848 participants reported incidence of severe disease, all of which except 1 (due to no cases of severe infection being reported and hence an OR not being estimable) were included in the meta-analysis. Nine trials (42.8%) defined severe COVID-19 according to the FDA criteria and 5 trials (23.8%) as a 6 or over on the WHO progression scale (Supplementary Table 7). The remaining trials (4 of 22, 18.2%) used alternative definitions. Detailed descriptions of endpoint definitions for each trial are included in the Supplementary Appendix (Table 5A and B).

As shown in Figure 4, all trials favored vaccine over placebo. However, the benefit of vaccine over placebo was not statistically significant for 6 trials: 2 on approved vaccines and 4 on unapproved vaccines. Again, efficacy values are calculated as ORs in the meta-analysis and presented as a percentage reduction in the body of text to aid clarity. Subgroup analysis showed a vaccine efficacy of 94% (95% CI, 75%–98%) for approved vaccines and 86% (95% CI, 76%–92%) for unapproved vaccines. Subgroup differences were not statistically significant ($P = .33$). Quality of evidence was rated as high using GRADE (Supplementary Table 6).

Safety

Nineteen RCTs in 16 publications including 417 406 participants reported an incidence of serious adverse events throughout the duration of the study. Overall, differences in reported adverse event rates between FDA/EMA-approved and -unapproved vaccines were not statistically significant ($P = .12$) (Figure 5).

Sensitivity Analysis

High between-study heterogeneity within subgroups was explored by performing subgroup meta-analyses by vaccine formulation. Subgroup differences in efficacy against symptomatic infection were statistically significant ($P < .00001$), with mRNA vaccines being superior to other vaccine formulations (OR, 0.08; 95% CI, .06–.10), whereas differences in efficacy against severe disease were not ($P = .08$) (Supplementary Figure 5A and B). Subgroup meta-analysis by follow-up time was also carried out. No statistically significant difference in efficacy against both symptomatic and severe disease was identified between vaccine trials with shorter-than-average and longer-than-average follow-up times (Supplementary Figure 6A and B), where the average was 3.44 months.

A separate sensitivity analysis was performed where data for Pfizer, Janssen, and IFV Finlay-FR-125 vaccines were replaced with data from studies on booster doses. No statistically significant difference was identified between approved and unapproved vaccines (Supplementary Figure 7A and B).

Further post hoc sensitivity analyses were also performed, where preprints, the worst-performing vaccine in each category, and trials using non-FDA-approved definitions for severe COVID-19 were removed one at a time from the meta-analysis to assess the strength of the analysis. A detailed breakdown of the results can be found in the Supplementary Appendix (Tables 8 and 9).

Immunogenicity Analysis

A post hoc analysis of vaccine seroconversion data was performed, using Phase II results in the absence of

