



SYSTEMATIC REVIEW

Interpreting estimates of coronavirus disease 2019 (COVID-19) vaccine efficacy and effectiveness to inform simulation studies of vaccine impact: a systematic review [version 1; peer review: 2 approved with reservations]

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Abstract

Background: The multiple efficacious vaccines authorised for emergency use worldwide represent the first preventative intervention against coronavirus disease 2019 (COVID-19) that does not rely on social distancing measures. The speed at which data are emerging and the heterogeneities in study design, target populations, and implementation make it challenging to interpret and assess the likely impact of vaccine campaigns on local epidemics. We reviewed available vaccine efficacy and effectiveness studies to generate working estimates that can be used to parameterise simulation studies of vaccine impact.

Methods: We searched MEDLINE, the World Health Organization's Institutional Repository for Information Sharing, medRxiv, and vaccine manufacturer websites for studies that evaluated the emerging data on COVID-19 vaccine efficacy and effectiveness. Studies providing an estimate of the efficacy or effectiveness of a COVID-19 vaccine using disaggregated data against SARS-CoV-2 infection, symptomatic disease, severe disease, death, or transmission were included. We extracted information on study population, variants of concern (VOC), vaccine platform, dose schedule, study endpoints, and measures of impact. We applied an evidence synthesis approach to capture a range of plausible and consistent parameters for vaccine efficacy and effectiveness that can be used to inform and explore a variety of vaccination strategies as the COVID-19 pandemic evolves.

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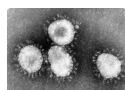
Any reports and responses or comments on the article can be found at the end of the article.

Results: Of the 602 articles and reports identified, 53 were included in the analysis. The availability of vaccine efficacy and effectiveness estimates varied by vaccine and were limited for VOCs. Estimates for non-primary endpoints such as effectiveness against infection and onward transmission were sparse. Synthesised estimates were relatively consistent for the same vaccine platform for wild-type, but was more variable for VOCs.

Conclusions: Assessment of efficacy and effectiveness of COVID-19 vaccines is complex. Simulation studies must acknowledge and capture the uncertainty in vaccine effectiveness to robustly explore and inform vaccination policies and policy around the lifting of non-pharmaceutical interventions.

Keywords

COVID-19, vaccine, efficacy, effectiveness, simulation studies, modelling



This article is included in the [Coronavirus \(COVID-19\)](#) collection.

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Competing interests: ABH and PW declare personal fees from the World Health Organization related to modelling COVID-19 vaccine impact, outside the submitted work. LW is currently employed by Gilead Sciences outside of the submitted work. AC has received payment from Pfizer for teaching of mathematical modelling of infectious disease transmission and vaccination. All other authors declare no competing interests.

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Introduction

It took just over a year from when the World Health Organization declared the coronavirus disease 2019 (COVID-19) epidemic to be a global pandemic for multiple vaccines to be authorised for emergency use^{1,2} with many more in the pipeline³. The rapid development of vaccines using a variety of technology platforms (Table 1) has been remarkable and provides the first preventative mass intervention against COVID-19 that does not rely on economically damaging social distancing measures.

Randomised controlled trials (RCTs) of COVID-19 vaccines have demonstrated high efficacy against symptomatic infection, with a range of primary endpoint efficacy estimates reported between 95.0% (95% confidence interval (CI): 90.3 – 97.6) for Pfizer (BNT162b2) and 50.7% (95% CI: 36.0 – 62.0) for CoronaVac. These studies have also demonstrated higher efficacy against severe outcomes (including hospitalisation and death)^{4–10}. Whilst direct comparison of these estimates is not possible (due to differences in trial design, endpoint definitions of symptomatic disease, and the epidemiological setting in which the trials were undertaken), they can be useful to assess the likely impact of vaccine introductions on local epidemics. However, the vaccine efficacy measured in tightly controlled RCTs is not always observed under “real-world” conditions¹¹. Thus, as vaccines have been rolled-out, real-world data on their effectiveness against symptomatic infection, severe disease, asymptomatic infection¹² and onward transmission^{13,14} are emerging.

Synthesising these data is challenging given the speed with which data are emerging and the different study designs. Furthermore, global vaccine deployment means that target populations will be highly heterogeneous even at national level. Achieved coverage can vary by age, sex, ethnicity, comorbidities,

and socio-economic background, all of which are known risk factors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and/or more severe COVID-19 disease outcomes^{15,16}. Even within RCTs, COVID-19 vaccine efficacy has varied by human immunodeficiency virus (HIV) status¹⁷ or dosing strategy⁶. Additionally, countries may adopt alternative roll-out strategies from those tested in RCTs. For example, the United Kingdom (UK) adopted a 12-week gap between vaccine doses based on early data suggesting that relatively high efficacy against symptomatic disease is conferred by the first dose in order to prioritise wider delivery of the first dose^{18,19} and other countries such as Canada, Norway, and Denmark, are now taking a similar approach^{20–22}. Conversely, due to delays in vaccine delivery for countries participating in the COVAX Facility, a longer gap between first and second doses may be inevitable²³. Coupled with this variability, the emergence of multiple variants of concern (VOCs) that carry mutations in the spike protein²⁴ mean that the effectiveness of the current vaccines could be reduced (notably against B.1.351, P.1, and B.1.617.2 which were first identified in South Africa²⁵, Brazil²⁶, and India²⁷, respectively). Whilst data on the vaccine efficacy against these VOCs remains limited, laboratory-based neutralisation assays are suggestive of a likely reduction for some, but not all, of the vaccines^{28,29}.

As countries continue mass vaccination campaigns, policy-makers must carefully consider the implications of different strategies. Optimal vaccination strategies are critically dependent on vaccine effectiveness, availability, roll out speed, and uptake. Relaxation of non-pharmaceutical interventions (NPIs) must be carefully balanced against progress in vaccination to prevent a surge in case numbers whilst population immunity remains below herd immunity threshold^{30,31}. Simulation studies can provide useful insights into highly uncertain

Table 1. Overview of coronavirus disease 2019 (COVID-19) vaccine platforms^{3,32,33}.

Platform	Overview	Leading candidates (<i>subtype</i>)
Whole viruses a) Live attenuated b) Inactivated	- Uses a weakened or inactivated form of the disease-causing pathogen to trigger an immune response. - Live attenuated viruses can still grow and replicate in the host but do not cause disease.	Serum Institute of India (<i>a</i>) Sinovac Biotech, “CoronaVac”, China (<i>b</i>) Sinopharm, “BIBP” and “WIBP”, China (<i>b</i>)
Viral vector	- DNA encoding the spike protein is inserted into an Adenovirus vector. - Viral vector can then infect host cells, which produce the spike protein against which an immune response is triggered.	AstraZeneca-Oxford, UK Johnson & Johnson, USA ¹ Sputnik V, Russia
Nucleic mRNA	- Induces the host cells to produce SARS-CoV-2 antigen spike proteins coded in the RNA². - Potential for rapid and flexible vaccine updates against VOCs³.	Pfizer-BioNTech, USA/Germany Moderna, USA
Protein subunit	- Uses the SARS-CoV-2 spike protein present on the surface of the virus. - Adjuvants are added to the vaccine to stimulate a robust immune response.	Novavax, USA

¹Single dose vaccine. ²RNA = ribonucleic acid. ³VOC = variants of concern.

medium-term dynamics of SARS-CoV-2 transmission under different vaccine prioritisation and NPI lifting strategies, capturing inherent uncertainties in vaccine characteristics^{34–37}.

Here we review the emerging data on COVID-19 vaccine efficacy and effectiveness, taking into consideration the study population, VOCs in circulation, and vaccine platforms. We take an evidence synthesis approach to capture a range of plausible and consistent parameters that can be used to inform and explore a variety of vaccination strategies. This article is reported inline with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines³⁸.

Methods

Literature review

We searched [MEDLINE](#) with no language restrictions up to 10 May, 2021, using the following search strategy for the title and abstract: (“Pfizer” OR “BNT162b2” OR “AstraZeneca” OR “ChAdOx1” OR “Moderna” OR “mRNA-1273” OR “Janssen” OR “Ad26.COV2.S” OR “Gam-COVID-Vac” OR “Sputnik V” OR “rAd26” OR “rAd5” OR “Novavax” OR “NVX-CoV2373” OR “Sinovac” OR “CoronaVac” OR “Sinopharm” OR “COVID-19 vaccination”) AND (“effectiveness” OR “phase 4” OR “efficacy” OR “impact” OR “reduction” OR “reduced risk” OR “real-world effect” OR “vaccine effect” OR “roll*”) AND (“COVID-19” OR “SARS-CoV-2” OR “nCov-19” OR “ncov-2019”). We also searched [MedRxiv](#) using the same search terms using the R package [medrxivr](#) version 0.0.5³⁹. We searched the [World Health Organization’s Institutional Repository for Information Sharing](#) for “COVID-19 vaccines” and restricted to documents in English only⁴⁰. Vaccine manufacturer websites were also searched for any press releases reporting COVID-19 vaccine efficacy or effectiveness. The search was supplemented by reviewing the reference list of relevant papers. Finally, all reports on vaccine effectiveness released on the UK government’s website were also reviewed⁴¹. The review protocol was not registered at PROSPERO ahead of data extraction. All records were imported into the [Covidence](#) systematic review software and deduplicated (v2014, accessed 2021). Study title and abstracts were initially screened by one reviewer (NI) and full texts meeting the inclusion criteria were reviewed (NI).

Inclusion criteria

Studies providing an estimate of the efficacy or effectiveness of a COVID-19 vaccine using disaggregated data against SARS-CoV-2 infection, symptomatic disease, severe disease, death, or transmission were eligible for review. Studies assessing protection in a specific patient setting e.g. amongst patients with liver damage, were excluded. Press releases were included for review if results were not already available as a pre-print manuscript or peer-reviewed paper. Studies were grouped by unique vaccine for the evidence synthesis.

Data collection

A single reviewer (NI) extracted summary data on study type (clinical trial or effectiveness study), study location, vaccine type, efficacy or effectiveness by endpoint given as percentage vaccine efficacy, odds ratio, or risk ratio

(infection, symptomatic disease, severe disease, death, or transmission), variant, number of doses, timing at which efficacy or effectiveness was assessed, and whether it was assessed in a particular subgroup.

