Transmissibility of COVID-19 among vaccinated individuals

Targeted Literature Search

Date of Literature Search: 2/26/2021
Date of Submission: 3/2/2021

Prepared By:
Oluwaseun Egunsola, Liza Mastikhina, Laura Dowsett, Fiona Clement, on behalf of the University of Calgary Health Technology Assessment Unit.

Contact:
Fiona Clement

Email: fclement@ucalgary.ca

Suggested citation: Egunsola O, Mastikhina L, Dowsett LE, Clement FM on behalf of the University of Calgary Health Technology Assessment Unit. Transmissibility of COVID-19 among Vaccinated Individuals: Targeted Literature Search. March 2, 2021

UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE

UNIVERSITY OF CALGARY
O'Brien Institute for Public Health
Health Technology Assessment Unit

Funding Acknowledgement(s)
The SPOR Evidence Alliance (SPOR EA) is supported by the Canadian Institutes of Health Research (CIHR) under the Strategy for Patient-Oriented Research (SPOR) initiative.

COVID-19 Evidence Network to support Decision-making (COVID-END) is supported by the Canadian Institutes of Health Research (CIHR) through the Canadian 2019 Novel Coronavirus (COVID-19) Rapid Research Funding opportunity.

Project Contributors
Oluwaseun Egunsola[1,2]; Liza Mastikhina[1,2]; Laura Dowsett[1,2]; and Fiona Clement[1,2]

Affiliations
1. The Department Community Health Sciences, Teaching Research and Wellness Building, 3280 Hospital Drive NW Calgary Alberta T2N 4N1
2. O'Brien Institute for Public Health, Teaching Research and Wellness Building, 3280 Hospital Drive NW Calgary Alberta T2N 4N1

Table of Contents

Abbreviations and Definitions

Abbreviations

CDC	Centres for Disease Control and Prevention
Ct	Cycle threshold
COVID-19	Coronavirus Disease 2019
IQR	Interquartile range
mRNA	Messenger ribonucleic acid
NR	Not Reported
PCR	Polymerase chain reaction
RCT	Randomized controlled trial
ROBINS-I	Risk of bias for non-randomized studies
SARS-Cov-2	Severe Acute Respiratory Syndrome Coronavirus 2
VOC	Variant of concern
WHO	World Health Organization

Executive Summary

Objectives: To identify observational studies and randomized controlled trials (RCTs) evaluating the effectiveness of COVID-19 vaccination in reducing forward transmission from vaccinated people. The question has arisen because most COVID-19 vaccine trials use an endpoint of symptomatic infection, so there is less data around whether asymptomatic infection and viral carriage may still occur after vaccination, and whether this incurs a risk for viral transmission from vaccinated persons.

Design: Targeted literature search.

Method: A targeted search of Clinicaltrials.gov, McMaster Health Forum (COVID-END), MedRxiv, Google, regulatory submissions, and websites of the Centres for Disease Control and Prevention (CDC) and World Health Organization (WHO) was conducted to identify RCTs or observational studies evaluating the effectiveness of COVID-19 vaccination in the prevention of asymptomatic infections and transmissibility of COVID-19 among vaccinated persons. Search was limited to studies with published efficacy data on vaccines approved in any jurisdiction. Literature was searched by a single reviewer and then reviewed in full text by two independent reviewers. This targeted search is current to February 26th, 2021.

A standardized data extraction sheet was used to extract the year of publication, country, study design, patient characteristics including sex, gender and age, variants of COVID-19, whether infection was symptomatic or asymptomatic, and all the reported outcomes. Quality assessment was conducted based on study design: ROBINS-I for non-randomized studies, Cochrane Risk of Bias for human-subject RCTs, and SYRCLE's Risk of Bias for animal studies. Data were extracted by one reviewer and verified by another.

Results: A total of 15 studies were included in this review. Ten studies were in humans and five were preclinical animal studies in macaques.

