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REVIEW ARTICLE

A Systematic Review of Coronavirus Disease 2019 Vaccine Efficacy and Effectiveness Against Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

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Billions of doses of coronavirus disease 2019 (COVID-19) vaccines have been administered globally, dramatically reducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) incidence and severity in some settings. Many studies suggest vaccines provide a high degree of protection against infection and disease, but precise estimates vary and studies differ in design, outcomes measured, dosing regime, location, and circulating virus strains. In this study, we conduct a systematic review of COVID-19 vaccines through February 2022. We included efficacy data from Phase 3 clinical trials for 15 vaccines undergoing World Health Organization Emergency Use Listing evaluation and real-world effectiveness for 8 vaccines with observational studies meeting inclusion criteria. Vaccine metrics collected include protection against asymptomatic infection, any infection, symptomatic COVID-19, and severe outcomes including hospitalization and death, for partial or complete vaccination, and against variants of concern Alpha, Beta, Gamma, Delta, and Omicron. We additionally review the epidemiological principles behind the design and interpretation of vaccine efficacy and effectiveness studies, including important sources of heterogeneity.

Keywords. COVID-19; SARS-CoV-2; systematic review; vaccine effectiveness; vaccine efficacy.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)'s rapid global spread and alarming clinical severity have accelerated demand for vaccines that safely and effectively prevent disease or reduce severity. To date, 30 coronavirus disease 2019 (COVID-19) vaccines have received emergency use authorization in at least 1 country, and approximately 5 billion people have been vaccinated [1, 2].

Evidence from clinical trials and observational studies overwhelmingly supports the safety and efficacy and/or effectiveness of numerous COVID-19 vaccines, especially against severe disease and death in fully vaccinated individuals. However, precise estimates of vaccine efficacy and effectiveness have varied across studies due to a variety of factors. For example, efficacy against symptomatic COVID-19 for AstraZeneca's 2-dose viral vector vaccine (AZD1222) ranged from 62% to 90% in Phase 3 clinical trials [3], which is attributed to differences in dosing schedules. Observational studies in a variety of settings also produced a wide range of effectiveness estimates (50%–100%) against different clinical outcomes [4–14]. The emergence of SARS-CoV-2 "variants of concern" (VOC), including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529), further confounds interpretation of estimates obtained from comparably designed vaccine studies. Some variants are associated with higher viral load [15–19], evasion of neutralizing antibodies ex vivo [20–25], and lower vaccine effectiveness [13, 19, 26–29]. However, separating diminished protection against a variant from the effects of waning immunity, study methodology, or other contextual factors (eg, lower use of nonpharmaceutical interventions) is complicated by their co-occurrence and endogeneity.

Previous reviews of COVID-19 vaccines have focused mainly on the developmental pathway and early results from preclinical and clinical trials, the immunological basis of vaccine-induced protection, a narrow subset of vaccines or clinical outcomes, or have been rapid in nature and limited to earlier studies [30–47]. There remains an urgent need for comprehensive, up-to-date review of COVID-19 vaccine effects, including real-world evidence. In this study, we systematically reviewed COVID-19

Received 18 January 2022; editorial decision 14 March 2022; accepted 17 March 2022; published online 18 April 2022.

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Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofac138

vaccine efficacy and effectiveness data against multiple clinical outcomes, for both full and partial immunization courses, by circulating SARS-CoV-2 variants of concern. We focused on studies conducted in primarily adult populations, for the primary vaccine course only (ie, excluding "booster" doses), and outcomes measured within the first 6 months after the final vaccine dose.

METHODS

We reviewed studies reporting vaccine "efficacy" (from randomized clinical trials) or "effectiveness" (from observational studies) [48, 49] for vaccines that had received or submitted applications for Emergency Use Listing from the World Health Organization (WHO) as of February 1, 2022 [50] and had at minimum publicly-released data from completed Phase 3 trials (Table 1). We searched for clinical trial results published in peer-reviewed scientific journals (via PubMed) and preprint servers (medRxiv, bioRxiv, SSRN), government public health, regulatory agency, and vaccine manufacturers' websites, and in news articles (Google). Searches were conducted using the vaccine's brand, trade, or research name. For observational studies, we applied detailed queries to multiple databases (Supplementary Methods), and we only included results that appeared in at least a detailed report and/or preprint. Study title and abstract were screened before progressing to full-text review (Supplementary Figure S1). We extracted vaccine efficacy and/or effectiveness against disease endpoints, specifically asymptomatic infection, any infection, symptomatic disease, severe disease (including "hospitalization"), and death (Supplementary Table S1).

Observational studies were only eligible if the comparison group included concurrent individuals (eg, modeled or historic controls were excluded), outcomes were laboratory-confirmed, the study design attempted to account for confounding, vaccination status was determined by self-report for <10% of participants, confidence intervals were reported, no significant bias was present as determined by expert opinion, and controls were unvaccinated (eg, excluded if "unvaccinated" included days 0–12 postvaccination). Only studies comparing persons with and without the clinical outcome under investigation and with and without vaccination were included. Impact studies and studies evaluating progression to severe disease among SARS-CoV-2-positive individuals were excluded. For full immunization (1 or 2 doses, depending on the vaccine) results were included if at least 1 week had passed between the final dose and case detection; for partial immunization, cases must have occurred at least 2 weeks after dose 1 but before dose 2. We excluded efficacy and/or effectiveness values for which (1) follow-up period after final dose was >6 months, (2) doses beyond the primary series were given (ie, boosters), or (3) multiple vaccines were combined. We classified efficacy and/or effectiveness against specific SARS-CoV-2 variants if sequencing (or other molecular methods) either (1) confirmed the variant in all cases contributing to the estimate or (2) confirmed the variant caused the vast majority of cases in sample of study participants or of the larger population from which they came. Our data are available on *VIEW-hub*, a weekly updated resource developed by Johns Hopkins' International Vaccine Access Center (https://view-hub.org/resources), and in Supplementary Table S1.

EPIDEMIOLOGICAL PRINCIPLES

Measuring How Well a Vaccine Prevents Infection and Disease

Vaccine efficacy is evaluated in randomized controlled trials (RCTs) and is defined as the relative reduction in the probability of developing disease in a particular time period in vaccinated individuals compared with unvaccinated individuals. In RCTs, subjects are randomly assigned to receive the vaccine or not (instead usually receiving a placebo or another vaccine). Vaccine efficacy (VE) is calculated using the formula:

$$\begin{aligned} VE &= 1 - \frac{\#cases\ among\ vaccinated / \#vaccinated}{\#cases\ among\ unvaccinated / \#unvaccinated} \\ &= 1 - \frac{risk\ in\ vaccinated\ group}{risk\ in\ unvaccinated\ group}, \end{aligned}$$

where sometimes the denominator "# vaccinated" ("# unvaccinated") is replaced with the sum of the total time enrolled in the study among vaccinated (unvaccinated) subjects (ie, the "person time") [51, 52]. Although RCTs are the gold standard for vaccine studies [53], they are costly and generally too small to evaluate rare outcomes (eg, death).

Vaccine efficacy describes the "relative", as opposed to "absolute", risk of disease. This is a desired feature of a metric for vaccine strength, because absolute risk may change over time as the background disease incidence changes during an epidemic due to factors such as seasonality and behavior change. For example, if the absolute risk of disease in one setting is reduced from 50% to 10% through vaccination, then the vaccine efficacy (80%) is the same as in another setting where the absolute risk was reduced from 5% to 1%. The value of vaccine efficacy also does not tell us whether vaccine failure occurs in a "leaky" or "all-or-nothing" way [52, 54, 55].