Evidence synthesis

Although the primary endpoint of clinical trials is typically efficacy against symptomatic COVID-19 disease, optimising vaccination strategies requires consideration of broader transmission dynamics and the full natural history of disease from infection to recovery or death. We therefore consider vaccine efficacy¹¹ against four endpoints: i) any infection (including asymptomatic); ii) symptomatic infection; iii) severe disease requiring hospitalisation (including admission to intensive care units or resulting in death); and iv) infectiousness of breakthrough infections in vaccinated individuals.

Where only a single efficacy estimate was available, we use that value. Where several trials and/or effectiveness studies report values, we present the range of these values and use the unweighted mean value across studies as our central estimate. Efficacy or effectiveness estimates within care home populations were excluded from the calculation of the mean value as these study populations are highly vulnerable and experienced high attack rates early in the pandemic, making estimates non-representative. Efficacy estimates from non-standard dosing regimes e.g. the low/standard dosing reported in the ChAdOx1 trial were also excluded.

Based on the extracted values, we apply a data synthesis approach to generate working estimates. First, we assume that efficacy after two doses is never lower than after one dose for a multidose vaccine. Second, to ensure consistency between the endpoints we assume that efficacy against severe disease is greater than or equal to efficacy against symptomatic disease across all vaccine types^{4–6}. Third, we assume that efficacy against B.1.351 and P.1, but not B.1.1.7 is never higher than that for wild-type SARS-CoV-2 (the variant originally in circulation that contains no major mutations) based on data on neutralising antibody levels^{28,42–44}. Estimates for VOCs with immune escape properties (B.1.351, P.1, and P.2) were grouped together. These three conditions were applied across all estimates.

Where data are not yet available, we first assume that the mechanism of action of the vaccines is similar. Specifically, to estimate vaccine efficacy or effectiveness (VE) against e.g. severe disease or infectiousness we maintain the same incremental relationships as observed for vaccines for which these data are available. For example, if data on efficacy against severe disease for B.1.1.7 are not available but are available for B.1.1.7 symptomatic infection, wild-type symptomatic infection, and wild-type severe disease, then we assume that the ratio of the odds of symptomatic and severe B.1.1.7 efficacy is the same as that for wild-type (WT).

$$odds(VE) = \frac{VE}{1 - VE}$$

$$\text{odds}(VE \text{ severe}_{B.1.1.7}) = \text{odds}(VE \text{ symptomatic}_{B.1.1.7}) \times \frac{\text{odds}(VE \text{ severe}_{WT})}{\text{odds}(VE \text{ symptomatic}_{WT})},$$

$$VE \text{ severe}_{B.1.1.7} = \frac{\text{odds}(VE \text{ severe}_{B.1.1.7})}{1 + \text{odds}(VE \text{ severe}_{B.1.1.7})}.$$

We make a similar assumption for the difference in efficacy between first and second doses. If there was not enough information available to calculate these ratios, we assumed that: i) the odds of the vaccine efficacies for B.1.1.7 were the midpoint between those for wild-type and B.1.351; ii) that the efficacy for first and second dose was the same; or iii) efficacy against the same endpoint was the same for the different variants.

Second, in the absence of data, we assume that efficacies against symptomatic disease and infection are the same^{45,46}. Third, for the AstraZeneca vaccine, immunogenicity data shows no significant boosting effect from the second dose^{47,48}. Furthermore, efficacy after the first AstraZeneca dose against symptomatic disease was not significantly different to efficacy after the second dose in clinical trials⁴⁷. Thus,

in the absence of data we therefore assume that first and second dose efficacy for viral vector vaccines is the same. It is possible that the second dose may prolong the duration of vaccine-induced immunity, but we do not consider duration of protection in this analysis. Fourth, again in the absence of data, we assume that vaccines using the same vaccine platform had similar efficacies.

Additionally, in our analysis we impose a minimum and maximum vaccine efficacy against any endpoint of 0% and 99% respectively. We do not consider the duration of vaccine-induced immunity as data are not yet available to assess this. We did not undertake a risk of bias assessment as the aim of the review was to collate and synthesise all available efficacy and effectiveness estimates. All values are rounded to the nearest percent. Analysis was conducted using R version 4.0.3⁴⁹ and Microsoft Excel.

Results

We identified 602 potentially relevant studies or reports, 53 of which were included after full-text screening (Figure 1).

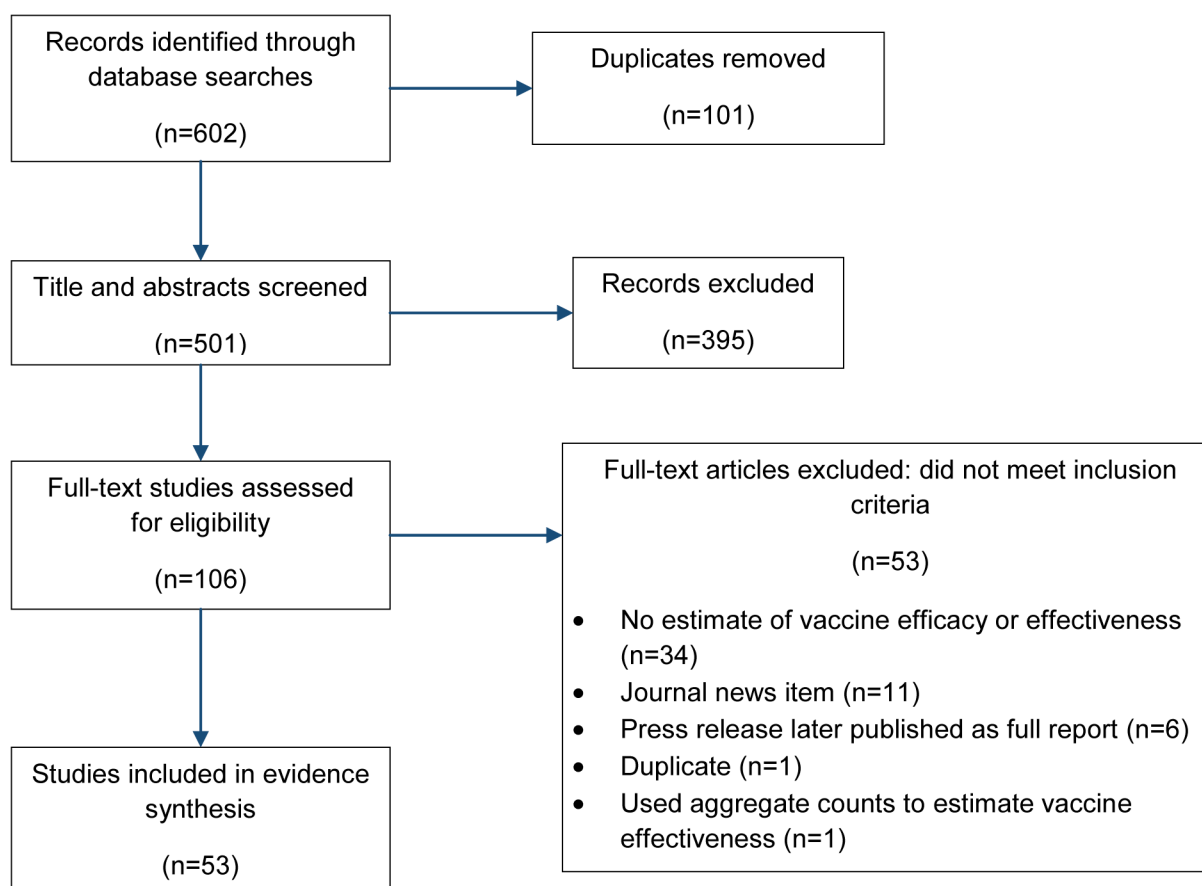


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

The Underlying data file⁵⁰ summarises efficacy/effectiveness values reported from clinical trials and observational effectiveness studies. Figure 2 and Table 2 give our summary estimates of vaccine effectiveness by endpoint, vaccine type, dose, and SARS-CoV-2 variant. There were 16 studies reporting clinical trial results, 36 effectiveness studies, and 1 observational study.

AstraZeneca-Oxford (viral vector)

We identified 12 eligible studies on vaccine efficacy or effectiveness for the AstraZeneca vaccine (Figure 3) which directly informed 8 out of 24 possible estimates in our evidence synthesis (Table 2). We estimated a 64%, 76%, and 99%, efficacy after two doses for wild-type against any infection, symptomatic disease, and severe disease, respectively, and a 43% efficacy against B.1.1.7 transmission.

The most data points were available for estimates of efficacy against symptomatic disease after two doses ($n = 13$) ranging from 62.1% (95% CI: 41.0, 75.7) to 90.0% (67.4, 97.0) against the wild-type variant⁶. The latter estimate was from a low-dose/standard-dose regime which was excluded from our final evidence synthesis. We also excluded the most recent UK-based clinical trial from our synthesis which reported a vaccine efficacy against disease caused by non-B.1.1.7 variants of 84.1% (95% CI: 71 – 91%). This was because inspection of the results indicated that over half of the samples in that post-hoc stratification were not sequenced and that efficacy was much lower in unsequenced samples⁵¹. In comparison, only one estimate of efficacy against severe disease after two doses was available compared to six estimates after one dose. Estimates for protection against transmission are still scarce with only two estimates