Asymptomatic infection data were presented for only the UK component of the AstraZeneca ChAdOx1 nCoV-19 vaccine studies. Participants were assessed by weekly self-administered nose and throat swabs for RT-PCR testing, with positive tests obtained regardless of symptoms. Neither one or two doses of AstraZeneca's standard dose ChAdOx1 nCoV-19 vaccine was effective against asymptomatic infection with the wild type virus (7.8% (95% CI: -46.7-42.1) and 27.3% (95% CI: -17-54.9)) or B.1.1.7 variant (26.5% (95% CI: -112-74.5)) in baseline seronegative participants. The baseline PCR results of the participants were not reported, therefore, persistent carriage after previous infection was not ruled out. In the subgroup of participants with an initial low dose of the vaccine, followed by a standard dose, two studies reported 49.3% (95% CI: 7.4-72.2) and 58.9% (95% CI: 1-82.9) respective efficacies against asymptomatic infection 14 days after the second dose. A phase 2/3 RCT comparing the minimum cycle threshold (Ct) values in ChAdOx1 nCoV-19 vaccinated individuals with a comparator group of meningococcal vaccine, reported statistically significantly higher PCR Ct values in the ChAdOx1 nCoV-19 vaccinated group.

Of the four Pfizer BioNTech's BNT162b2 observational studies with data on asymptomatic infection, only one, involving almost 1.2 million Israeli participants reported vaccine efficacy against asymptomatic infection. This study, which did not establish baseline seronegativity, found one dose of BNT162b2 to significantly reduce asymptomatic infection by 29% (95% CI: 17-39) and 52% (95% CI: 41-60) after 14 to 20 days and 21 to 27 days of follow-up respectively, as assessed by confirmed positive PCR SARS-CoV-2 test without documented symptoms. No routine swabbing was documented for the participants. The vaccine was reported to be 90% effective (95% CI: 83-94) against asymptomatic infection seven days after the second dose. The other three BNT162b2 studies did not report effect estimates for vaccine protection against asymptomatic infection. Two of these studies however measured Ct for BNT162b2

vaccinated and unvaccinated individuals; one of which found significantly higher Ct values (suggesting lower amounts of virus detected) in infected vaccinated individuals between 12 and 28 days after the first dose ($p<10^{-8}$). In the other study, an asymptomatic screening program among health care workers (HCWs) who were vaccinated with one dose of BNT162b2, the median Ct values of infected health care workers were reported to have shown a non-significant trend towards increase between unvaccinated (Median=20.3) and vaccinated HCWs after 12 days post-vaccination (Median=30.3), suggesting that samples from infected vaccinated individuals had lower viral loads

One study showed that, among participants who received the first dose of the mRNA-1273 vaccine while negative for COVID-19 by RT-PCR or antibody testing at baseline, 0.1% were found to have positive swabs but no symptoms at the time of their second dose, compared with 0.27% of the unvaccinated group.

Among participants who were seronegative at baseline (defined as negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on day 1), the Ad26.COV2.S vaccine by Janssen Biotech, was not effective against asymptomatic infection in the first 28 days of follow-up. However, the vaccine was 74% effective after 28 days. Asymptomatic infection was assessed by lack of symptoms on the day preceding, the day of, or any time after a positive PCR test. The frequency of swabbing for PCR testing was not reported in this study.

All the animal studies showed the vaccines to significantly reduce viral load in vaccinated animals compared with controls. Viral load in fully vaccinated animals were assessed in bronchoalveolar lavage and nasal swabs, between one and seven days after viral challenge.

Conclusion: Some studies, such as the ChAdOx1 nCoV-19 vaccine studies, included data on cross sectional prevalence of positive SARS-CoV-2 RT-PCR from routine swabbing, which suggest effectiveness against asymptomatic infection, although this was not routinely assessed in a comparable way across studies. Limited evidence regarding the Ct values for AstraZeneca's ChAdOx1 nCoV-19 vaccine and the BNT162b2 vaccine suggest their potential to reduce viral load and possibly transmission. There are no publications yet that detail transmission of COVID-19 from vaccinated persons to their contacts. There are very limited studies on the efficacy of the approved vaccines against the variants of concern. Further research is needed to evaluate post-vaccination infectivity and transmission of both the wild type COVID-19 virus and the variants of concern.

Protocol/Topic Registration: Not Applicable.

Introduction

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of February 2021, there have been more than 110,000,000 confirmed cases of COVID-19, which have resulted in more than 2,500,000 confirmed deaths worldwide.[1] COVID-19 is transmitted primarily through direct person-to-person contact, with asymptomatic infection estimated to occur in up to 17% of people who have tested positive for the virus.[2] Since the start of the pandemic, several clinical trials have been underway to examine the safety and effectiveness of different vaccines to prevent COVID-19, with preliminary phase 2/3 results pointing to high vaccine effectiveness. The objective of this targeted literature search was to identify observational studies and randomized controlled trials (RCTs) evaluating the effectiveness of COVID-19 vaccination in reducing asymptomatic viral carriage and other proxies of possible transmission.