Once a vaccine is shown to be safe and efficacious in clinical trials and is authorized for general use, further RCTs to evaluate efficacy under new conditions or in special populations are often considered unethical or impractical, especially in the setting of a wide-spread epidemic, because it necessitates withholding vaccines from people who might benefit from them. Instead, observational studies evaluating real-world effectiveness are used to augment efficacy trials, and they include designs such as case-control studies (including test-negative designs) and cohort studies (prospective or retrospective) [52, 56, 57]. Although observational studies must carefully address biases due to differences in those who chose to or were eligible to receive vaccines compared with those who did not, they

Table 1. Status of COVID-19 Vaccines Within the World Health Organization Emergency Use Listing Evaluation Process[a]

Vaccine Name		Vaccine Type	WHO Status	Countries		Phase 3 Efficacy Trial			Ref
				Developed in	No. Approved	Data?	CIs?	Peer Reviewed?	
AstraZeneca/ Oxford	AZD1222 ChAdOx1-nCoV-19 Vaxzevria Covishield	Viral vector	EUL Authorized	UK	162	Yes	Yes	Yes	[3, 68, 82, 86]
Pfizer/ BioNTech	BNT162b2 Comirnaty Tozinameran	mRNA	EUL Authorized	Germany	134	Yes	Yes	Yes	[64, 71, 88]
Janssen/ Johnson & Johnson	Ad26.COV2.S	Viral vector	EUL Authorized	USA	105	Yes	Yes	Yes	[66]
Sinopharm-Beijing	BBIBP-CorV Covilo	Inactivated virus	EUL Authorized	China	87	Yes	Yes	Yes	[89]
Moderna	mRNA-1273 Spikevax	mRNA	EUL Authorized	USA	85	Yes	Yes	Yes	[67]
Gamaleya Institute	Sputnik V Gam-COVID-Vac	Viral vector	Submission in Progress	Russia	74	Yes	Yes	Yes	[72]
Sinovac	CoronaVac	Inactivated virus	EUL Authorized	China	52	Yes	Yes	Yes	[73, 74, 90]
Novavax	NVX-CoV2373 Nuvaxovid Covovax	Protein subunit	EUL Authorized	USA	31	Yes	Yes	Yes	[70, 83, 223]
Bharat Biotech	BBV152 Covaxin	Inactivated virus	EUL Authorized	India	13	Yes	Yes	Yes	[65]
CanSinoBIO	Ad5-nCoV Convidecia	Viral vector	EOI Accepted	China	10	Yes	Yes	Yes	[75]
BioCubaFarma	Abdala CIGB-66	Protein subunit	Submission in progress	Cuba	6	Yes	Yes	No	[91]
BioCubaFarma	Soberana 02 FINLAY-FR-2	Conjugate	Submission in progress	Cuba	4	Yes	Yes	No	[92]
Vector Institute	EpiVacCorona	Protein subunit	Submission in Progress	Russia	4	No	No	No	
Anhui Zhifei Longcom	ZF2001 ZIFIVAX	Protein subunit	EOI accepted	China	3	Yes	No	No	
Sinopharm-Wuhan	WIBP-CorV	Inactivated virus	EOI accepted	China	2	Yes	Yes	Yes	[89]
IMBCAMS	Covidful	Inactivated virus	Submission in progress	China	1	No	No	No	
BioCubaFarma	Soberana 02+ FINLAY-FR-1A	Protein subunit	Submission in progress	Cuba	1	Yes	Yes	No	[92]
Clover	SCB-2019	Protein subunit	EOI accepted	China	0	Yes	Yes	Yes	[76]
CureVac	CVnCoV	mRNA	EOI accepted/ withdrawn	Germany	0	Yes	Yes	Yes	[224]
Sanofi	CoV2 preS dTM-AS03 Vidprevtyn	Protein subunit	EOI accepted	France	0	No	No	No	

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; EOI, expression of interest; EUL, emergency use listing; WHO, World Health Organization.

[a]Vaccine products are listed in descending order based on the number of countries in which the vaccine is approved for emergency use as of February 2022. Vaccines included in the current study—based on availability of efficacy data from Phase 3 clinical trials—are highlighted in gray. Vaccine details were obtained from McGill University's COVID-19 Vaccine Tracker: https://covid19.trackvaccines.org/, which aggregates data from multiple sources. Original source for the WHO. EUL status: https://extranet.who.int/pqweb/key-resources/documents/status-covid-19-vaccines-within-who-eulpq-evaluation-process.

may provide a more realistic picture of population heterogeneity and include more high-risk groups compared with RCTs. During massive vaccination campaigns like those occurring for COVID-19, observational studies can have much larger sample sizes.

To measure vaccine efficacy and/or effectiveness, the specific clinical outcome that the vaccine is meant to prevent must be carefully defined. The ideal goal of vaccination is to completely prevent infection (and thus disease and transmission), meaning that vaccine-induced immunity blocks the earliest attempts of the pathogen to replicate within the body. This "sterilizing immunity" is rare, and vaccine efficacy and/or effectiveness against infection is difficult to measure [58, 59] for short-lived and commonly asymptomatic infections like SARS-CoV-2 because it requires frequent testing of the study cohort. To reduce the public health impact of an infectious disease, prevention of severe disease (including hospitalization and death) is desired, even if infection still occurs [53, 59, 60]. However, because most individuals with COVID-19 recover completely with only mild or moderate symptoms [61–63], studies of severe outcomes can require hundreds of thousands of participants or months to years of observation time. For COVID-19, the primary endpoint for most clinical trials was symptomatic, laboratory-confirmed COVID-19 disease [53], defined as the occurrence of COVID-19-associated symptoms (eg, cough, shortness of breath, fever) in the presence of detectable SARS-CoV-2. This outcome choice represents a trade-off between public health importance and practicality. Symptomatic disease is on the spectrum leading to severe disease but much more common, and testing can be restricted to those self-reporting symptoms. Although some trials reported efficacy against severe disease as secondary outcomes despite small numbers [64–76], large observational studies provide more precise estimates.

Sources of Heterogeneity Across Studies

The COVID-19 vaccine studies were conducted by many independent research teams in diverse epidemic settings around the world (Table 1, Table 2, Supplementary Table S1, Figure 1). As a result, there are several potential sources of heterogeneity between studies that make comparing vaccine efficacy and/or effectiveness estimates difficult [57, 77]:

- Study population: Efficacy/effectiveness can be lower in studies including more participants at high risk of disease (eg, comorbid individuals) or with reduced immune function (eg, people with human immunodeficiency virus).
- Outcome and case definition: Vaccine efficacy and/or effectiveness differs between disease outcomes with varying severity. Even when studies have the same stated outcome, the case definition can vary substantially. For example, most clinical trials used "symptomatic COVID-19 disease" as the primary outcome, but included anywhere from 5 (for AstraZeneca/AZD1222 [3]) to 16 (Janssen/Ad26.COV2.S [66]) different potential symptoms, and varied in requiring 1 or 2 to be present. These differences are exacerbated in effectiveness studies that often rely on passive surveillance by health systems. In addition, different definitions in the timing of the disease outcome (eg, death within 30 days after diagnosis) can lead to heterogeneities.
- Follow-up period: Because developing an adaptive immune response after vaccination takes time [59, 78–80], studies that begin the follow-up period sooner could observe lower efficacy and/or effectiveness (eg, 7+ days for Novavax/NVX-CoV2373 [70] vs 28+ days for Janssen/Ad26.COV2.S [66]). In addition, if immune protection wanes, studies with longer follow-up could have lower estimates.
- Predominant variants: Some SARS-CoV-2 variants of concern have been observed to exhibit immune-escape properties [21, 81] (eg, Beta [28, 82–84], Delta [13, 19, 65], Omicron [26, 27, 29]). Studies conducted when such variants account for a large proportion of infections could have lower efficacy and/or effectiveness (Figure 1).
- Study design and analysis: To make up for lack of randomization, vaccine effectiveness studies can attempt to reduce confounding through study design (eg, the test-negative design) and during analyses (eg, controlling for potential confounding variables in regression models). Some studies, especially those that use administrative data, may not collect and therefore cannot control for such possible confounders.