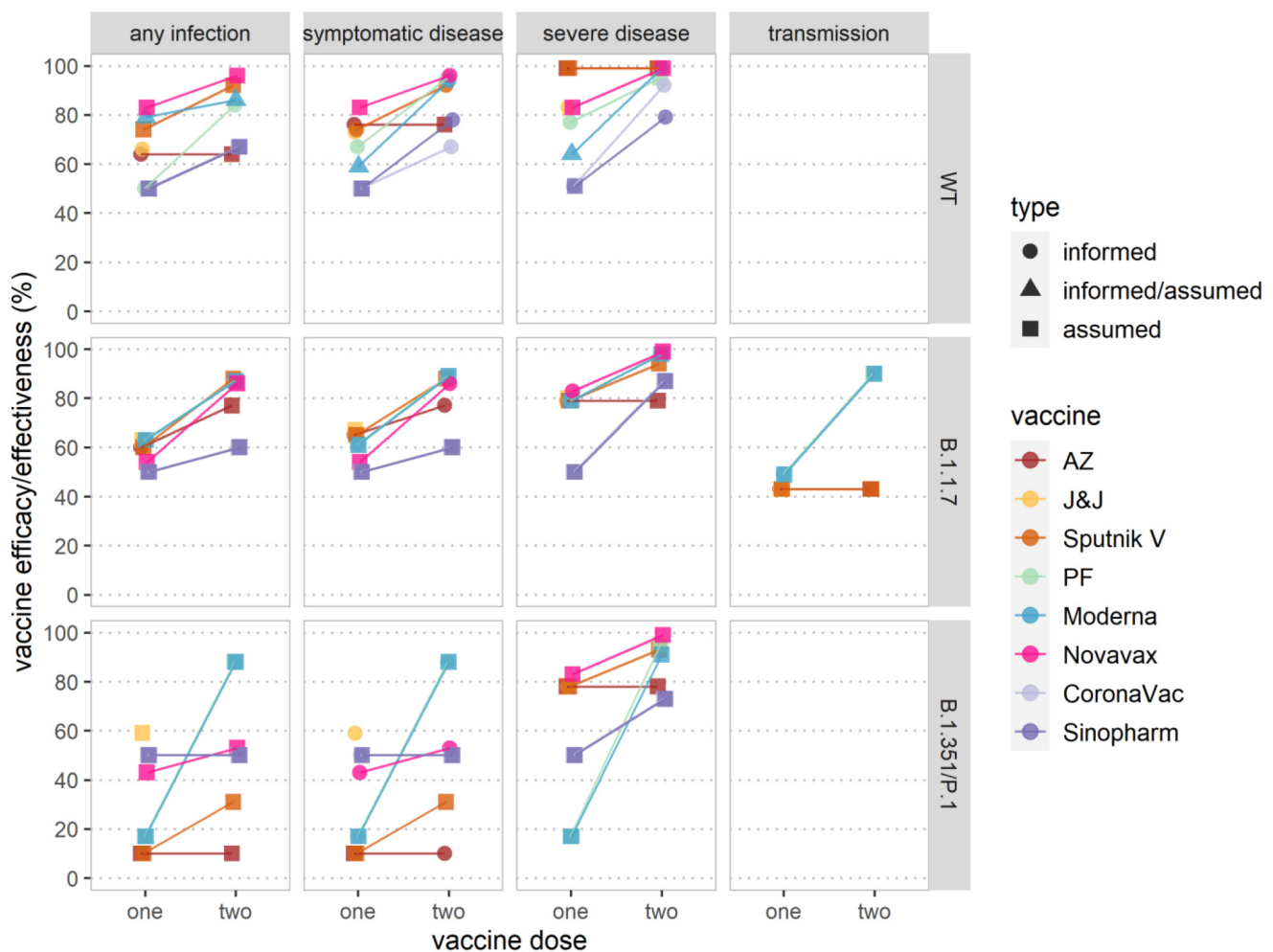


Figure 2. Summary of synthesised vaccine efficacy or effectiveness parameters by vaccine dose, vaccine product, endpoint, and SARS-CoV-2 variant. Circles show estimates that are informed by clinical trials and/or effectiveness studies, triangles show where some estimates are available but an assumption was made in the evidence synthesis, and squares show estimates based on assumptions. AZ = AstraZeneca, J&J = Johnson & Johnson (note this is a single dose vaccine), PF = Pfizer.

Table 2. Summary of vaccine efficacy and effectiveness synthesis showing by vaccine, endpoint, dose, and variant, the number of studies with data, the mean, and the final synthesised estimate. All values are rounded to the nearest percent. WT = wild-type variant. AZ = AstraZeneca, PF = Pfizer, J&J = Janssen. *Note that J&J is a single dose product.

Platform	Vaccine	Endpoint	Dose	variant	No. of studies	Efficacy (%)	Type	Reasoning
vector	AZ	any infection	one	WT	1	64	informed	-
			one	B.1.1.7	1	60	informed	-
			one	B.1.351/P.1	0	10	assumed	assumed same as symptomatic infection
			two	WT	0	64	assumed	unlikely second dose VE would be lower, assumed same as first dose
			two	B.1.1.7	0	77	assumed	assumed same as symptomatic infection
			two	B.1.351/P.1	0	10	assumed	assumed same as symptomatic infection
		symptomatic disease	one	WT	1	76	informed	-
			one	B.1.1.7	2	65	informed	-
			one	B.1.351/P.1	0	10	assumed	assumed same first and second dose efficacy
			two	WT	0	76	assumed	unlikely that second dose has lower efficacy, assume same as first
			two	B.1.1.7	2	77	informed	-
			two	B.1.351/P.1	1	10	informed	-
		severe disease	one	WT	0	99	assumed	capped to upper limit of 99
			one	B.1.1.7	3	79	informed	-
			one	B.1.351/P.1	0	78	assumed	assumed that ratio of odds was the same as WT difference between symptomatic and severe disease
			two	WT	0	99	assumed	capped to upper limit of 99
			two	B.1.1.7	0	79	assumed	assumed same first and second dose efficacy
			two	B.1.351/P.1	0	78	assumed	assumed that ratio of odds was the same as WT difference between symptomatic and severe disease
		transmission	one	B.1.1.7	2	43	informed	-
			two	B.1.1.7	0	43	assumed	assumed same first and second dose efficacy
			one	WT	1	66	informed	-
	J&J*	any infection	one	B.1.1.7	0	63	assumed	assumed odds(VE) was midway between WT and B.1.351
			one	B.1.351/P.1	0	59	assumed	assumed same as symptomatic infection
			one	WT	3	73	informed	-
		symptomatic disease	one	B.1.1.7	0	67	assumed	assumed odds(VE) was midway between WT and B.1.351
			one	B.1.351/P.1	2	59	informed	-

Platform	Vaccine	Endpoint	Dose	variant	No. of studies	Efficacy (%)	Type	Reasoning
		severe disease	one	WT	3	83	informed	-
			one	B.1.1.7	0	80	assumed	assumed odds(VE) was midway between WT and B.1.351
			one	B.1.351/P.1	2	78	informed	-
	Sputnik V	any infection	one	WT	0	74	assumed	assumed same as symptomatic infection
			one	B.1.1.7	0	60	assumed	assumed same as AZ (same vaccine platform)
			one	B.1.351/P.1	0	10	assumed	assumed same as AZ (same vaccine platform)
			two	WT	0	92	assumed	assumed same as symptomatic infection
			two	B.1.1.7	0	88	assumed	assumed same as symptomatic infection
			two	B.1.351/P.1	0	31	assumed	assumed same as symptomatic infection
		symptomatic disease	one	WT	1	74	informed	-
			one	B.1.1.7	0	65	assumed	assumed same as AZ (same vaccine platform)
			one	B.1.351/P.1	0	10	assumed	assumed same as AZ (same vaccine platform)
			two	WT	2	92	informed	-
			two	B.1.1.7	0	88	assumed	assumed same odds ratio as WT one and two doses
			two	B.1.351/P.1	0	31	assumed	assumed same odds ratio as WT one and two doses
		severe disease	one	WT	0	99	assumed	assumed same as AZ (same vaccine platform)
			one	B.1.1.7	0	79	assumed	assumed same as AZ (same vaccine platform)
			one	B.1.351/P.1	0	78	assumed	assumed same as AZ (same vaccine platform)
			two	WT	0	99	assumed	assumed upper limit of 99, not lower than first dose
			two	B.1.1.7	0	94	assumed	assumed same odds ratio as WT symptomatic disease one and two doses
			two	B.1.351/P.1	0	93	assumed	assumed same odds ratio as WT symptomatic disease one and two doses
		transmission	one	B.1.1.7	0	43	assumed	assumed same as AZ (same vaccine platform)
			two	B.1.1.7	0	43	assumed	assumed same as AZ (same vaccine platform)
mRNA	PF	any infection	one	WT	11	50	informed	-
			one	B.1.1.7	5	63	informed	-
			one	B.1.351/P.1	0	17	assumed	assumed same as symptomatic infection
			two	WT	10	84	informed	-
			two	B.1.1.7	3	87	informed	-
			two	B.1.351/P.1	0	88	assumed	assumed same as symptomatic infection

Platform	Vaccine	Endpoint	Dose	variant	No. of studies	Efficacy (%)	Type	Reasoning
		symptomatic disease	one	WT	4	67	informed	-
			one	B.1.1.7	9	61	informed	-
			one	B.1.351/P.1	1	17	informed	-
			two	WT	6	95	informed	-
			two	B.1.1.7	7	89	informed	-
			two	B.1.351/P.1	2	88	informed	-
		severe disease	one	WT	4	77	informed	-
			one	B.1.1.7	9	79	informed	-
			one	B.1.351/P.1	0	17	assumed	assumed same as symptomatic infection one dose (as cannot be lower)
			two	WT	8	91	informed	-
			two	B.1.1.7	4	98	informed	-
			two	B.1.351/P.1	0	91	assumed	assumed same as WT
		transmission	one	B.1.1.7	2	49	informed	
			two	B.1.1.7	0	90	assumed	assumed same odds ratio as for symptomatic disease one vs two doses
Moderna		any infection	one	WT	3	79	informed/ assumed	estimate from mRNA vaccine studies that did not differentiate PF vs Mod
			one	B.1.1.7	0	63	assumed	assumed same as PF
			one	B.1.351/P.1	0	17	assumed	assumed same as PF
			two	WT	3	86	informed/ assumed	estimate from mRNA vaccine studies that did not differentiate PF vs Mod
			two	B.1.1.7	0	87	assumed	assumed same as PF
			two	B.1.351/P.1	0	88	assumed	assumed same as PF
		symptomatic disease	one	WT	1	59	informed/ assumed	estimate from mRNA vaccine studies that did not differentiate PF vs Mod
			one	B.1.1.7	0	61	assumed	assumed same as PF
			one	B.1.351/P.1	0	17	assumed	assumed same as PF
			two	WT	1	94	informed	-
			two	B.1.1.7	0	89	assumed	assumed same as PF
			two	B.1.351/P.1	0	88	assumed	assumed same as PF