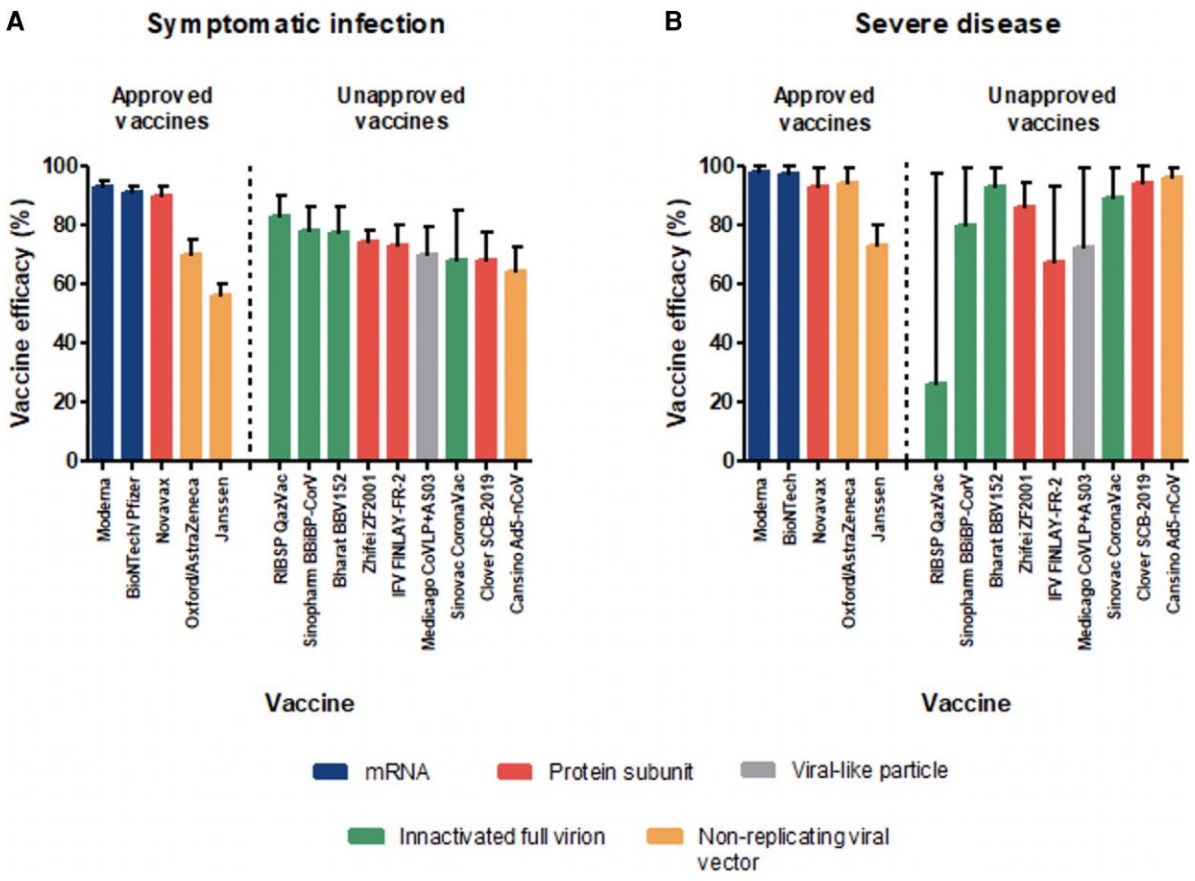

Figure 2. Pooled vaccine efficacy estimates against symptomatic infection (*A*) and prevention of severe disease (*B*) for approved (left of discontinuous line) and unapproved vaccines (right of discontinuous line). Error bars represent 95% confidence intervals (CIs). Bars are color-coded by vaccine type.

Phase III data. Immunogenicity values were obtained from Phase III results for 5 vaccines (CanSino Ad5-nCoV, Sinopharm BBIBP-CorV, Bharat BBV152, FINLAY-FR-2-25, and Oxford/AstraZeneca) and from Phase II trials for 6 vaccines (RIBSP QazVac [46], Medicago CoVLP + AS03 [47], Zhifei ZF2001 [48], Moderna [49], Pfizer/BioNTech [50], and Novavax [51]). Immunogenicity data were not found for 2 vaccines: Medicago SCB-2019 and Janssen). Data on neutralizing antibodies were available for 10 vaccines, and antispike and/or anti-RBD antibody data were available for 9 vaccines (Supplementary Table 10).

As seen in Supplementary Figure 8, seroconversion values were available for 7 unapproved vaccines and 2 approved vaccines. Meta-analysis (Supplementary Figure 9A and B) showed no statistically significant difference between approved and unapproved vaccines for both neutralizing antibody and antispike/RBD antibody seroconversion values.

DISCUSSION

This systematic review and meta-analysis of 21 RCTs in 390 459 participants provides a comprehensive compilation of available evidence on the effects of FDA/EMA-approved and -unapproved COVID-19 vaccines. Both approved and unapproved vaccines were shown to be effective at preventing symptomatic and severe COVID-19 disease, with no statistically significant difference between them. The risk of serious adverse events was again not significantly different between both vaccine groups.

Subgroup analysis showed mRNA vaccines to be superior to other vaccine types at preventing symptomatic infection, further supporting findings from previous systematic reviews [52–54]. However, unlike these other systematic reviews, we also assessed protection against severe COVID-19 disease, which makes this systematic review one of the first ones assessing both outcomes as measures of vaccine efficacy. In this case, subgroup differences were not statistically significant.