Other reviews of COVID-19 vaccine efficacy and/or effectiveness have tended to summarize results from studies with different designs, participant pools, and settings with a single effectiveness value or range, sometimes via formal meta-analysis [36, 37, 39, 41, 42, 44, 47, 85]. In this study, we have taken a different approach and show individual efficacy and/or effectiveness measures and their sources, and we discuss reasons for the observed heterogeneity, while also highlighting the consensus that emerges among them.

RESULTS OF CORONAVIRUS DISEASE 2019 VACCINE STUDIES

Data Available From Clinical Trials of Vaccine Efficacy

As of February 3, 2022, 20 unique vaccine products were in the WHO Emergency Use Listing (EUL) evaluation process, including messenger ribonucleic acid (mRNA), viral vector, inactivated virus, protein subunit, and conjugate vaccine platforms, and were developed by a mix of pharmaceutical companies, nonprofit research institutes, and government agencies (Table 1). Eight vaccines representing 4 platforms had received authorization. Efficacy estimates with uncertainty intervals from Phase 3 clinical trials were publicly available for 15 of the 20 vaccine candidates in 22 separate reports [3, 64–70, 72–76, 82, 83, 86–92] (Figure 2, Supplementary Figure S1). Vaccine

Table 2. Summary of Vaccine Effectiveness Studies[a]

	Vaccine								
	BNT162b2 (Pfizer-BioNTech)	mRNA-1273 (Moderna)	AZD1222 (AstraZeneca-Oxford)	Ad26.COV2.S (Janssen/Johnson & Johnson)	Sputnik V (Gamaleya)	CoronaVac (Sinovac)	BBV152 (Bharat)	BBIBP-CorV (Sinopharm-Beijing)	All
Total	86	39	30	16	1	6	1	2	107
Outcome Type									
Death	12	6	5	6	1	4	0	1	21
Severe disease	38	19	12	10	0	3	0	1	50
Symptomatic disease	28	12	12	4	0	3	1	0	38
Asymptomatic infection	5	3	1	0	0	0	0	0	9
Any infection	58	25	14	7	1	2	0	1	67
Population Type									
General population	40	26	15	9	1	2	0	2	45
Health care workers	18	4	1	1	0	0	1	0	20
Older adults (≥60 years)	8	0	8	1	0	2	0	0	11
Other age groups	6	3	3	2	0	0	0	0	7
Contacts of cases	6	2	3	2	0	0	0	0	6
LTCF/SNF residents	5	1	1	0	0	0	0	0	5
Other groups	6	3	1	1	0	2	0	0	9
Study Design									
Test-negative case control	30	21	13	7	0	3	1	1	42
Traditional case-control	4	1	0	0	0	0	0	0	3
Prospective cohort	17	4	7	1	0	1	0	0	21
Retrospective cohort	36	13	9	8	1	2	0	1	41
No. of Doses									
Complete	76	36	19	16	1	6	1	2	96
Partial	44	14	25	N/A	0	3	1	0	53
Variants of Concern									
Alpha	33	8	17	2	1	0	1	0	35
Beta	4	2	1	1	0	0	0	0	6
Gamma	2	2	3	1	0	1	0	0	5
Delta	22	13	9	5	0	1	1	0	29
Omicron	4	4	0	0	0	0	0	0	5

Abbreviations: COVID-19, coronavirus disease 2019; LTCF, long-term care facility; N/A, not applicable; SNF, skilled nursing facility.

[a]Number of included studies by COVID-19 vaccine and by outcome, population, study design, number of doses, and variant of concern. No studies reported for other vaccine candidates met our inclusion criteria (see Methods). Details of all the individual studies are included in Supplementary Table S1.

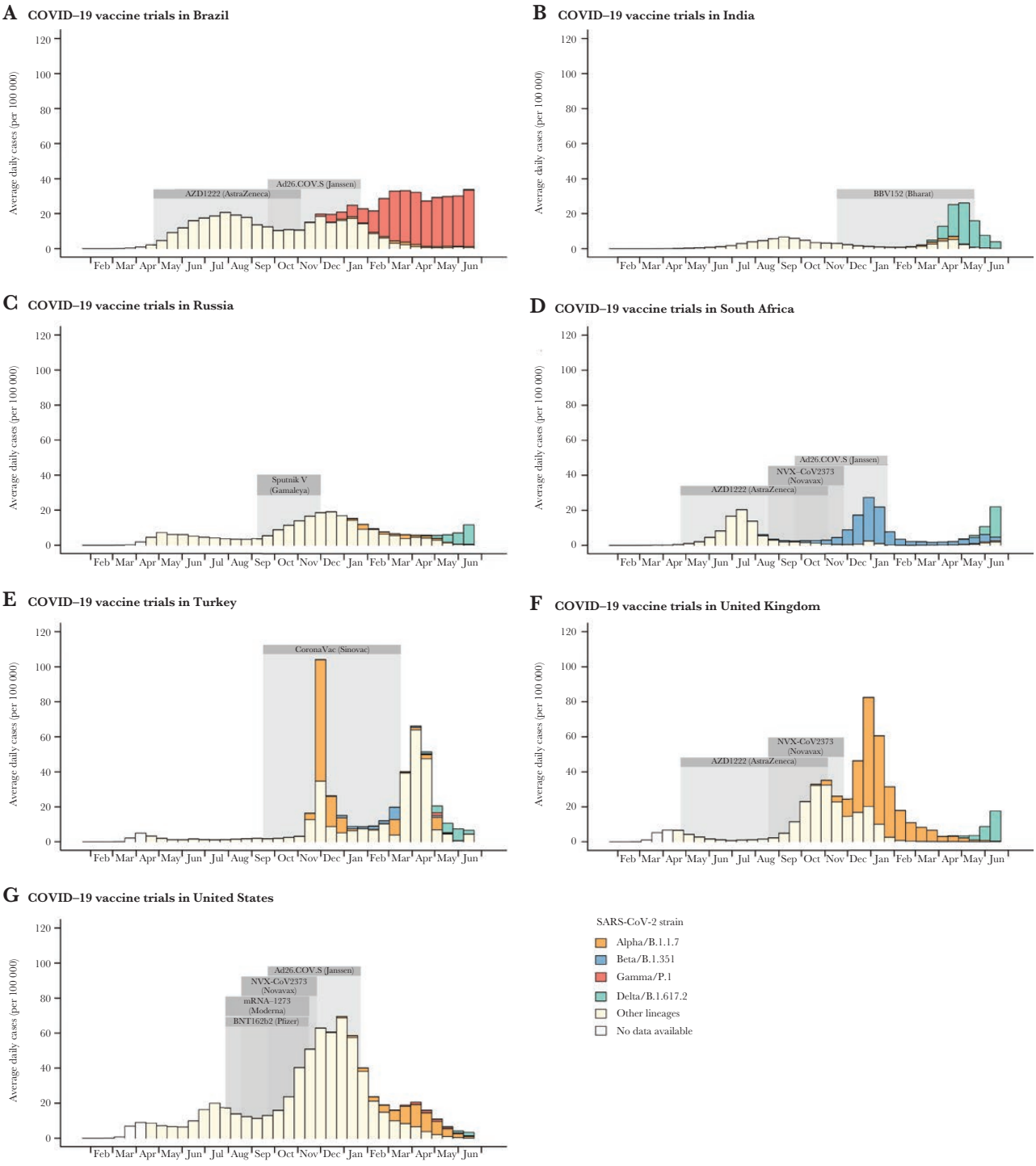

Figure 1. Local context of Phase 3 clinical trials of coronavirus disease 2019 (COVID-19) vaccines. For each country, the time period (2020-2021) during which outcomes were observed during each vaccine trial is shaded gray. For each 2-week period, the average daily incidence of reported cases is shown (height of bars) [225]. The contribution of each major variant of concern to total case counts is estimated from the reported fraction of sequenced severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) samples belonging to that strain (fill color) [226]. Figure includes only vaccine trials described in published or preprint reports, trial sites with at least 10 000 individuals from the general adult population, and countries regularly reporting SARS-CoV-2 lineages to the GISAID database.