Platform	Vaccine	Endpoint	Dose	variant	No. of studies	Efficacy (%)	Type	Reasoning
		severe disease	one	WT	1	64	informed/assumed	estimate from mRNA vaccine studies that did not differentiate PF vs Mod
			one	B.1.1.7	0	79	assumed	assumed same as PF
			one	B.1.351/P.1	0	17	assumed	assumed same as PF
			two	WT	1	99	informed	capped at upper limit of 99
			two	B.1.1.7	0	98	assumed	assumed same as PF
			two	B.1.351/P.1	0	91	assumed	assumed same as PF
		transmission	one	B.1.1.7	0	49	assumed	assumed same as PF
			two	B.1.1.7	0	90	assumed	assumed same as PF
subunit	Novavax	any infection	one	WT	0	83	assumed	assumed same as symptomatic infection
			one	B.1.1.7	0	54	assumed	assumed same as symptomatic infection
			one	B.1.351/P.1	0	43	assumed	assumed same as symptomatic infection
			two	WT	0	96	assumed	assumed same as symptomatic infection
			two	B.1.1.7	0	86	assumed	assumed same as symptomatic infection
			two	B.1.351/P.1	0	53	assumed	assumed same as symptomatic infection
		symptomatic disease	one	WT	0	83	assumed	assumed same as efficacy estimated for mix of WT and B.1.1.7 variants
			one	B.1.1.7	0	54	assumed	assumed same odds ratio as for symptomatic disease one vs two doses
			one	B.1.351/P.1	1	43	informed	-
			two	WT	2	96	informed	-
			two	B.1.1.7	1	86	informed	-
			two	B.1.351/P.1	2	53	informed	-
		severe disease	one	WT	0	83	assumed	assumed same odds ratio as for severe disease B.1.1.7
			one	B.1.1.7	1	83	informed	-
			one	B.1.351/P.1	0	83	assumed	assumed same odds ratio as for severe disease B.1.1.7
			two	WT	1	99	assumed	capped at upper limit, estimate is 100%
			two	B.1.1.7	1	99	assumed	capped at upper limit, estimate is 100%
			two	B.1.351/P.1	1	99	assumed	capped at upper limit, estimate is 100%

Platform	Vaccine	Endpoint	Dose	variant	No. of studies	Efficacy (%)	Type	Reasoning
whole virus	CoronaVac	any infection	one	WT	0	50	assumed	assumed same as symptomatic infection
			one	B.1.1.7	0	50	assumed	assumed same as symptomatic infection
			one	B.1.351/P.1	0	50	assumed	assumed same as symptomatic infection
			two	WT	0	67	assumed	assumed same as symptomatic infection
			two	B.1.1.7	0	60	assumed	assumed same as symptomatic infection
			two	B.1.351/P.1	0	50	assumed	assumed same as symptomatic infection
		symptomatic disease	one	WT	0	50	assumed	assumed same as B.1.351 first dose as applying odds ratio of WT severe disease results in lower VE than for B.1.351
			one	B.1.1.7	0	50	assumed	assumed same as B.1.351 first dose as applying odds ratio of WT severe disease results in lower VE than for B.1.351
			one	B.1.351/P.1	1	50	informed	-
			two	WT	3	67	informed	-
			two	B.1.1.7	0	60	assumed	assumed odds(VE) was midway between WT and B.1.351
			two	B.1.351/P.1	0	50	assumed	unlikely that second dose has lower efficacy, assume same as first
		severe disease	one	WT	1	51	informed	-
			one	B.1.1.7	0	50	assumed	assumed same as symptomatic disease as applying odds ratio of WT severe disease results in lower VE than symptomatic disease
			one	B.1.351/P.1	0	50	assumed	assumed same as symptomatic disease as applying odds ratio of WT severe disease results in lower VE than symptomatic disease
			two	WT	2	92	informed	-
			two	B.1.1.7	0	87	assumed	assumed odds(VE) was midway between WT and B.1.351
			two	B.1.351/P.1	0	73	assumed	assumed same as "mixed" first dose which is a mix of B.1.351 and P.1 but with unknown ratio
	Sinopharm BIBP	any infection	one	WT	0	50	assumed	assume same as Coronavac same vaccine platform
			one	B.1.1.7	0	50	assumed	assume same as Coronavac same vaccine platform
			one	B.1.351/P.1	0	50	assumed	assume same as Coronavac same vaccine platform
			two	WT	0	67	assumed	assume same as Coronavac same vaccine platform
			two	B.1.1.7	0	60	assumed	assume same as Coronavac same vaccine platform
			two	B.1.351/P.1	0	50	assumed	assume same as Coronavac same vaccine platform

Platform	Vaccine	Endpoint	Dose	variant	No. of studies	Efficacy (%)	Type	Reasoning
		symptomatic disease	one	WT	0	50	assumed	assume same as Coronavac same vaccine platform
			one	B.1.1.7	0	50	assumed	assume same as Coronavac same vaccine platform
			one	B.1.351/P.1	0	50	assumed	assume same as Coronavac same vaccine platform
			two	WT	1	78	informed	
			two	B.1.1.7	0	60	assumed	assume same as Coronavac same vaccine platform
			two	B.1.351/P.1	0	50	assumed	assume same as Coronavac same vaccine platform
		severe disease	one	WT	0	51	assumed	assume same as Coronavac same vaccine platform
			one	B.1.1.7	0	50	assumed	assume same as Coronavac same vaccine platform
			one	B.1.351/P.1	0	50	assumed	assume same as Coronavac same vaccine platform
			two	WT	1	79	informed	-
			two	B.1.1.7	0	87	assumed	assume same as Coronavac same vaccine platform
			two	B.1.351/P.1	0	73	assumed	assume same as Coronavac same vaccine platform

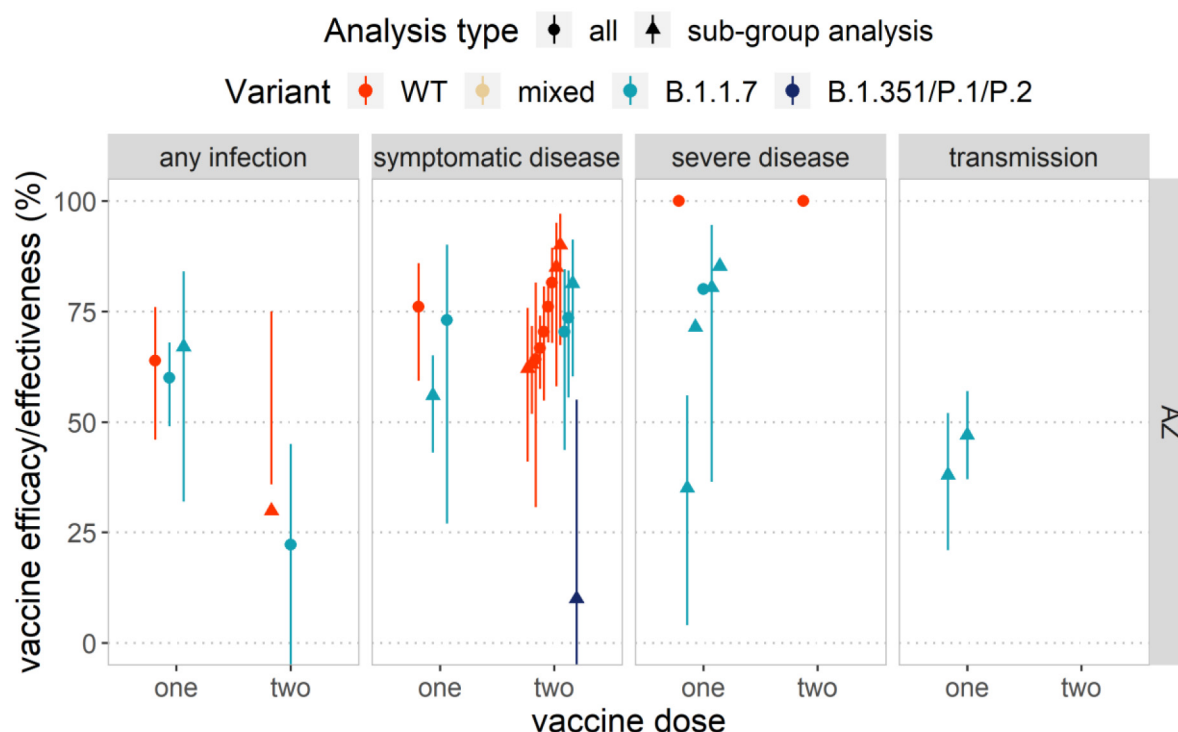


Figure 3. Summary of reported first and second dose vaccine efficacy and effectiveness estimates for the AstraZeneca vaccine for, from left to right: i) any infection; ii) symptomatic disease; iii) severe disease; and iv) transmission. Red points show estimates for the wild-type (WT), yellow for a mix of variants, turquoise for B.1.1.7, and navy for B.1.351, P.1, or P.2.

available from the same study¹⁴. There were insufficient data to inform estimates of protection against transmission for wild-type or B.1.351. Finally, only one estimate of efficacy against B.1.351, against symptomatic disease after two doses (10.0%, 95% CI: -77.0, 55.0), was identified⁵².

Sputnik V (viral vector)

Only one eligible study was identified for Sputnik V (Figure 4) which reported an efficacy against wild-type symptomatic disease after one and two vaccine doses of 73.6% (95% CI: 13.1, 91.9) and 91.6% (95% CI: 85.6, 95.2) respectively⁹. This informed 2 of the 24 possible synthesised estimates (Underlying data⁵⁰). An effectiveness study reported a 79.4% efficacy for Sputnik Light, the first component of Sputnik V which is now authorised as a single dose product in Russia⁵³. No data on efficacy against VOCs were available. Other endpoint estimates were assumed to be the same as AstraZeneca ChAdOx1, which is also a viral vector vaccine. We thus estimated a 92%, 92%, and 99% efficacy after two doses for wild-type against any infection, symptomatic disease, and severe disease respectively. There were not enough data to inform estimates of protection against transmission for wild-type or B.1.351.

Johnson & Johnson (viral vector)

Two studies reported efficacy and effectiveness estimates for the single dose Johnson & Johnson vaccine which informed

5 of the 12 possible estimates^{54,55} (Figure 5 and Table 2). We estimated a 66%, 73%, 83%, efficacy for wild-type against any infection, symptomatic disease, and severe disease respectively. Five estimates for efficacy against symptomatic disease were identified ranging from 66.9% (95% CI: 59.0, 73.4)⁵⁴ to 76.7% (95% CI: 30.3, 95.3)⁵⁵. No data were available for efficacy against transmission, therefore we assumed this to be the same as for AstraZeneca. There were not enough data to inform estimates of protection against transmission for wild-type or B.1.351.