Methods

A targeted search of Clinicaltrials.gov, McMaster Health Forum (Covid-End), MedRxiv, Google, regulatory submissions, and websites of the Center for Disease Control and Prevention (CDC) and World Health Organization (WHO) was conducted to identify preclinical and clinical observational studies or RCTS evaluating the effectiveness of COVID-19 vaccination in the prevention asymptomatic viral detection as a proxy of a possible infective state. The search was limited to studies conducted in 2020 and 2021, current to February 26th, 2021. There were no language limitations.

A screening form based on the eligibility criteria was prepared. Citations identified as potentially relevant from the targeted literature search were read in full text by two reviewers and assessed for eligibility based on the criteria outlined below (Table 1). Discrepancies were resolved by discussion or by a third reviewer. Reference lists of included studies were hand searched to ensure all relevant literature is captured.

Table 1. Criteria for Inclusion

Population	Persons who had received COVID-19 vaccination irrespective of age, sex or gender. Animal studies were also included.
Intervention	COVID-19 vaccination, and its impact on prevention of symptomatic and asymptomatic infections. Studies evaluating the transmissibility or infectivity of COVID-19 among vaccinated individuals were included.
Comparator	Non-vaccinated persons.
Outcome	Include, but are not limited to, viral load, symptomatic or asymptomatic laboratory confirmed cases by RT-PCR post-vaccination and the number of persons who are infected by someone who has COVID-19 and has had the vaccine.
Study Design	Observational studies and RCTs evaluating the effectiveness of COVID-19 vaccination in the prevention of asymptomatic viral infections as a proxy of a possible transmission will be included. Studies eligible for inclusion must have a control group.

A standardized data extraction sheet was used to extract year of publication, country, study design, patient characteristics including sex, gender and age, variants of COVID-19, whether infection was symptomatic or asymptomatic, and all the reported outcomes, after all reviewers

had completed a calibration exercise. Data were extracted by one reviewer and verified by another reviewer.

Quality assessment was conducted based on study design: Cochrane risk of bias for non-randomized studies (ROBINS-I) for non-randomized studies,[3] Cochrane Risk of Bias (version 5.1.0) for human-subject RCTs,[4] and SYRCLE's Risk of Bias for animal studies.[5] Quality assessment was conducted by one reviewer and verified by a second reviewer.

Results

Study Characteristics

A total of 15 studies were included in this review. Ten were human studies (Tables 2 and 3)[6-15] and five were preclinical animal studies in macaques, with viral challenge 1-8 weeks post vaccination (Table 4).[16-20] Five of the human studies were randomized controlled trials,[6-8,13,14] two were prospective cohort studies[10,11] and two were retrospective cohort studies.[9,12,15] The studies were conducted across several countries including USA, UK, Israel, Brazil, South Africa and several South American countries. There were five studies evaluating Pfizer BioNTech's BNT162b2 vaccine,[9-12,15] three studies evaluated ChAdOx1 nCoV-19 by AstraZeneca,[6-8] one study each evaluated Janssen's Ad26.COV2.S vaccine,[13] and mRNA-1273 by Moderna.[14] The five animals studies evaluated ChAdOx1 nCoV-19,[16] NVX-CoV2373,[17] mRNA-1273,[18] piCoVacc[19] and a DNA vaccine.[20]