efficacy against symptomatic COVID-19 was available for all 15 vaccines, ranging from 58% to 95%, with highest efficacy (>90%) from 6 products representing mRNA, protein subunit, and viral vector platforms. Efficacy against any infection was available for 5 EUL-authorized vaccines and against severe disease for 6, although confidence intervals (CIs) for severe disease

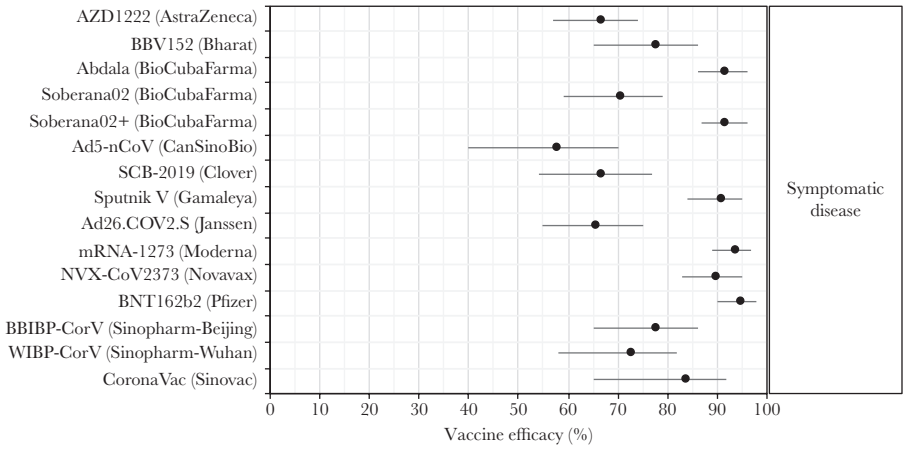

Figure 2. Vaccine efficacy against symptomatic coronavirus disease 2019 (COVID-19), from Phase 3 clinical trials. Each efficacy value is for the complete vaccine course (1 dose for Ad26.COV2.S/Janssen and Ad5-nCoV/CanSinoBio, 3 doses for BioCubaFarma/Abdala and Soberana02+/BioCubaFarma, and 2 doses for all others). Two vaccines which withdrew from the World Health Organization Emergency Use Listing evaluation process but completed Phase 3 trials were not included (CureVac's mRNA vaccine CVnCoV, reporting 48% efficacy [224], and Kazakhstan RIBSP's inactivated virus vaccine QazCovid-in, reporting 82% efficacy [227]).

tended to be wide due to limited sample sizes and trial durations (Figures 3–7, Supplementary Table S1).

Data Available From Observational Studies of Vaccine Effectiveness

We identified 107 real-world vaccine effectiveness studies that met our inclusion criteria [4–14, 19, 26–29, 38, 84, 93–179]. These studies covered 8 vaccines: 7 with WHO EUL authorization (all but Novavax's NVX-CoV2373) and 1 with EUL submission in progress (Gamaleya's Sputnik V) (Table 2, Supplementary Figure S1, Supplementary Table S1). These observational studies provided metrics not reported in clinical trials for some vaccines, including effectiveness against severe outcomes, asymptomatic infection, any infection, specific circulating variants, and effectiveness of a single dose of 2-dose vaccines (Figures 3–7). In general, effectiveness estimates overlapped with efficacy estimates and were high for full vaccine courses. Vaccines were more effective at preventing severe infection or death compared with symptomatic COVID-19. The degree to which vaccines prevented any infection, and the degree to which partial courses prevented infection or disease, varied widely by product. Data were sparse for effectiveness against death or asymptomatic infection and the Gamma variant.

Efficacy and/or Effectiveness of Messenger Ribonucleic Acid Vaccines

The most data were available for BNT162b2, the 2-dose mRNA vaccine developed by Pfizer/BioNTech, mainly due to its early 2021 use in Israel, the United Kingdom, and the United States (Figure 3). Efficacy and/or effectiveness estimates after 2 doses in the general population, pre-Omicron, ranged from 90% to 99% for death, 80% to 100% for severe infection, 70% to 100% for symptomatic disease, 65% to 98% for any infection, and 65% to 90% for asymptomatic infection. These values were lower after only a single dose: 70%–90% for death, 55%–95% for severe infection, 35%–93% for symptomatic disease, and 30%–80% for any infection. Some studies found lower effectiveness in special populations, including residents of long-term care facilities [84, 149, 150], priority groups [122], the elderly [147], and those previously infected [113, 179]. Heterogeneities between studies made direct comparisons of efficacy and/or effectiveness for variants difficult. A few studies with head-to-head comparisons suggested slightly reduced effectiveness for BTN162b2 against Beta and Delta compared with Alpha or non-VOC, for symptomatic cases or any infection [13, 28, 96, 123, 145, 162]. Evidence for reduced effectiveness against Omicron was more pronounced, with protection dropping to ~70% for severe disease, ~65% for symptomatic disease, and ~55% for any infection [26, 27, 136].

The other authorized 2-dose mRNA vaccine, Moderna's mRNA-1273, was also relatively well studied, largely using data from the United States, Canada, and Qatar (Figure 4). After dose 2, efficacy and/or effectiveness estimates in the general population (pre-Omicron) were between 94% and 99% for death, 85% and 100% for severe disease, 87% and 100% for symptomatic disease, 83% and 100% for any infection, and 73% and 93% for asymptomatic infection. With only a single dose, values were 60%–95% for severe disease, 60%–95% for symptomatic disease, 65%–95% for any infection, and 45%–60% for asymptomatic infection. Studies in the United Kingdom, United States, and Denmark [27, 29, 136] estimated effectiveness against the Omicron variant after 2 doses was reduced to ~75% for symptomatic infection and to 30%–40% for any infection. Some evidence for reduction in effectiveness against infection or severe disease with Beta after only 1 dose was observed in studies in Canada and Qatar [12, 114]. Significant reductions were not consistently reported for effectiveness against other VOC.