Our chosen methodology was based on PRISMA recommendations and used a clear predefined search strategy, inclusion criteria, and statistical analysis. Our literature search was comprehensive with no restrictions on publication status. The exclusion of studies at a high risk of bias further increased the quality of collated evidence. Lastly, with almost 400 000 participants, this systematic review on vaccine effectiveness is to our

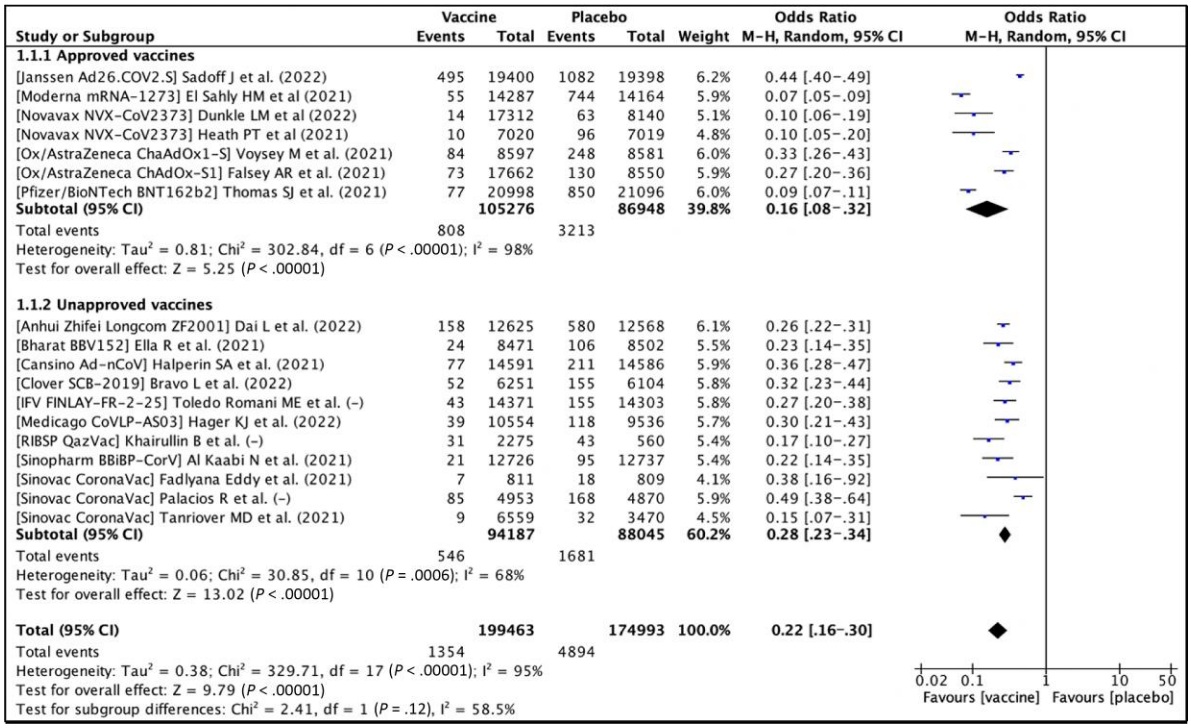

Figure 3. Forest plot comparing vaccine efficacy at preventing symptomatic coronavirus disease 2019 disease between approved and unapproved vaccines.

knowledge the largest and most current analysis of Phase III RCTs of COVID-19 vaccines.

The main limitation of our study was the lack of a direct comparison between vaccines. Whereas some studies followed similar protocols, they mostly used different endpoint definitions and different inclusion and exclusion criteria, making comparison difficult. Moreover, differences in timing and location of trials (and hence in COVID-19 case rates and strain prevalence) introduce confounding factors for which current vaccine efficacy rates do not account. We tried to address some of these factors via leave-one-out sensitivity analyses outlined in the Supplementary Material, which showed no changes in conclusion reached. However, we could not account for all influencing factors, and hence head-to-head studies, in which vaccines are assessed under the same circumstances, would be needed to make stronger comparisons.

Follow-up time also varied between trials, with trials on unapproved vaccines having on average shorter follow-up times than trials on approved vaccines. Real-life evidence has shown that vaccine effectiveness declines with time [55–57]. However, the lack of long-term efficacy assessments for most unapproved vaccines meant we could not predict whether our conclusions would be sustained over time. Large, real-life studies would be needed to assess the durability of protection, and although several of these studies have been conducted for approved vaccines, this is not the case for unapproved vaccines. Moreover, this progressive decline in vaccine efficacy suggests the need for regular boosters to maintain immunity.