Table 2: Characteristics of included RCTs

Author/Country/Design	Trial Information	Participant Inclusion/Exclusion Criteria	Vaccine Information	Efficacy Outcomes
Author: Voysey 2021[7] **County:** UK, Brazil, S.Africa **Date of Recruitment:** May-Nov 2020 **Trial Phase:** 2/3 **Design:** Single Blind RCT **Funding:** UK Research and Innovation, National Institutes for Health Research (NIHR), Coalition for Epidemic Preparedness Innovations, Bill & Melinda Gates Foundation, Lemann Foundation, Rede D'Or, Brava and Telles Foundation, NIHR Oxford Biomedical Research Centre, Thames Valley and South Midland's NIHR Clinical Research Network, and AstraZeneca.	**Age:** NR **%Female:** Varied **Type of comparator:** Meningococcal vaccine **Sample Size Vaccine:** Varied **Sample Size Control**: Varied **Total Sample:** Varied **VOC:** NR	Healthy volunteers aged over 18; at risk of virus, stable pre-existing conditions	**Vaccine:** ChAdOx1 nCoV-19 **Manufacturer:** AstraZeneca **Dose:** Low or Standard Doses **Number of Doses:** 2	• Symptomatic Infection • Severe Cases • Asymptomatic infection (weekly self- administered nose and throat swab for NAAT testing from 1 week after first vaccination using kits provided by the UK Department of Health and Social Care)
Author: Voysey, 2021[8] **County:** UK, Brazil, S.Africa **Date of Recruitment:** May-Dec 2020 **Trial Phase:** 1/2/3 **Design:** Single Blind RCT **Funding:** UKRI, NIHR, CEPI, the Bill & Melinda Gates Foundation, the Lemann Foundation, Rede D'OR, the Brava and Telles Foundation, NIHR Oxford Biomedical Research Centre, Thames Valley and South Midland's NIHR Clinical Research Network, and Astra Zeneca	**Age**: NR **%Female:** NR **Type of comparator:** Meningococcal vaccine **Sample Vaccine:** 8567 **Sample Control:** 8580 **Total Sample:** 17177 **VOC:** NR	NR	**Vaccine:** ChAdOx1 nCoV-19 **Manufacturer:** AstraZeneca **Dose:** Low or Standard Doses **Number of Doses:** 2	• Symptomatic Infection • Severe Cases • Asymptomatic infection (measured by means of weekly self-administered nose and throat swabs using kits provided by the Department of Health and Social Care)
Author: Emary 2021[6] **County**: UK **Date of Recruitment:** Oct-Jan 2021 **Trial Phase:** 2/3	**Age:** NR **%Female:** NR **Type of comparator:** Meningococcal vaccine	Aged 18 and over; high-exposure populations eligible for vaccination under the government National Health	**Vaccine:** ChAdOx1 nCoV-19 **Manufacturer:** AstraZeneca	• Symptomatic Infection • Ct Values (weekly swabs processed.The minimum Ct value across the N and

Author/Country/Design	Trial Information	Participant Inclusion/Exclusion Criteria	Vaccine Information	Efficacy Outcomes
Design: RCT **Funding:** UK Research and Innovation, National Institutes for Health Research (NIHR), Coalition for Epidemic Preparedness Innovations, NIHR Oxford Biomedical Research Centre, Thames Valley and South Midlands NIHR Clinical Research Network, and AstraZeneca.	**Sample Vaccine:** 4236 **Sample Control:** 4270 **Total Sample:** 8506 **VOC:** B.1.1.7, Other	Service coronavirus vaccine programme.	**Dose:** Low or Standard Doses **Number of Doses**: 2	ORF1ab genes from each PCR test was computed) • Asymptomatic Unknown infection (upper airway swabs every week during the trial. Cases were excluded if they occurred before 15 days post the second dose of vaccine or occurred in participants who were not seronegative on a SARS-CoV-2 N protein assay at baseline)
Author: Janssen Biotech, 2021[13] **County:** Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States **Date of Recruitment:** Sept 2020-Jan 2021 **Trial Phase:** 3 **Design:** Double Blind RCT **Funding:** Janssen Biotech	**Age:** 51.1 (15.0) **%Female:** 44.5 **Comparator:** Placebo **Sample Vaccine:** 19514 **Sample Control:**19544 **Total Sample:** 39058 VOC:NR	Adults 18+ with or without comorbidities.	**Vaccine:** Ad26.COV2.S **Manufacturer**: Janssen Biotech **Dose:** NR **Number of Doses**: 1	• Severe cases • Moderate to Severe infections • Asymptomatic infection (No symptoms on the day preceding, the day of, or any time after the positive PCR test AND has a SARS-CoV-2 positive RT-PCR test result OR develops a positive serology based on a SARS-CoV-2 N-specific immunoglobulin assay (Elecsys®, Roche) during the study. SARS CoV-2 seropositivity by non-S protein was assessed at Day 1 (pre-vaccination), Day 29 (28 days post-vaccination), and Day 71)
Author: Baden, 2021[14] **County**: USA **Date of Recruitment:** Jul-Nov, 2020	**Age:** 51.4 **%Female:** 47.3 **Comparator:** saline	**Include:** Eligible participants were persons 18 years of age or older with no known history of SARS-CoV-2 infection and with	**Vaccine:** mRNA-1273 **Manufacturer:** Moderna	• Symptomatic infection • Severe cases • Any Positive PCR