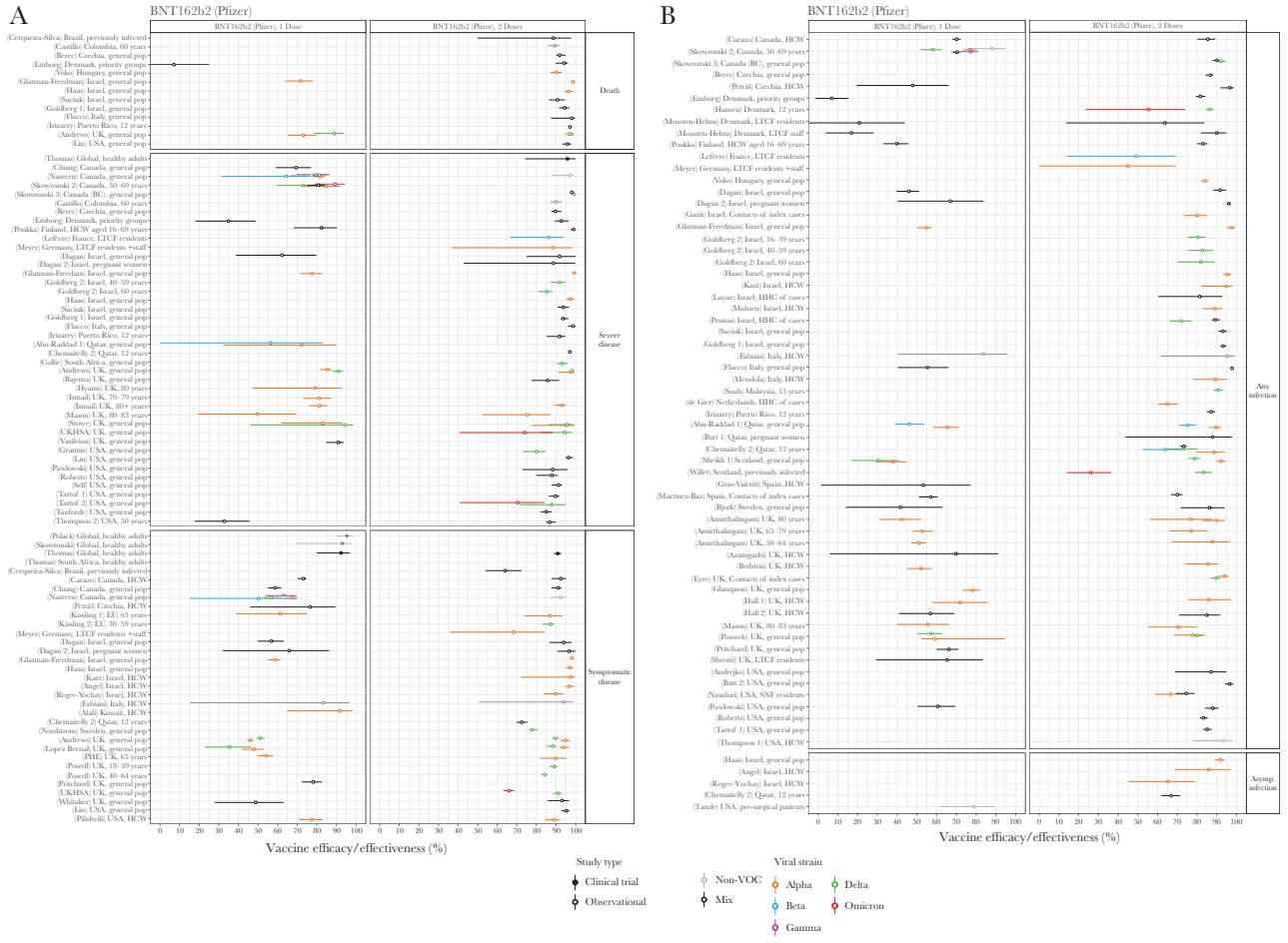

Figure 3. Vaccine efficacy and effectiveness estimates for BNT162b2, a 2-dose mRNA vaccine developed by Pfizer/BioNTech. (A) Efficacy and/or effectiveness against death, severe disease, or symptomatic disease. (B) Efficacy and/or effectiveness against any or asymptomatic infection. Estimates are colored by the viral variant against which the vaccine efficacy or effectiveness value was measured. Solid markers are estimates from randomized clinical trials (efficacy values), and open markers are estimates from observational studies (effectiveness values). The source of each estimate is given by the labels on the left side ("(reference number) Country, population"). Within each disease severity level, estimates are ordered alphabetically by country and then by population.

Efficacy and/or Effectiveness of Viral-Vector Vaccines

AstraZeneca's 2-dose viral vector vaccine (AZD1222) was also frequently studied, especially after only 1 dose, likely because the recommended interval between doses is longer than other vaccines (12 weeks) and some countries including the United Kingdom and Canada adopted the strategy of prioritizing first doses over second doses in early 2021 (Figure 5). Efficacy and/or effectiveness against non-VOC strains, the Alpha variant (predominant during most studies), or mixes of strains after 2 doses was 85%–100% for death or severe disease, 65%–100% for symptomatic disease, 60%–80% for any infection, and 22% for asymptomatic infection in the general population. After a single dose, efficacy and/or effectiveness was 80%–96% for death, 75%–92% for severe disease, 45%–75% for symptomatic disease, and 35%–95% for any infection. The Delta variant appeared to reduce effectiveness against symptomatic disease or infection compared with the earlier Alpha variant by 10%–15% after 2 doses and ~20%–30% after a single dose in some [13, 19, 96, 145, 171] but not all [12, 123] studies. Effectiveness against the Gamma variant was within the range of earlier strains. Clinical trial evidence from the South Africa site [82] suggested loss of efficacy against symptomatic infection with the Beta variant but with much uncertainty (efficacy 10% CI, <0–55). No studies meeting our inclusion criteria reported on the protection that AZD1222 alone provided against the Omicron variant.

Janssen's Ad26.COV2.S single-dose viral vector vaccine was studied in a variety of settings around the world (Figure 6), with efficacy and/or effectiveness estimates of 70%–100% against death, 60%–90% for severe disease, 50%–80% for symptomatic disease, 50%–80% for any infection, and 65% for asymptomatic infection. Protection against infection or severe outcomes appeared to be preserved with SARS-CoV-2 variants of concern, although confidence intervals were extremely wide and no data for Omicron were available meeting inclusion criteria.

Data were sparse for Gamaleya Institute's 2-dose viral vector vaccine Sputnik V (Figure 6), despite its use in dozens

Figure 4. Vaccine efficacy and effectiveness estimates for mRNA-1273, a 2-dose mRNA vaccine developed by Moderna. Estimates are colored by the viral variant against which the vaccine efficacy or effectiveness value was measured. Solid markers are estimates from randomized clinical trials (efficacy values), and open markers are estimates from observational studies (effectiveness values). The source of each estimate is given by the labels on the left side ("(reference number) Country, population"). Within each disease severity level, estimates are ordered alphabetically by country and then by population.

of countries (Table 1). A single clinical trial estimated efficacy against symptomatic disease with non-VOC virus of 91% [72], whereas an observational study in Hungary in the context of the Alpha variant reported effectiveness of 98% against death and 88% against any infection [178]. No studies measuring protection against the Beta, Delta, or Omicron variant met our inclusion criteria.