Due to insufficient research on booster doses being available, our study could not assess their effects. Nevertheless, studies assessing the efficacy of heterologous booster administration have shown positive results [58]. This suggests that the administration of unapproved vaccine booster doses could increase immune protection and further narrow the gap in efficacy between approved and unapproved vaccines. In addition, in this meta-analysis, we included studies that used the approved doses of each vaccine. However, we need to consider the association between the number of doses and vaccine efficacy. For example, in a preprint study from China, it has been demonstrated that the Chinese CoronaVac (Sinovac) vaccine offers higher protection against severe disease after 3 doses [59]. Furthermore, because some patient groups do not mount an effective immune response with normal dosing regimens, such as those who are immunosuppressed with hematological malignancy or solid organ transplants [60], some are now being offered their fifth dose booster of an mRNA vaccine in the United Kingdom [61].

Furthermore, the assessment of safety outcomes in Phase III trials is not always accurate. For example, Phase III trial results failed to detect anaphylactoid reactions triggered by mRNA vaccines or the association between PF4-dependent thrombotic thrombocytopenic events and the administration of Oxford/AstraZeneca's vaccine [62]. For greater accuracy, postmarketing analysis is needed.

Finally, patient-level databases are generally not available for the unapproved vaccines, whereas the patient-level data for

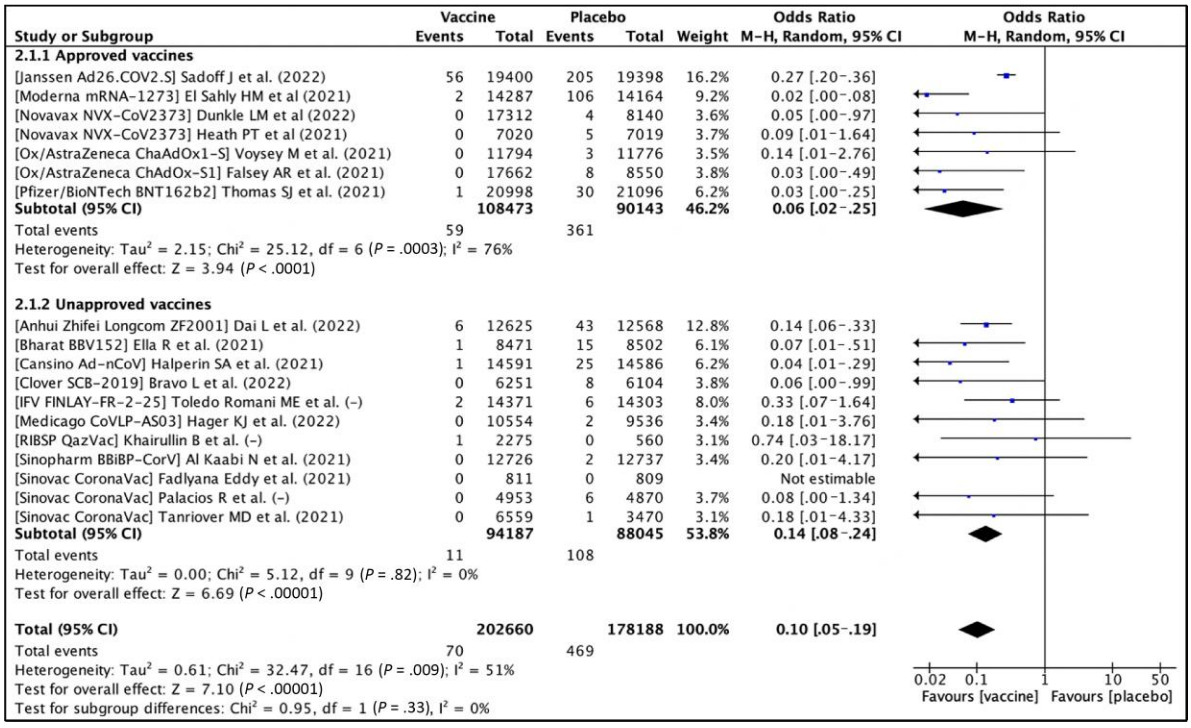

Figure 4. Forest plot comparing vaccine efficacy at preventing severe coronavirus disease 2019 infection between approved and unapproved vaccines.