Author/Country/Design	Trial Information	Participant Inclusion/Exclusion Criteria	Vaccine Information	Efficacy Outcomes
Trial Phase: 3 **Design:** Observer Blinded RCT **Funding:** Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases	**Sample Vaccine:** 14550 **Sample Control:** 14598 **Total Sample:** 29148	locations or circumstances that put them at an appreciable risk of SARSCoV-2 infection, a high risk of severe COVID-19, or both. **Exclude:** Pregnant women and children	**Dose:** 100mcg **Number of Doses**: 2	• Asymptomatic infection (Surveillance swab at the second dose visit)

IQR: interquartile range, NR: Not Reported, PCR: Polymerase Chain Reaction, RCT: randomized controlled trial, VOC: Variant of Concern

Table 3: Characteristics of Observational Studies

Author/Country/Design	Trial Information	Participant Inclusion/Exclusion Criteria	Vaccine Information	Efficacy Outcomes
Author: Hall, 2021[11] **County:** UK **Date of Recruitment**: Dec 2020-Feb, 2021 **Trial Phase:** Post Approval **Design:** Prospective Cohort **Funding:** Public Health England and the Department of Health and Social Care; NIHR	**Age:** NR **%Female**: 84 **Type of comparator:** Unvaccinated **Sample Vaccine**: NR **Sample Control:** NR **Total Sample:** NR **VOC**: B.1.1.7	Health care workers at hospital, who could provide informed consent and anticipated remaining engaged in follow-up for 12 months.	Vaccine: BNT162b2 Manufacturer: Pfizer BioNTech Dose: NR Number of Doses: 1 or 2	• Symptomatic Infection • Asymptomatic infection (fortnightly asymptomatic PCR testing (anterior nasal swabs or combined nose and oropharyngeal swabs) and monthly antibody testing) • Any positive PCR
Author: Amit, 2021[9] **County:** Israel **Date of Recruitment:** Dec 2020-Jan 2021 **Trial Phase:** Post Approval **Design:** Retrospective Cohort **Funding:** NR	**Age:** NR **%Female:** NR **Comparator:** Unvaccinated **Sample Vaccine:** NR **Sample Control**: NR **Total Sample:** NR **VOC:** NR	NR	**Vaccine:** BNT162b2 **Manufacturer**: Pfizer BioNTech **Dose:** 1 or 2 **Number of Doses**:2	• Symptomatic Infection • Any positive PCR
Author: Dagan, 2021[10] **County:** Israel **Date of Recruitment:** Dec 2020-Feb, 2021 **Trial Phase:** Post Approval **Design:** Prospective Cohort **Funding:** NR	**Age:** Unvaccinated 45 (IQR:35–62), vaccinated: 45 (35–62 **%Female:** 50 **Comparator:** Unvaccinated **Sample Vaccine:** 596618 **Sample Control:** 596618 **Total Sample:** 1193236 **VOC**: B.1.1.7	**Include:**16 years or older, not having a previously documented positive SARS-CoV-2 PCR test, and being a member of the health care organization during the previous 12 months. **Exclude:** probability of exposure or the outcomes is high and controlling for the high variability is not feasible.	**Vaccine:** BNT162b2 **Manufacturer**: Pfizer BioNTech **Dose:** NR **Number of Doses**:2	• Symptomatic Infection • Severe Cases • Asymptomatic infection (testing protocol not defined, however SARS-CoV-2 infection without documented symptoms used as proxy)
Author: Levine-Tiefenbrun, 2021[12] **County:** Israel **Date of Recruitment:** Dec 2020-Jan, 2021 **Trial Phase:** Post Approval	**Age:** NR **%Female:** NR **Comparator:** Unvaccinated	**Include:** All positive post-vaccination samples; **Exclude:** Patients who had a positive sample prior to	**Vaccine:** BNT162b2 **Manufacturer**: Pfizer BioNTech **Dose:** NR	• Ct values

Design: Retrospective Cohort **Funding:** NR	**Sample Vaccine:** Varied **Sample Control**: Varied **Total Sample:** Varied **VOC:** NR	vaccination; patients age 90 and above	**Number of Doses**:1	
Author: Weekes, 2021[15] **Country:** UK **Date of Recruitment:** Jan 18-31, 2021 **Trial Phase:** Post Approval **Design:** Retrospective Cohort **Funding:** Wellcome Senior Clinical Research Fellowship to MPW (108070/Z/15/Z), a Wellcome Principal Research Fellowship to PJL (210688/Z/18/Z), and an MRC Clinician Scientist Fellowship (MR/P008801/1) and NHSBT workpackage (WPA15-02) to NJM. Funding was also received from Addenbrooke's Charitable Trust and the Cambridge Biomedical Research Centre.	**Age:** NR **%Female:** NR **Comparator:** Unvaccinated **Sample Vaccine:** 3535 **Sample Control**: 3252 **Total Sample:** Varied **VOC:** B.1.1.7	**Include:** vaccinated and unvaccinated Health Care Workers **Exclude:** NR	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer BioNTech **Number of Doses**:1	• Any positive PCR • Ct values • Asymptomatic (weekly Screening)