Efficacy and/or Effectiveness of Inactivated Virus Vaccines

Estimates of vaccine efficacy and effectiveness were available for 3 different 2-dose inactivated virus vaccines: CoronaVac (Sinovac), BBIBP-CorV (Sinopharm-Beijing), and BBV152 (Bharat) (Figure 7). Effectiveness studies of Sinovac's inactivated virus vaccine CoronaVac were available from only 6 studies, despite being one of the most widely used vaccines worldwide. These complemented results from 3 separate clinical trials, including one restricted to healthcare workers. After 2 doses, in the general population, efficacy and/or effectiveness was 86% against death, 88%–100% against severe disease, 65%–85% against symptomatic disease, and 65%–75% against any infection. With only 1 dose, these values were significantly reduced, to 46% for death, 37% for severe disease, and 16% for any infection. Lower values were reported in studies in older adults, including one study conducted in adults over 70 years old in

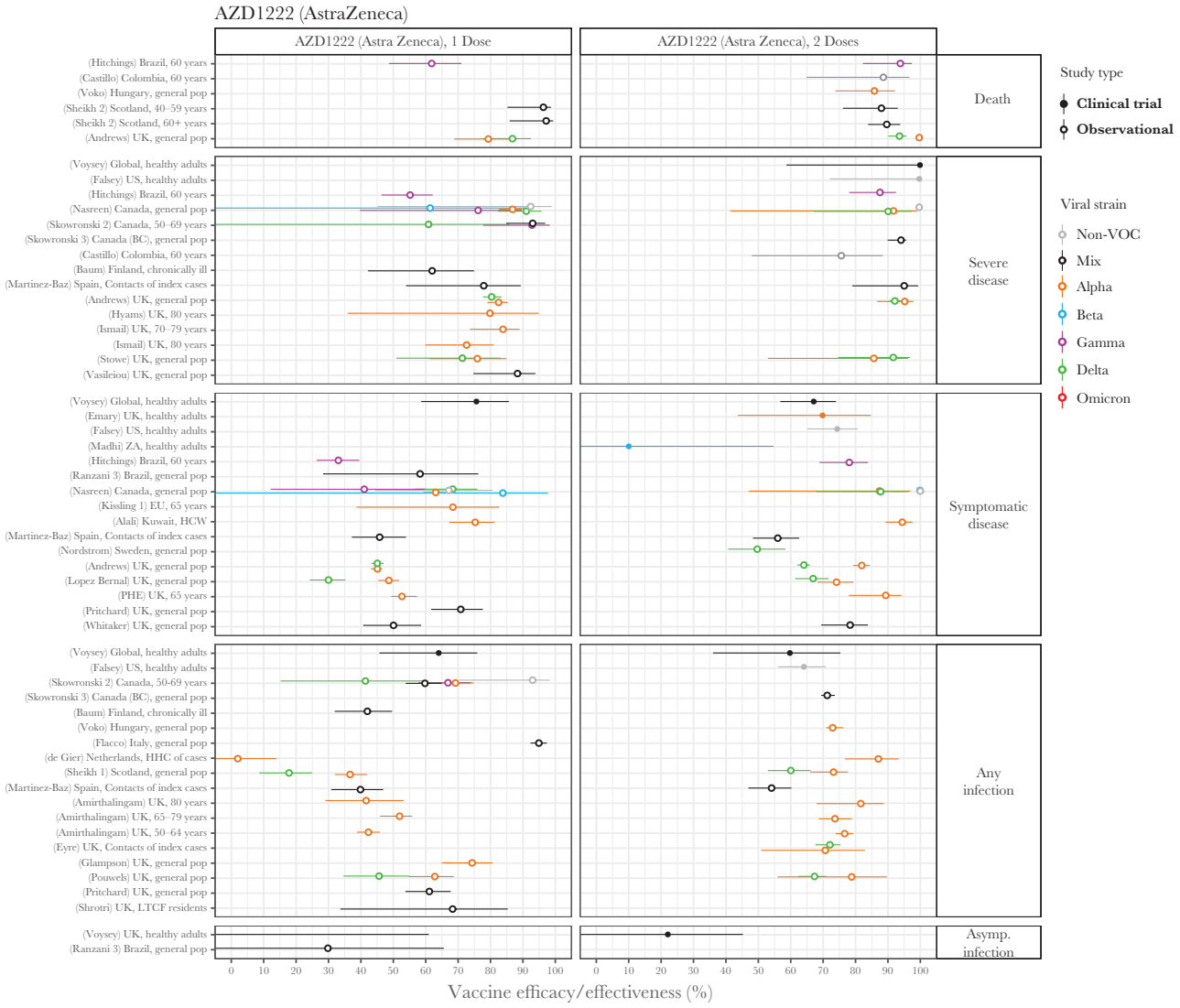

Figure 5. Vaccine efficacy and effectiveness estimates for AZD1222, a 2-dose viral vector vaccine developed by AstraZeneca. Estimates are colored by the viral variant against which the efficacy or effectiveness value was measured. Solid markers are estimates from randomized clinical trials (efficacy values), and open markers are estimates from observational studies (effectiveness values). The source of each estimate is given by the labels on the left side ("(reference number) Country, population"). Within each disease severity level, estimates are ordered alphabetically by country and then by population.

Brazil during a time when Gamma was predominant [163]. The only other variant-specific study suggested effectiveness against any infection was preserved against the Delta variant [180]. Sinopharm-Beijing's BBIBP-CorV could only be assessed after both doses and using 2 observational studies [104, 178] and a single clinical trial [89]. Efficacy and/or effectiveness was 86% for death, 88% for severe disease, 78% for symptomatic disease, and 74% for any infection. The only information on variant-specific protection came from the study from Hungary, which was conducted during a time when the Alpha variant dominated, and suggested that protection against any infection was similar to non-VOC strains. Bharat's BBV152 was evaluated in only a single effectiveness study in healthcare workers [121] in addition to the initial Phase 3 trial [65]. Efficacy was 93% for severe disease, 78% for symptomatic disease, 69% for any infection, and 64% for asymptomatic infection. The RCT suggested that protection against symptomatic disease with the Delta variant was reduced by 10-15 percentage points, whereas the observational study suggested <50% effectiveness against Delta after 2 doses and none after only 1 dose.

Efficacy and/or Effectiveness of Other Vaccines

Although at the time of writing there were at least 10 other COVID-19 vaccines that had received emergency authorization for widespread use in at least 1 country, we did not identify effectiveness studies that met our inclusion criteria.

DISCUSSION

The development of COVID-19 vaccines has been an astounding feat of science. Within 1 year of detecting the first