Pfizer-BioNTech (mRNA)

We identified 27 eligible studies on vaccine efficacy or effectiveness for the Pfizer vaccine (Figure 6) which directly informed 14 of the 24 synthesised estimates (Table 2). We estimated 84%, 95%, and 95%, efficacy after two doses against wild-type for any infection, symptomatic disease, and severe disease, and 90% efficacy against B.1.1.7 transmission.

The majority of data available described estimates of efficacy against symptomatic disease after two doses ($n = 15$) ranging from 91.3% (95% CI: 89.0, 75.7)⁵⁶ to 99.3% (95.3, 99.9)⁵⁷ against the wild-type variant. Similarly to AZ, there were not enough data to inform estimates of protection against transmission for wild-type or B.1.351. For all other endpoints there were 13 to 16 estimates available to inform our evidence synthesis. However, estimates against non-B.1.1.7 variants

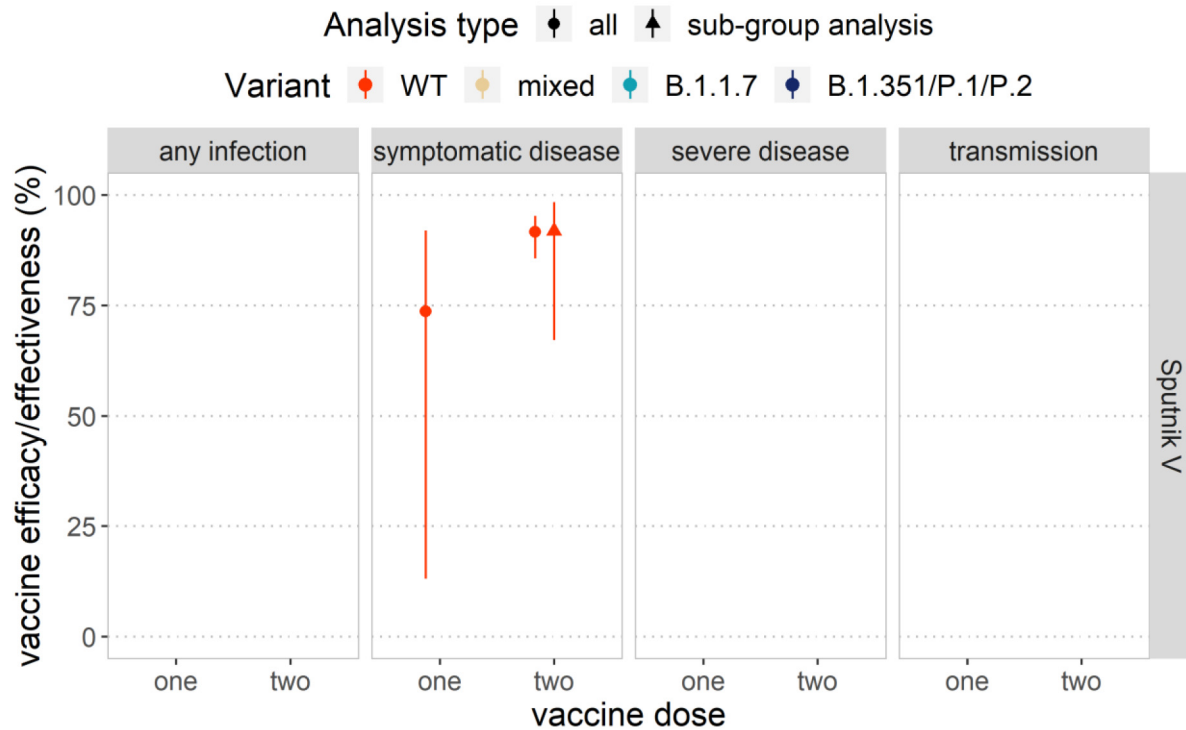


Figure 4. Summary of reported first and second dose vaccine efficacy and effectiveness estimates for the Sputnik V vaccine for, from left to right: i) any infection; ii) symptomatic disease; iii) severe disease; and iv) transmission. Red points show estimates for the wild-type (WT), yellow for a mix of variants, turquoise for B.1.1.7, and navy for B.1.351, P.1, or P.2.

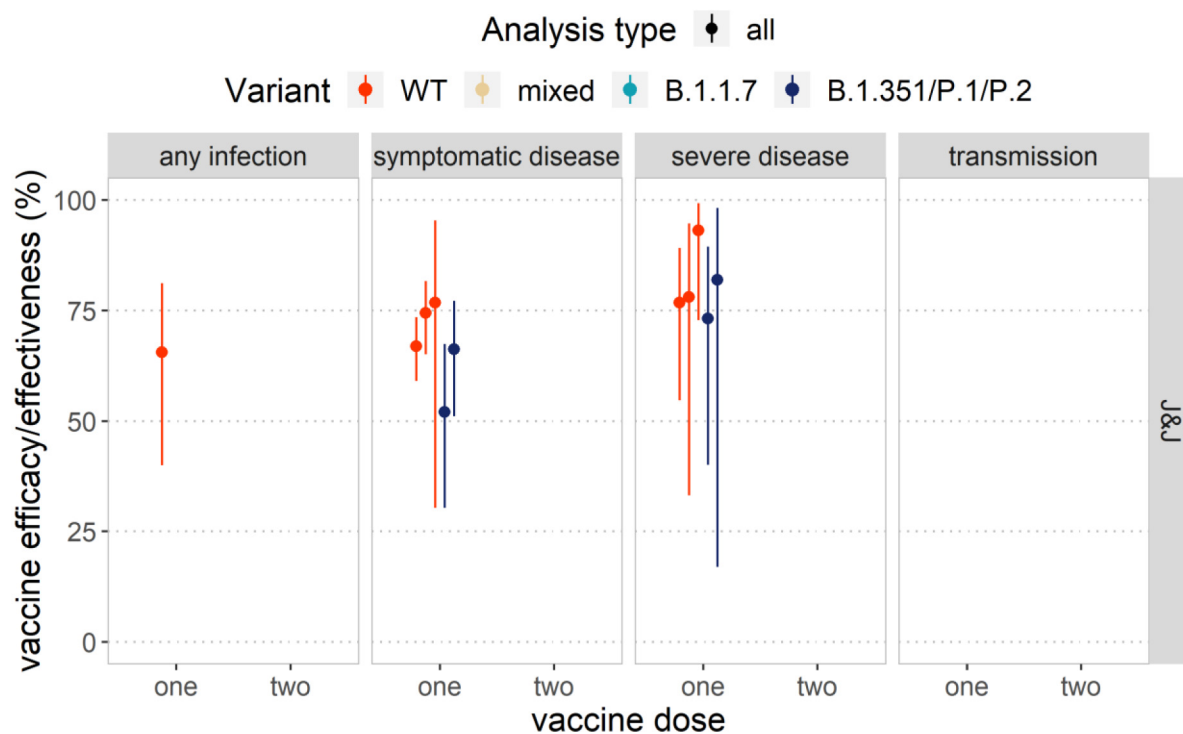


Figure 5. Summary of reported first and second dose vaccine efficacy and effectiveness estimates for the Johnson & Johnson vaccine for, from left to right: i) any infection; ii) symptomatic disease; iii) severe disease; and iv) transmission. Red points show estimates for the wild-type (WT), yellow for a mix of variants, turquoise for B.1.1.7, and navy for B.1.351, P.1, or P.2.

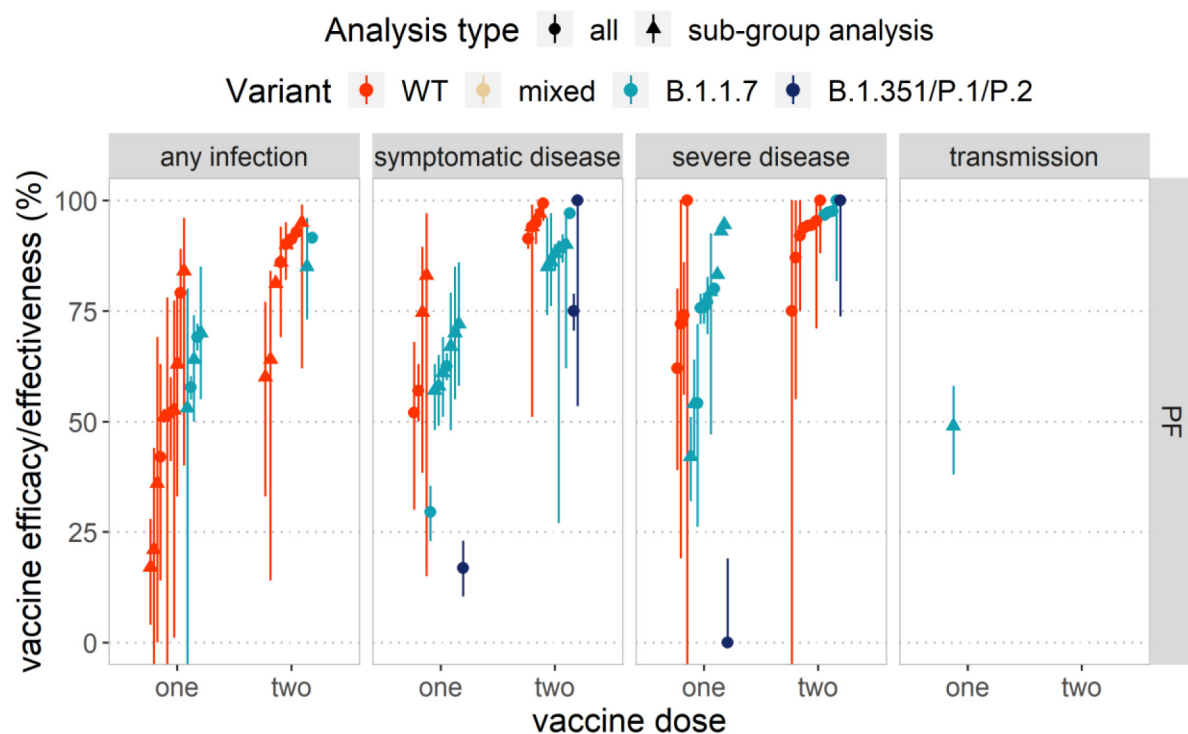


Figure 6. Summary of reported first and second dose vaccine efficacy and effectiveness estimates for the Pfizer vaccine for, from left to right: i) any infection; ii) symptomatic disease; iii) severe disease; and iv) transmission. Red points show estimates for the wild-type (WT), yellow for a mix of variants, turquoise for B.1.1.7, and navy for B.1.351, P.1, or P.2.

were scarce with only one press release and a Qatari effectiveness study reporting estimates for B.1.351^{56,58}. In our synthesis we assumed that the efficacy against severe disease reported by Vasilieou *et al.* was 80%, estimated from the weighted average (by the number of observations) of efficacy from 21 days onwards⁵⁹.