IQR: interquartile range, NR: Not Reported, PCR: Polymerase Chain Reaction, RCT: randomized controlled trial, VOC: Variant of Concern

Table 4: Characteristics of Included Animal Studies

Author (Year) Country	Type of experimental animal	Vaccine Sample Size	Control Sample Size	Type of virus	Virus strain	Route of Challenge	Dose/quantity of virus (PFU)	Time of Viral Challenge	Vaccine Name/ Number of Doses	Vaccine Dose	Vaccine Sponsor	Status of Vaccine
Corbett (2020)[18] USA	Rhesus Macaque	16	8	Wild type	SARS-CoV-2 (USAWA1/2020 strain)	Intratracheal and/or intranasal	7.6×10^5	8 weeks	mRNA-1273 2 doses	10 mcg or 100 mcg	Moderna	Approved
Van Doremalen (2020)[16] USA	Rhesus Macaque	6	6	Wild type	nCoV-WA1-2020	Others	2.6×10^2	28 days	ChAdOx1 nCoV-19 2 doses	2.5×10^{10} virus particles	AstraZeneca	Approved
Gao (2020)[19] China	Rhesus macaques (Macaca mulatta)	8	8	Wild type	CN1	Intratracheal	10^6 TCID50 of SARS-CoV-2 CN1	day 22 (1 week after the third immunization)	PiCoVac 3 doses	medium dose (3 mg per dose) or high dose (6 mg per dose)	Sinovac	Unknown
Guebre-Xabier (2020)[17] USA	Cynomolgus macaques	12	4	Wild type	2019-nCoV/USA-WA1/2020	Intratracheal and/or intranasal	1.04×10^4	35 days	NVX-CoV2373 2 doses	2.5mcg or 5mcg or 25mcg	Novavax	Phase 3
Yu (2020)[20] USA	Rhesus macaques	25	10	Variants of Concern	S.dCT, S.dTM, S1, RBD, S.dTM.PP	Intratracheal and/or intranasal	1.2×10^8 virus particles [1.1×10^4] of SARS-CoV-2, administered as 1 ml by the intranasal route and 1 ml by the intratracheal route	week 6 (3 weeks after the boost immunization)	DNA vaccine 2 doses + boost	5-mg	Janssen	Unknown

full-length deletion of the cytoplasmic tail (S.dCT), deletion of the transmembrane ™ domain and cytoplasmic tail (CT) reflecting the soluble ectodomain (S.dTM), S1 domain with a foldon trimerization tag (S1), receptor-binding domain with a foldon trimerization tag (RBD), prefusion-stabilized soluble ectodomain with deletion of the furin cleavage site, two proline mutations, and a foldon trimerization tag (S.dTM.PP)

Risk of Bias Assessment

The five included RCTs[6-8,13,14] were assessed with the Cochrane Risk of Bias Assessment Tool.[4] Two studies had some concerns regarding randomization,[6,13] two were of low risk[7,14] and one study had no sufficient information for assessment.[8] All but one low risk study[14] was assessed to have some concerns regarding deviation from intended intervention. Four studies were of some concerns for missing outcome data,[7,8,13,14] one was assessed to be of high risk of bias.[6] All the studies were of low risk of bias for the measurement of outcomes. All but one study with some concern [6] were of low risk for the selection of reported results [6-8,13,14] Overall, four of the RCTs were of some concerns for bias[7,8,13,14] and one had a high risk of bias[6] (Figure **1**).