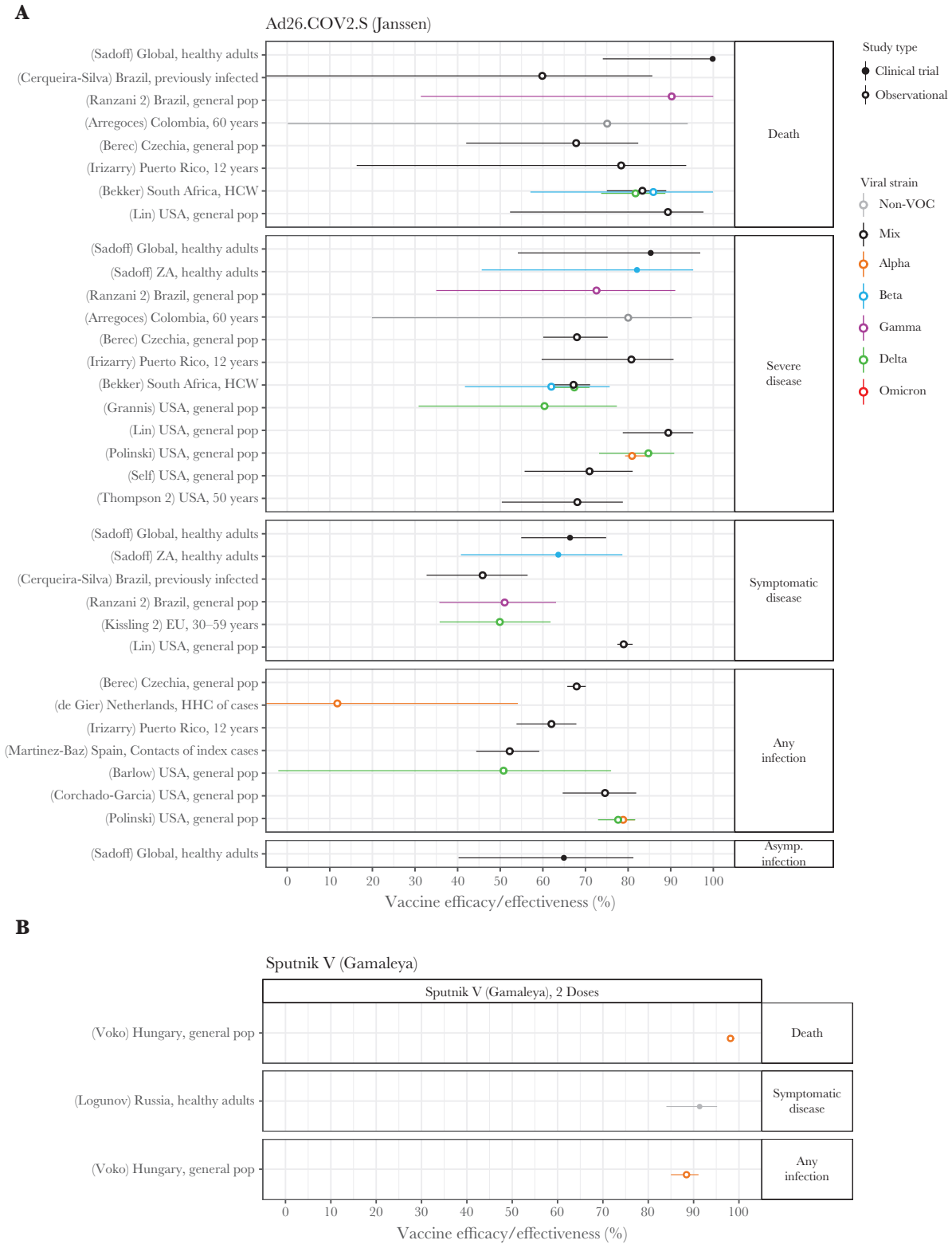

Figure 6. Vaccine efficacy and effectiveness estimates for 2 viral vector vaccines: (A) Ad26.COV2.S, a single-dose vaccine developed by Janssen/Johnson & Johnson, and (B) Sputnik V, a 2-dose vaccine developed by Gamaleya Institute. Estimates are colored by the viral variant against which the efficacy or effectiveness value was measured. Solid markers are estimates from randomized clinical trials (efficacy values), and open markers are estimates from observational studies (effectiveness values). The source of each estimate is given by the labels on the left side ("(reference number) Country, population"). Within each disease severity level, estimates are ordered alphabetically by country and then by population.

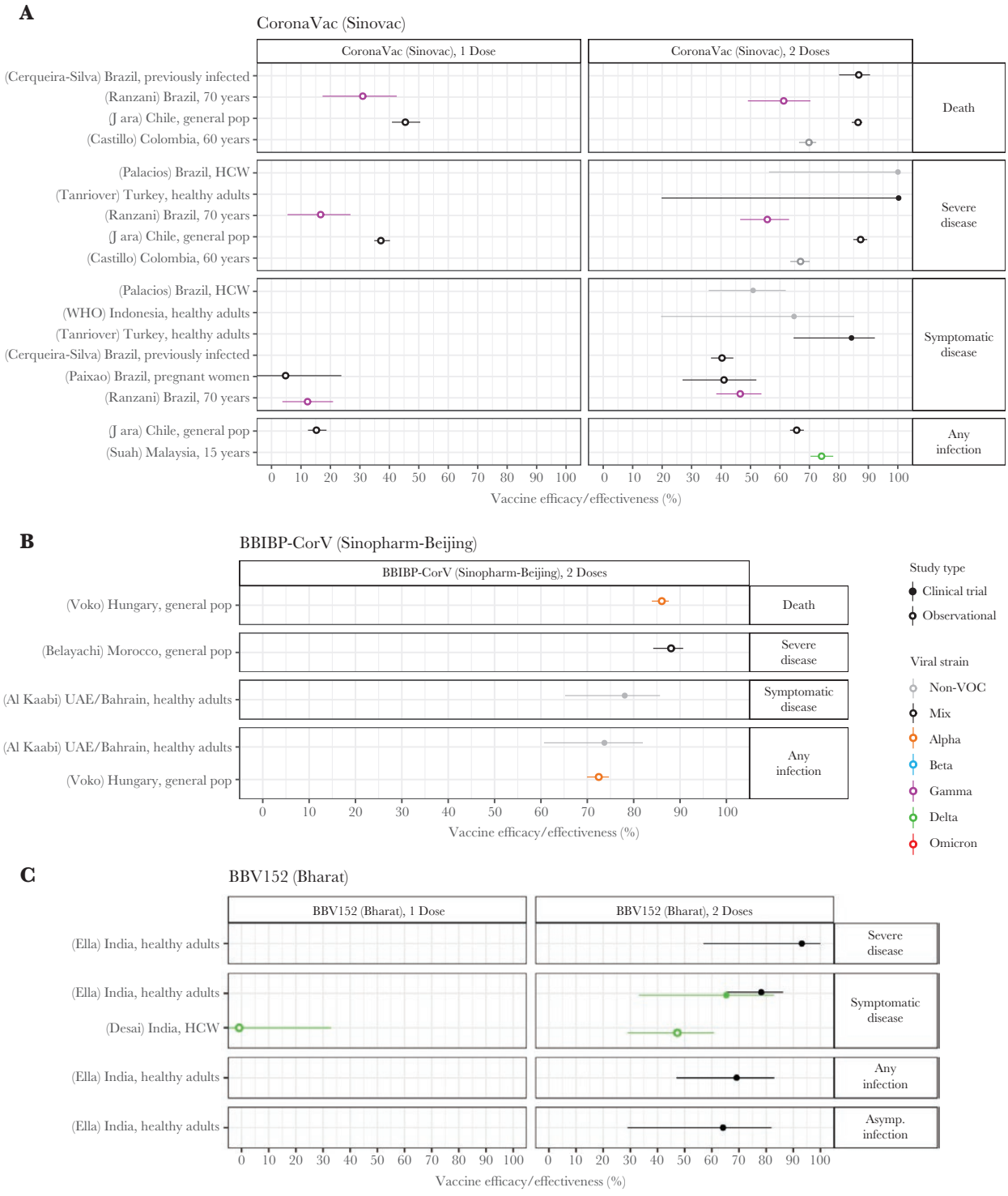

Figure 7. Vaccine efficacy and effectiveness estimates for three 2-dose inactivated virus vaccines: (A) CoronaVac, developed by Sinovac (B) BBIBP-CorV, developed by Sinopharm Beijing, and (C) BBV152, developed by Bharat Biotech. Estimates are colored by the viral variant against which the efficacy or effectiveness value was measured. Solid markers are estimates from randomized clinical trials (efficacy values), and open markers are estimates from observational studies (effectiveness values). The source of each estimate is given by the labels on the left side ("(reference number) Country, population"). Within each disease severity level, estimates are ordered alphabetically by country and then by population.

outbreak and isolating the SARS-CoV-2 virus, multiple vaccines were deployed around the world. In this review, we systematically collected efficacy and effectiveness values by vaccine platform, disease outcome, number of doses, and SARS-CoV-2 variant. These findings demonstrate robust evidence for the high efficacy of COVID-19 vaccines in clinical trials and high

effectiveness in real-world settings. We found that across all vaccine platforms, protection against severe infection or death in the general population was at least 60% and most often close to 100%. Efficacy and/or effectiveness against symptomatic disease was heterogeneous between vaccine products and studies but was almost always greater than 50% and often greater than 90%. The vast majority of studies showed that vaccines provided protection against infection—not just disease—demonstrating the potential for indirect protective effects ("herd immunity") via reduced transmission. The degree of protection offered by only a single dose of 2-dose vaccine courses varied by product. Most vaccines retained high levels of protection for most SARS-CoV-2 variants, especially against severe outcomes. Some studies provided evidence of slight reductions in efficacy and/or effectiveness for infection or mild disease with the Beta and Delta strains for some vaccines. Although few studies of the Omicron variant were available at publication time, the available evidence supports larger reductions in protection against both mild and severe infection.