Moderna (mRNA)

Available efficacy and/or effectiveness data for Moderna were not as comprehensive compared to Pfizer with only a single study reporting efficacy estimates for symptomatic (94.1%, 95% CI: 89.3, 96.8) and severe disease (100%, 95% CI: NA) after two doses for wild-type⁵ (Figure 7). In our synthesis, we therefore used the mean value from effectiveness studies that did not differentiate between the mRNA vaccines (Pfizer or Moderna) to inform our estimates for wild-type against any infection after one and two doses, symptomatic disease after one dose, and severe disease after one dose (Table 2). We thus estimated 86%, 94%, 99%, and 90% efficacy after two doses against wild-type for any infection, symptomatic disease, severe disease, and transmission respectively.

Novavax (protein subunit)

We identified two eligible studies on vaccine efficacy for the Novavax vaccine (Figure 8) which informed 8 of the 24 estimates (Table 2). We estimated a 96%, 96%, and 99%

efficacy after two doses against wild-type for any infection, symptomatic disease, and severe disease respectively. There were not enough data to inform estimates of protection against transmission for any non-wild type variant.

CoronaVac (whole virus)

We identified four eligible studies for the CoronaVac vaccine (Figure 9) which informed 4 of the 24 possible estimates (Table 2). We estimated 67%, 67%, and 92% efficacy after two doses against wild-type for any infection, symptomatic disease, and severe disease. There were not enough data to inform estimates of protection against transmission for wild-type or B.1.351/P.1. The most datapoints were available for efficacy against symptomatic (n=6) and severe (n=6) disease ranging from 50.7% (95% CI: 36.0, 62.0)⁶⁰ to 84.0% (65.0, 92.0)¹⁰ and 83.7% (95% CI: 58.0, 93.7)⁶⁰ to 100.0% (20.0, 100.0)¹⁰ respectively against the wild-type variant. There were not enough data to inform estimates of protection against transmission for any variant.

Sinopharm (whole virus)

Only two eligible studies were identified for the Sinopharm BIBP vaccine (Figure 10) which reported efficacy after two doses against symptomatic and severe disease of 78.1% (64.8, 86.3)⁶¹ and 79.0% (95% CI: 26.0, 94.0)⁶², respectively. This informed 2 of the 24 possible synthesised estimates with

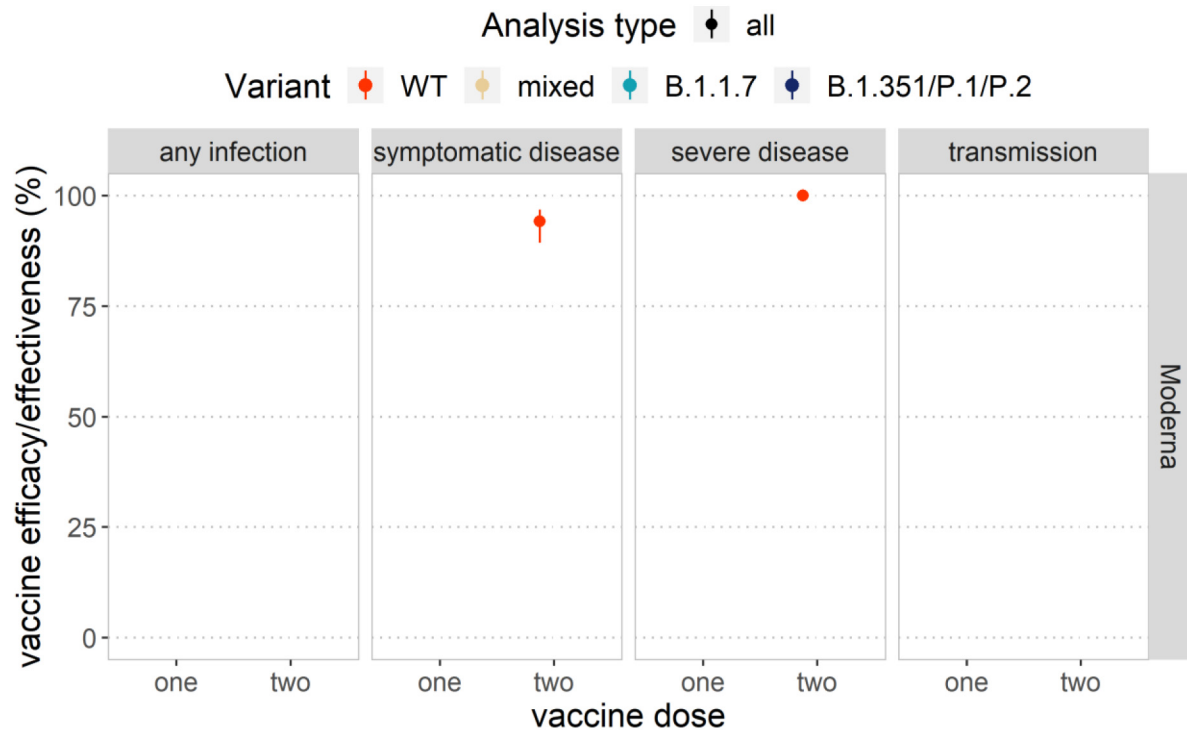


Figure 7. Summary of reported first and second dose vaccine efficacy and effectiveness estimates for the Moderna vaccine for, from left to right: i) any infection; ii) symptomatic disease; iii) severe disease; and iv) transmission. Red points show estimates for the wild-type (WT), yellow for a mix of variants, turquoise for B.1.1.7, and navy for B.1.351, P.1, or P.2.

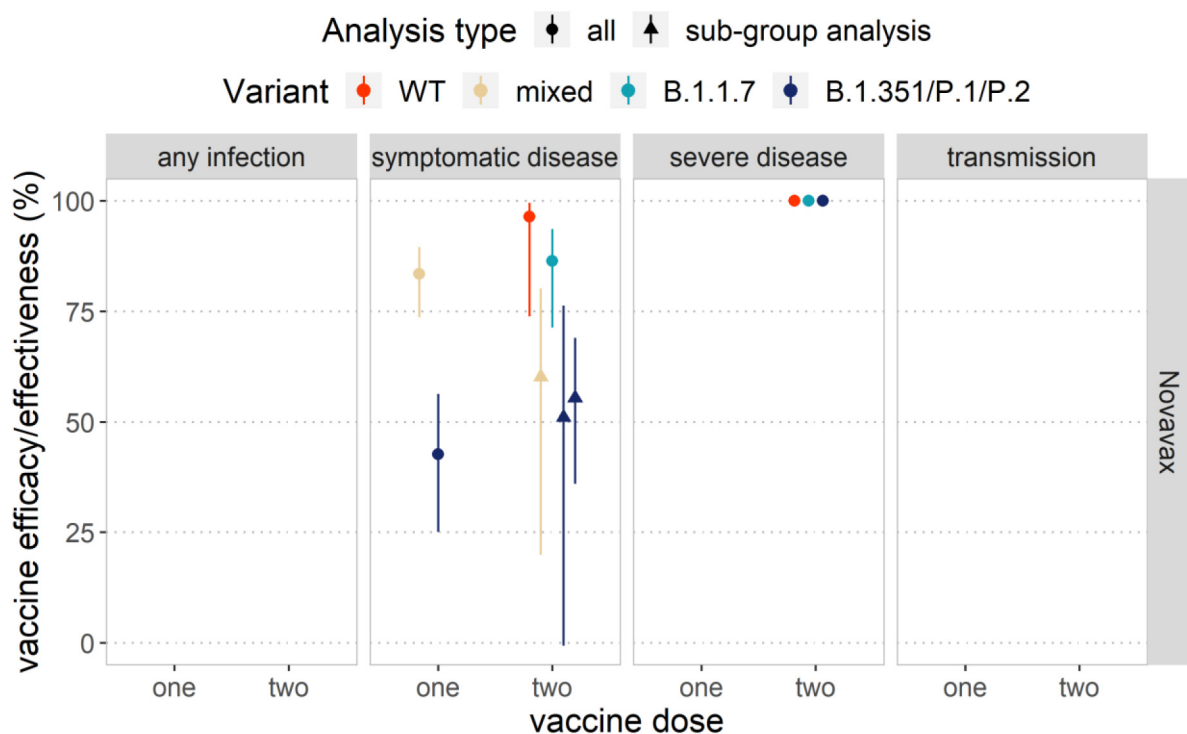


Figure 8. Summary of reported first and second dose vaccine efficacy and effectiveness estimates for the Novavax vaccine for, from left to right: i) any infection; ii) symptomatic disease; iii) severe disease; and iv) transmission. Red points show estimates for the wild-type (WT), yellow for a mix of variants, turquoise for B.1.1.7, and navy for B.1.351, P.1, or P.2.