The five non-RCTs[9-12,15] were assessed using ROBINS-I tool.[3] All, but one study,[9] were of moderate risk of bias due to confounding. Two studies were of moderate[10,11] and three of low risks of bias[9,12,15] for participants' selection. All, but one moderate risk study,[9] were of low risk for the classification of intervention and the measurement of outcomes. There were three studies with low risk of bias[10,12,17] and one with moderate risk for deviation from intervention.[11] All, but one low risk of bias study,[10] did not have sufficient information on missing data or the selection of reported results. Overall, four studies were considered to be of moderate risk,[10-12,15] while one study did not have enough information for risk assessment.[9] (Figure **2**)

The five included animal studies[16-20] were assessed with the Systematic Review Centre for Laboratory animal Experimentation's (SYRCLE) risk of bias tool for animal studies.[5] All but one study[16] had unclear bias for allocation sequence, blinding of investigators and blinding of assessors. All studies were of unclear risk of bias for baseline similarity, random housing of animals, random selection of animals for assessment, incomplete outcome data, selective outcome data, and 'any other possible bias'. (Figure **3**)

Figure 1: Risk of Bias Assessment for RCTs

Author	Randomization	Deviation from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported results	Overall Bias
Baden et al.[14]	Low	Low	Some concerns	Low	Low	Some concerns
Emary et al.[6]	Some concerns	Some concerns	High	Low	Some concerns	High
Janssen Biotech[13]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Voysey et al.[7]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Voysey et al.[8]	NI	Some concerns	Some concerns	Low	Low	Some concerns

All studies were published in 2021 except Polack et al, 2020; NI: No information

Figure 2: ROBINS-I Risk of Bias for non-RCTs

Author	Bias due to confounding: Risk of bias judgment	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall Risk of Bias
Hall et al.[11]	Moderate	Moderate	Low	Moderate	NI	Low	NI	Moderate
Levine-Tiefenbrun et al.[12]	Moderate	Low	Low	Low	NI	Low	NI	Moderate
Amit et al.[9]	NI	Low	Moderate	NI	NI	Moderate	NI	NI
Dagan et al.[10]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Weekes et al.[15]	Moderate	Low	Low	Low	NI	Low	NI	Moderate

All studies were published in 2021; NI: No information

Figure 3: SYRCLE risk of bias assessment for animal studies

Author	Allocation Sequence	Similar Baseline	Allocation Concealment	Random Housing of Animals	Blinding of Investigators and Caregivers	Random Selection for Assessment	Blinding of Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Any other possible Bias
Corbett et al.[18]	Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Van Doremalen et al.[16]	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Unclear
Gao et al.[19]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Yu et al.[20]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Guebre-Xabier et al.[17]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

All studies were published in 2020

Vaccine Efficacy

Several RCTs have shown full dose vaccination with ChAdOx1 nCoV-19 (AstraZeneca), BNT162b2 (Pfizer BioNTech), Ad26.COV2.S (Janssen), mRNA-1273 (Moderna) and NVX-CoV2373 (Novavax) vaccines to be effective at preventing symptomatic COVID-19 infection, with efficacy ranging between 66.1% (95% CI: 55-74.8) to 94.8% (95% CI 89.8–97.6). These have been compiled and presented in details in Appendix **1**. This review however focuses on the transmissibility of COVID-19 in asymptomatic individuals and the effect of vaccines on post-infection proxy measures of infectivity such as Ct values and viral load.

Vaccine Efficacy Against Asymptomatic Infection

Eight studies reported vaccine efficacy against asymptomatic COVID-19 infection (Table **5**). Three of these involved ChAdOx1 nCoV-19 vaccine,[6-8] another three examined BNT162b2[9-11] and one study each evaluated mRNA-1273[14] and Ad26.COV2.S[13] vaccines. The methods of assessing efficacy against asymptomatic infection used in these studies include RT-PCR nasopharyngeal swabs at time intervals.

All the ChAdOx1 nCoV-19 vaccine trials implemented weekly self-administered nose and throat swab for testing on baseline seronegative participants. The PCR status of these participants were not established at baseline. Only two of the BNT162b2 studies documented a testing protocol; one utilized a fortnightly asymptomatic PCR testing;[11] while the other conducted weekly testing.[15] Neither of these two studies documented baseline serology or PCR. The Moderna mRNA-1273 trial conducted surveillance swabs at the second dose visit among participants who were PCR negative and seronegative at baseline;[14] while the Janssen vaccine trial conducted surveillance swabs at unspecified intervals among baseline seronegative participants (defined as negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on day 1).[13]

Asymptomatic data were presented for only the UK component of the AstraZeneca ChAdOx1 nCoV-19 vaccine study. Neither one or two doses of the standard dose vaccine was effective against asymptomatic infection with the wild type virus (7.8% (95% CI: -46.7-42.1) and 27.3% (95% CI: -17-54.9))[7,8] or the B.1.1.7 variant (26.5% (95% CI: -112-74.5))[6] in baseline seronegative participants. The baseline PCR results of the participants were not reported, therefore, persistent carriage after previous infection was not ruled out. In the subgroup of participants with an initial low dose of the vaccine, followed by a standard dose, two studies reported 49.3%(95% CI: 7.4-72.2)[8] and 58.9%(95% CI: 1-82.9)[7] respective efficacies against asymptomatic infection 14 days after the second dose (Table **5**).