There are several important components of COVID-19 vaccine efficacy and/or effectiveness not addressed here. Vaccine-induced protection can wane over months or years [59, 60, 78, 79, 181]. Although all estimates reviewed here were restricted to within 6 months of vaccination, waning is a critical issue to monitor for COVID-19 vaccines. A recent meta-analysis estimated efficacy and/or effectiveness drops ~10% for severe disease and ~20% for infection over 5 months [85]. These drops appear to be more extreme for the Omicron variant; nevertheless, evidence suggests booster doses—administered in many countries during Fall/Winter 2021—enhance immunogenicity and effectiveness [20, 26, 27, 29, 136, 182, 183]. However, the WHO stresses prioritization of primary doses globally [184].

Unvaccinated individuals previously infected with SARS-CoV-2 have some protection against reinfection, which is estimated in recent study to be ~90% [185, 186]. As a result, including previously infected persons in the unvaccinated group of studies could bias estimates of effectiveness downward. As an alternative, if prior immunity synergizes with vaccine-induced immunity to enhance protection, this bias could be in the opposite direction. Of 107 observational studies included in this review, 33 are known to have included persons with previous SARS-CoV-2 infection. For studies that stratified efficacy and/or effectiveness estimates by prior infection status, results were mixed, finding higher, lower, or unchanged values in previously infected individuals [107, 187].

For multidose vaccine regimens, the time interval between doses may affect protection. Efficacy of AZD1222 (AstraZeneca) increased from 55% with <6 weeks between doses to 81% with >12 weeks [3]. In real-world settings, dose interval sometimes varied due to policies of delaying second doses in favor of universal partial vaccination [188, 189], allowing for evaluation of its impact on neutralizing antibody levels and effectiveness [6, 19, 190].

Although most vaccine manufacturers and international advisory committees (including WHO [191]) initially recommended all doses be with the same product, many countries allowed for "mixing and matching" of doses [192–194]. Effectiveness studies have shown that boosting AZD1222 with either mRNA vaccine increases neutralizing antibody levels compared with 2 doses of AZD1222 alone [195–199], and this is also more effective against preventing infection [153, 171, 200]. Further evaluation is needed to understand which COVID-19 vaccine combinations are safe and effective.

For an individual, the goal of vaccination against COVID-19 is to prevent disease, but from a population perspective, there is an additional goal to reduce transmission, which can eliminate the need for complete vaccine coverage. Some studies have observed a reduction in transmission in vaccinated individuals infected with SARS-CoV-2 [201] by testing close contacts of cases [10, 123, 143, 149, 162, 202–204]. Others have reported reductions in viral load in the respiratory tract—expected to be a determinant of infectiousness—in vaccinated (versus unvaccinated) cases [19, 166, 176, 205].

At this time, approval of new COVID-19 vaccines typically requires Phase 3 trials directly measuring vaccine efficacy. However, as vaccine availability increases in the face of an ongoing epidemic, further placebo-controlled trials may be considered impractical or unethical. Instead, new vaccines or immunization schedules will likely be evaluated using "immunobridging": indirectly inferring vaccine efficacy by measuring immunological biomarkers (like neutralizing antibody levels) identified as correlates of protection [53, 55, 206–208]. Such study designs—not reviewed here—have already been used for early assessment of waning rates [207, 209], identifying potential loses in protection against new variants [24, 25, 210], promoting the need for booster doses [24, 25, 211, 212], justifying heterologous vaccine courses [212, 213], expanding eligible age groups to children [214, 215], and to grant initial emergency approval to some vaccines (eg, Medigen's MVC-COV1901 in Taiwan [216]). As preapproval efficacy trials become rarer, postauthorization vaccine effectiveness studies will become even more important.

Although our review focused on studies conducted in adults, some countries have now expanded vaccination campaigns to include children as young as 2 years old [217, 218]. Limited studies suggest that comparable safety, immunogenicity, efficacy, and effectiveness to adults can be achieved with adjusted dosing [219–222]. Although children are at lower risk for severe disease, they are susceptible to infection, contribute to transmission, and—because they are more likely to have mild symptoms—may be less likely to be tested or reported as cases, and to isolate during infection. Thus, the ability of COVID-19 vaccines to prevent asymptomatic infection and reduce transmission is

especially relevant to the population-level impact of pediatric vaccination.

CONCLUSIONS

In conclusion, data from a wide variety of study types and settings demonstrate that COVID-19 vaccines provide high levels of protection against severe disease, and they additionally protect against infection and mild disease, even those caused by most SARS-CoV-2 variants of concern. Preliminary evidence supports the idea that the spread of the Omicron variant beginning late 2021 is at least partially driven by reductions in vaccine effectiveness.

Acknowledgments

We thank M. Kate Grabowski and the Johns Hopkins University Novel Coronavirus Research Compendium for bringing the study authors together to work on this paper.

Author contributions. A. L. H. proposed the Review with input from B. W., C. B. J., J. G. R., M. D. K, M. M. H., and S. A. T. A. A. N., A. L. H. , B. W., C. B. J., and J. G. R. and conducted the search for clinical trials of coronavirus disease 2019 (COVID-19) vaccines and extracted efficacy values. A. B., P. A. S.Z., K. K. W., and M. M. H. conducted the search for observational studies of COVID-19 vaccines and extracted effectiveness values. M. D. K., D. R. F., and M. K. P. supervised the collection of vaccine effectiveness studies including designing the search strategy, choosing the inclusion criteria, and evaluating studies against these criteria. A. L. H. and M. M. H. synthesized and interpreted the data on efficacy and effectiveness. B. W. assembled data on clinical trial timing, location, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant prevalence. A. L. H. , B. W., and M. M. H. created the tables and figures. A. L. H., C. B. J., B. W., J. G. R., and M. M. H. drafted the manuscript. All authors revised the manuscript and approved it for submission.

Disclaimer. The study sponsors had no role in the study design, the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit the paper for publication. The views represented in this article do not necessarily reflect the views of the World Health Organization or the National Institutes of Health (NIH).

Financial support. M. M. H., A. B., P. A. S.Z., K. K. W., and M. D. K. received funding to collect the data used in work through a contract from the Center for Epidemic Preparedness Innovations (CEPI) to the International Vaccine Access Center at Johns Hopkins University. C. B. J. and J. G. R. received funding from the Novel Coronavirus Research Compendium at Johns Hopkins to conduct reviews of COVID-19 vaccine papers for other purposes. A. L. H. and A. A. N. received support from the US National Institutes of Health (NIH DP5OD019851).

Potential conflicts of interests. M. M. H. and M. D. K. have previously received support from a grant from Pfizer Inc. to Johns Hopkins University for a non-COVID-19 vaccine. B. W. provided unpaid technical support to Bharat Biotech related to the clinical development of the BBV152 vaccine candidate. D. R. F. previously served on an independent data monitoring committee for GlaxoSmithKline for a non-COVID-19 vaccine candidate. S. A. T. served as an expert consultant for Milliman, Inc. on future COVID-19 trajectories. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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