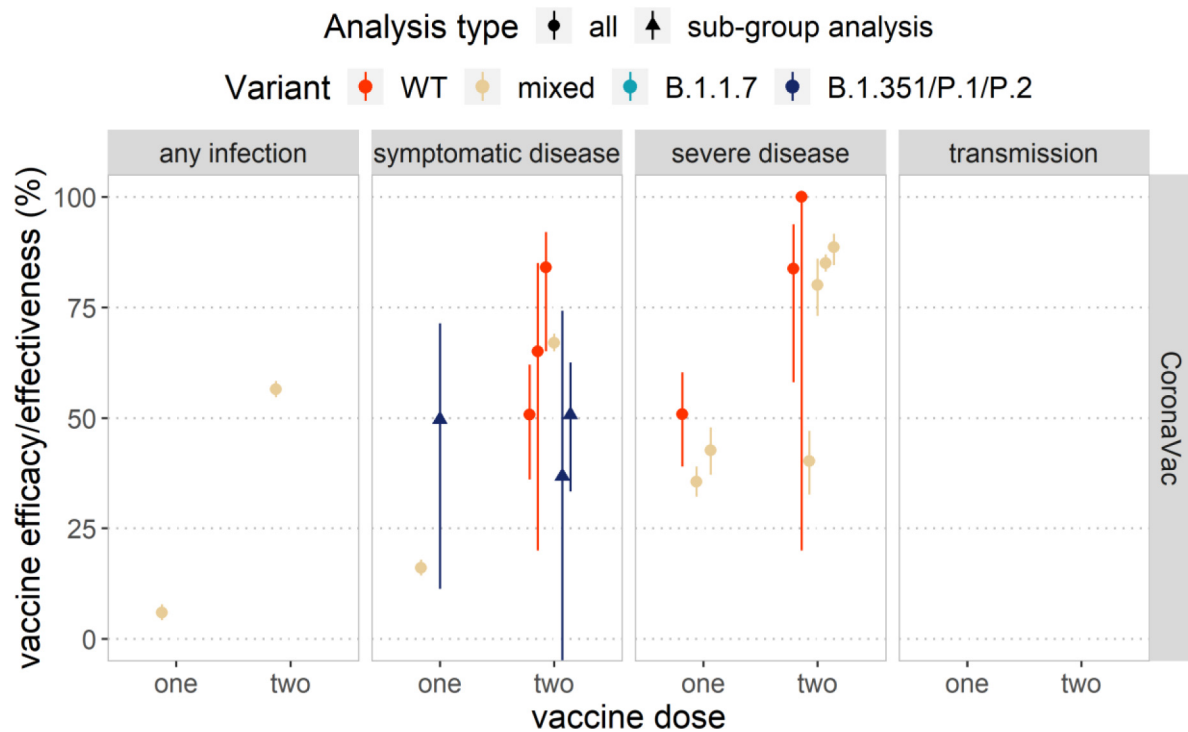


Figure 9. Summary of reported first and second dose vaccine efficacy and effectiveness estimates for the CoronaVac vaccine for, from left to right: i) any infection; ii) symptomatic disease; iii) severe disease; and iv) transmission. Red points show estimates for the wild-type (WT), yellow for a mix of variants, turquoise for B.1.1.7, and navy for B.1.351, P.1, or P.2.

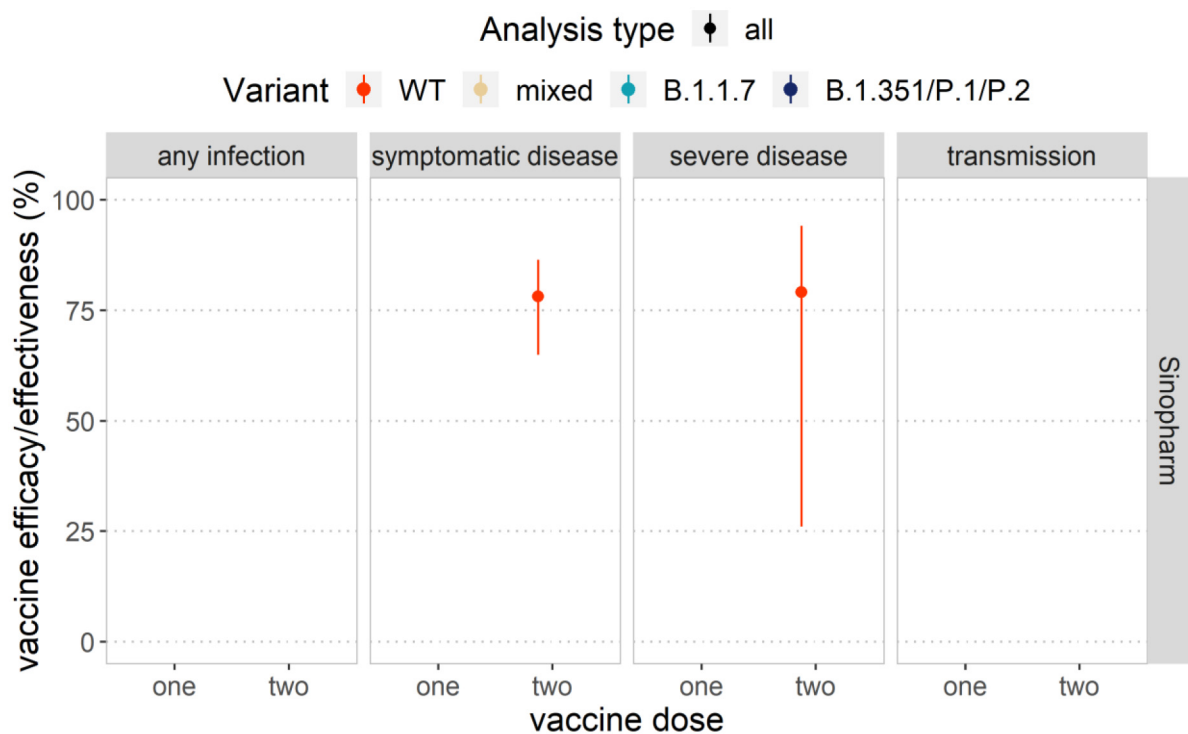


Figure 10. Summary of reported first and second dose vaccine efficacy and effectiveness estimates for the Sinopharm BIBP vaccine for, from left to right: i) any infection; ii) symptomatic disease; iii) severe disease; and iv) transmission. Red points show estimates for the wild-type (WT), yellow for a mix of variants, turquoise for B.1.1.7, and navy for B.1.351, P.1, or P.2.

the remainder assumed to be the same as CoronaVac (Table 2). We estimated a 67%, 78%, and 79% efficacy after two doses against wild-type for any infection, symptomatic disease, and severe disease respectively. There were not enough data to inform estimates of protection against transmission for any variant. No studies were identified reporting results for the WIBP vaccine.

Discussion

This review and evidence synthesis provides an overview of the currently available vaccine efficacy and effectiveness estimates for COVID-19 across multiple vaccine trials and platforms capturing the differences and considerable uncertainty in the protective impact of vaccines. We found the largest number of studies for the AstraZeneca and Pfizer vaccines whilst estimates for Sputnik V and Sinopharm were the most limited. For some vaccines, estimates relied on manufacturer press releases rather than peer-reviewed papers which limited its interpretation. Furthermore, efficacy estimates against VOCs, particularly B.1.351 and P.1 are limited. This is partly due to their more recent emergence compared to B.1.1.7, but also the lack of systematic sequencing in many affected countries. Thus variant-specific estimates are difficult to assess and are often reported as a mix of variants¹⁰. Our evidence synthesis suggests that efficacy estimates for the same vaccine platform are relatively consistent for wild-type, but there is greater variability for VOCs.

Assessment of efficacy and effectiveness of any vaccine is complex, especially for SARS-CoV-2 where our knowledge of the pathogen and the immune response is still evolving. Adding to this complexity is the emergence of new VOCs, some of which carry mutations allowing a degree of immune escape^{24,63}. With COVID-19 vaccines being rolled out globally on an unprecedented scale, heterogeneities such as demographics and comorbidities between different populations will also impact vaccine effectiveness⁵⁷. With some countries prioritising delivery of the first dose to as many individuals as possible over delivery of the second^{18,20}, understanding how protection may differ after each dose of vaccine (for a multi-dose product) is also crucial. Furthermore, while most countries have focused on minimising COVID-19 mortality, or reducing pressures on the health system^{64,65} by vaccinating the elderly, at least one country has prioritised younger adults who contribute most to transmission⁶⁶. A nuanced understanding of how each vaccine acts is therefore important in accurately assessing how effective these strategies may be.

Stringent lockdown measures have been implemented by countries in response to rising case numbers and the threat to hospital capacity. Most countries, including the UK, Israel, and the USA, have adopted strategies that minimise COVID-19 deaths and hospitalisations by prioritising the elderly and vulnerable populations most at risk^{31,67,68}. For this approach, it is important to understand how vaccine efficacy against symptomatic COVID-19 differs from efficacy against severe COVID-19, which is more likely to require hospitalisation.

Conversely, strategies adopted by Indonesia and China aim to minimise transmission by prioritising the younger working population who contribute most to transmission^{69–71}. This can be an effective strategy if efficacy in older age groups is poor and/or vaccines can prevent infection or reduce the infectiousness of breakthrough cases in vaccinated individuals³⁴. Assessment of the extent to which vaccination can prevent SARS-CoV-2 infection varies by study and for many vaccines direct estimates are not yet available. Early effectiveness studies from Israel have suggested high efficacy of 94% against asymptomatic infection after two doses of the Pfizer vaccine⁷². In the UK, 56% (95% CI: 19 – 76) effectiveness against any infection 28 days after the first dose of Pfizer or AstraZeneca⁷³ amongst care home residents and a 72% (95% CI: 58 – 86) and 86% (95% CI: 76 – 97) effectiveness against asymptomatic and symptomatic infection amongst health-care workers has been reported after the first and second dose of the Pfizer vaccine respectively¹⁹. Vaccine effectiveness in reducing the infectiousness of a vaccinated individual if they are infected is not typically reported in clinical trials⁷⁴. Recent effectiveness studies have estimated a 30% reduction in risk of infection amongst household members of vaccinated healthcare workers in Scotland¹³ and that one dose of AstraZeneca and Pfizer provided 47% and 49% protection respectively against onward transmission in England. A population-wide study from Israel found decreased viral loads amongst infected vaccinated individuals suggestive of a reduction in infectiousness⁷⁵. Robust estimates of vaccine efficacy against infection and transmission will be vital in understanding the potential success of a reduced transmission strategy.