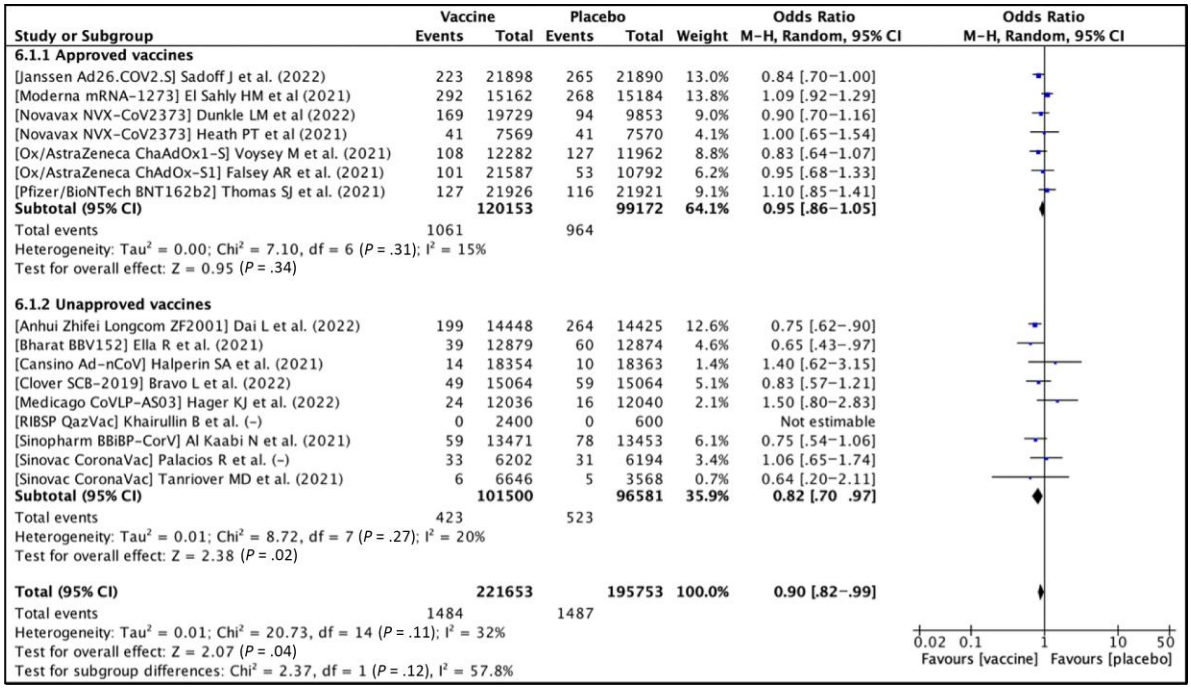

Figure 5. Forest plot comparing risk of serious adverse events for approved and unapproved vaccines.

approved vaccines will have been reviewed in detail by regulatory authorities in North America and Europe. Access to patient-level data gives an additional safeguard against the risk of bias or even medical fraud. However, it is worth noting that some of the unapproved vaccines presented in this paper have been included in the WHO Emergency Use Listing,

namely, Sinovac, Sinopharm, and Bharat [63]. This suggests that the quality and thoroughness of the clinical trial evidence provided was sufficient to guarantee the vaccines' approval. The reason why the FDA and EMA have decided not to approve these vaccines is therefore not well understood.

Our findings could have important economic and public health impacts. Financial, legal, and logistical barriers to vaccine procurement have effectively hindered low- and middle-income countries from accessing approved vaccines. The effects of this unequal vaccine distribution are striking with only 10 countries accounting for 75% of total doses administered globally [64]. Only 22% of the population in low-income countries are partially vaccinated [65]. In contrast, in high- and upper-middle-income countries, 78% of the population is partially vaccinated, with 69 times more doses per person administered, compared with low-income countries [66]. Moreover, the low vaccine coverage rates in developing nations and hence the higher rates of person-to-person transmission increase the risk of new viral strains emerging [66]. As seen with the Delta and Omicron variants, new COVID-19 strains can be highly transmissible and capable of evading natural and vaccine-mediated immunity [67].

Our results suggest that the use of currently unapproved vaccines could provide comparable protection against symptomatic and more importantly severe COVID-19 infection, without significant safety concerns. This could render the vaccine landscape more competitive, lead the way to wider vaccine access, save millions of lives, and help reduce the risk of new COVID-19 variants.

CONCLUSIONS

In conclusion, our results suggest that approved and unapproved COVID-19 vaccines are comparable in their efficacy and safety profiles. Head-to-head studies and large, real-life observational studies are required to more accurately compare both vaccine types and to assess protection continuity over time.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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