Most clinical trials were planned and undertaken before the emergence of VOCs and studies that specifically address efficacy against variants are sparse. Interpreting efficacy results for VOCs typically requires polymerase chain reaction (PCR)-sequencing of cases. If vaccination reduces viral loads in breakthrough cases, as suggested by clinical trials and effectiveness studies for AstraZeneca⁵¹ and Pfizer⁷⁵, it will make samples more difficult to sequence. This increases the possibility of missing variant-specific samples in the vaccine arm which could lead to overestimation of efficacy, as may have occurred in the Emary *et al.* study⁵¹. Nonetheless, studies that systematically sequence cases are valuable and should be considered wherever possible. The recent emergence of the B.1.617.2 variant first identified in India²⁷ has contributed to the surge in cases in India and is now the cause of an increasing proportion of new cases in the UK^{76,77}. Effectiveness studies have shown no significant difference in effectiveness of the Pfizer and AstraZeneca vaccines after the second dose compared to B.1.1.7. However there was a substantial decrease in effectiveness after a single dose of 33.2% (95% CI: 8.3, 51.4) compared to 49.2% (95% CI: 42.6%, 55.0) and 32.9% (95% CI: 19.3, 44.3) compared to 51.4% (95% CI: 47.3, 55.2) for the Pfizer and AstraZeneca vaccines respectively⁷⁸. Especially for countries opting to delay delivery of the second dose in order to deliver as many

first doses as possible, emerging data and continued assessment of vaccine effectiveness against VOCs are crucial in determining the optimal vaccination strategy.

The duration of follow-up in clinical trials and effectiveness studies is not yet sufficient to robustly estimate the duration of vaccine-induced immunity. How waning of immunity may affect the design of booster campaigns being considered to mitigate the potential impact of VOCs⁷⁹ will be a critical factor shaping the trajectory of the pandemic in the coming one or two years. Longitudinal cohort studies are needed to better assess the duration of both natural and vaccine-induced immunity.

Until results of forthcoming studies on efficacy against VOCs, transmission, and infection are available^{80,81}, simulation studies must acknowledge and capture current uncertainty in order to robustly explore and inform vaccination policies and policy around the lifting of NPIs. Finally, it is important to note that this overview, at the time of writing, represents our best

interpretation of the available efficacy and effectiveness data. As more results from clinical trials and effectiveness studies become available, available evidence should be re-evaluated.

Data availability

Underlying data

Figshare: Interpreting estimates of coronavirus disease 2019 (COVID-19) vaccine efficacy and effectiveness to inform simulation studies of vaccine impact. <https://doi.org/10.6084/m9.figshare.14869272>⁵⁰.

Reporting guidelines

Figshare: PRISMA checklist for 'Interpreting estimates of coronavirus disease 2019 (COVID-19) vaccine efficacy and effectiveness to inform simulation studies of vaccine impact: a systematic review' <https://doi.org/10.6084/m9.figshare.14883717.v1>³⁸.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Current Peer Review Status: ? ?

Version 1

Reviewer Report 04 June 2024

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Ian Plumb

CDC, Atlanta, Georgia, USA

General comments

1. This paper is well written, with some observations that seem prescient, but much has changed since it was first published in July of 2021. The authors could consider reflecting that by reframing the writing as historic, at the time of analysis. This remains important to report, and is relevant for future pandemic preparedness, but may otherwise appear odd to read about events in the present tense.
2. Overall, the study was well conducted, but suffers an inherent challenge in trying to aggregate studies that are not only varied in design, but also in potential biases, which can warp VE estimates. A related analysis was published in 2022 (Feikin DR, et al., 2022[Ref 1]) and IVAC have provided a website summarising available evidence (<https://view-hub.org/vaccine/covid/effectiveness-studies>). In general, the best-designed studies appear to have generated comparable estimates, and analyses by subgroup have generally found similar VE. The implication of this is that differences in estimates are more likely to reflect different biases, or measuring different interventions or outcomes.
3. During the period of this analysis, one would expect that most vaccine doses in intervention groups were received recently, but it would be helpful to add clarifications of time since dose. We now know that waning of VE can be quite dramatic, particularly when VE starts lower, as is expected for milder outcomes.
4. It should be noted that VE by a single dose of vaccines with a two-dose primary series was initially highly relevant, but became less so. This is okay to include but could be de-emphasized.
5. The authors could consider removing the analysis of effectiveness against 'transmission' from the analysis and report. Effects of vaccines on transmission can include lower risk of infecting others (as measured in a household transmission study), lower shedding (which might lead to shedding a lower amount of viable virus, whether or not that results in less transmission), less risk of acquisition of infection once exposed (VE against infection), or lower risk of exposing others in the population (by indirect protection). Although the authors could clarify which of these they focus on, an added problem is that there seemed to be few studies, and in the table, it appears that some of these findings were simply

assumed. So it would probably be simplest to remove the 'transmission' component altogether.

6. There appears to be some inconsistency in the results, which needs to be addressed. For example, in the results section for the Pfizer-BioNTech vaccine, the authors state that they estimated 90% protection against transmission, but the chart for that section indicates a lower %, and the authors also state there was no evidence available. The summary chart (Figure 2) omits this estimate. For the Sputnik section, the authors state that no data were available, so it is then not clear why an estimate is presented in the summary figure (Figure 2). As above, it might be simplest to remove the transmission endpoint, given that data were sparse and the definition seems ambiguous.

Additional comments are added below for consideration.

Introduction

1. Given changes since publication, consider reframing the paper as a historic account, and clarifying the timeline from the outset (based on the methods, up to May 2021). For example, 'has been remarkable' can be changed to 'was remarkable'. With hundreds of VE analyses now included in IVAC's review, it may be difficult to say 'real-world data... are emerging'. The language in the third paragraph indicates this was originally written before roll-out strategies that countries 'may adopt', so would also benefit from an update.
2. Recommend clearly distinguishing efficacy, effectiveness, and impact throughout. In the third introductory paragraph, varying coverage could be delineated more clearly from assessing whether effectiveness varies by subgroup.
3. Some references cited now appear out of date. For example, there are a range of studies on the effects of variants on decreased neutralization, and lower VE. For example, see <https://europepmc.org/article/MED/36864253> (Feikin DR, et al., 2022[Ref 1]), (Carabelli AM, et al., 2023 [Ref 2]). Would consider citing these or other more recent references, and update the text accordingly. Existing references may also need to be updated.
4. Would not state that the population 'remains below herd immunity threshold' here, given misinterpretation of that term during the COVID-19 pandemic. Would also consider modifying the language because seroprevalence studies indicate a high proportion of populations developed some immunity from infection or vaccination.
5. The objective seems very broad. It sounds like the goal was to summarize evidence of efficacy and effectiveness for different products and different variants, which is already a huge undertaking (see IVAC's review online, <https://view-hub.org/vaccine/covid>), before considering different populations, endpoints, and time since vaccination. Of course it's fine to summarize broad scope if that is the reality, but it would help the reader to specify objectives more clearly. For an example synthesis of efficacy and effectiveness data from earlier in the pandemic, please see (Wallace M, et al., 2022[Ref 3]). Please note that this approach explicitly prioritises higher-quality evidence (i.e. RCTs) before considering observational data. It would help if the authors also clarify how they prioritized evidence.

Methods:

1. Inclusion criteria: recommend clarifying the criteria for excluding specific subgroups — did that also apply to studies assessing VE among certain age groups, or regional populations?
2. It would help to clarify the timing of the review — were press releases considered for results unavailable by a particular date?
3. Does 'infectiousness' refer to viral shedding or some other proxy of possible infectiousness? It is difficult to assess infectiousness directly, and this is distinct from indirect protection

(assessing the effect of indirectly protecting others via decreased exposure). Would also recommend using an alternative to 'breakthrough' infection, since the number of infections after vaccination depends on coverage as well as effectiveness.

4. The assumption of the same efficacy against any infection and symptomatic infection seems difficult to justify, because the immune system encounters more challenges preventing infection outright, than preventing infection with symptoms, and observational data support that. This could be reframed as a simplifying assumption for analysis purposes.
5. 'We do not consider the duration of vaccine-induced immunity as data are not yet available to assess this.' Recommend rephrasing in the past tense, at the time of review.

Results:

1. Since effectiveness studies are observational, it would help to clarify what is meant by 'and 1 observational study'.
2. Recommend adding confidence intervals to estimates, and considering carefully in the discussion whether such differences might have arisen from different study designs, resulting in different biases. Similarly, it would help to note that differences in VE between products might reflect differences in study designs as well as any biological differences between products, or differences in timing.
3. For Moderna, it would help to clarify if the same ratio of VE between Pfizer and Moderna was extrapolated to obtain other estimates of VE by the Moderna vaccine.

Discussion:

1. As above, would consider reframing this as a historical narrative by simple changes to the language (for example, instead of 'most countries... have adopted', 'most countries... adopted'). For anything that has become outdated, it may be best to say 'at the time of this analysis'.
2. Recommend adding a short paragraph that frankly acknowledges several limitations, such as assumptions made (for example, assuming VE is the same against severe illness and milder infection), and changes in variants, vaccines and host immunity since this analysis was performed. A risk-of-bias assessment was considered to be outside of scope, but would be worth noting as a limitation.
3. Under implications it would be helpful to mention how this might inform pandemic preparedness, including the potential benefit of rapidly assessing and summarizing evidence to inform vaccine policy.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease epidemiology, vaccine effectiveness

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 31 May 2024

<https://doi.org/10.21956/wellcomeopenres.18762.r50305>

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Srikanth Umakanthan

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1. Abstract—This abstract is well structured and summarizes the overall purpose of the study and the research problem(s) investigated. It also showcases the basic design of the study and the major findings and trends found as a result of the study.
2. Materials and methods—The authors have included a proper survey questionnaire and the assessment scale to analyze their objectives.
3. Statistics: The involvement of regression methods (logistic and linear models) clears bias that may have been generated by the different variables. The statistical methods well neutralize the confounding/impending factors.

4. Discussion: The discussion requires more additional statements with regard to the existing literature search. Include the following references and citations reflecting the COVID-19 updates to strengthen the manuscript:

- **Origin and transmission**
- **To briefly mention vaccines and the geographical distribution of vaccines compared with your study.**
- **Definition of vaccine resistance and hesitance, as well as the advantages and disadvantages of seeking public involvement and assistance in vaccine publicity.**
- **Compare the global vaccine status and relate it with the current vaccine status**

5. Conclusion: The authors have shown the importance of variables that can influence the adherence of preventive measures and willingness to vaccinate against COVID-19.

The main bulletin messages showcase the summary of the manuscript very well.

I advocate this article for revision pending the inclusion of the points I recommended.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am an active researcher in COVID-19 with a high number of original studies and reviews published in high impact factor journals. I am also an editor and active reviewer in numerous refuted journals.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