Of the four BNT162b2 observational vaccine studies with data on asymptomatic infection,[9-11,15] only one, involving almost 1.2 million Israeli participants reported vaccine efficacy against asymptomatic infection.[10] This study, which did not establish baseline seronegativity, showed that one dose of BNT162b2 significantly reduced asymptomatic infection by 29% (95% CI: 17-39) and 52% (95% CI: 41-60) after 14 to 20 days and 21 to 27 days of follow-up respectively, as assessed by confirmed positive PCR SARS-CoV-2 test without documented symptoms. No routine swabbing was documented for the participants. The vaccine was reported to be 90% effective (95% CI: 83-94) against asymptomatic infection seven days after the second dose.[10] The other two studies did not report effect estimates for vaccine protection against asymptomatic infection. One of the studies however showed 2.7 cases of asymptomatic infection per 10000 person-days in the vaccinated people compared with 2.4 cases per 10000 person-days in the unvaccinated people during the first 14 days after the first dose; and 1.9 cases per 10000 person-days in the vaccinated compared with 2.4 cases per 10000 person-days in the unvaccinated group, 14 to 20 days after the first dose.[9] An asymptomatic weekly screening program among health care workers (HCWs) who were vaccinated with one dose of BNT162b2 compared with unvaccinated HCWs, showed that 0.8% of tests from unvaccinated HCWs were positive compared with 0·37% and 0.2% from vaccinated ones at <12 days and >12 days post-vaccination respectively (p=0.023 and p=0.004, respectively).[15]

A study of the mRNA-1273 by Moderna showed that 0.1% of the patients receiving the first dose developed asymptomatic infection compared with 0.27% of the unvaccinated group. Participants in this trial were negative for COVID-19 by RT-PCR or antibody testing at baseline.[14]

The Ad26.COV2.S vaccine by Janssen Biotech did not show statistically significant efficacy against asymptomatic infection in the first 28 days of follow-up. However, after 28 days of follow-up, asymptomatic infection was significantly lower among vaccinated participants (74%, 95% CI: 46.8-88.4%).[13] Asymptomatic infection in this trial was assessed by lack of symptoms on the day preceding, the day of, or any time after a positive PCR test.

Table 5: Vaccine Efficacy against Asymptomatic Infection

Vaccine	Author	Country	Strain targeted by PCR	Baseline Serology	Dosing Schedule	Dose	Follow-up days*	Vaccine Efficacy (95%CI)
AstraZeneca (ChAdOx1 nCoV-19)	Voysey et al.[7]	UK	Wild type	Negative	LD or SD vs SD	2nd	>14	27.3% (-17-54.9)
	Voysey et al.[7]	UK	Wild type	Negative	LD vs SD	2nd	>14	58.9% (1-82.9)
	Voysey et al.[7]	UK	Wild type	Negative	SD vs SD	2nd	>14	3.8% (-72.4-46.3)
	Voysey et al.[7]	UK	Wild type	Negative	LD or SD vs SD	1st	>21	7.8% (-46.7-42.1)
	Voysey et al.[8]	UK	Wild type	Negative	LD or SD vs SD	2nd	>14	22.2% (-9.9-45)
	Voysey et al.[8]	UK	Wild type	Negative	SD vs SD	2nd	>14	2.0% (-50.7-36.2)
	Voysey et al.[8]	UK	Wild type	Negative	LD vs SD	2nd	>14	49.3% (7.4-72.2)
	Voysey et al.[8]	UK	Wild type	Negative	SD vs SD	1st	22 -90	16% (-88-62)
	Emary et al.[6]*	UK	Wild type, B.1.1.7, Other	Negative	LD or SD vs SD	2nd	>14	15.7% (-10.7-35.8)
	Emary et al.[6]*	UK	B.1.1.7	Negative	LD or SD vs SD	2nd	>14	26.5% (-112-74.5)
	Emary et al.[6]*	UK	Variants not B.1.1.7	Negative	LD or SD vs SD	2nd	>14	75.4% (39.9-89.9)
Janssen Biotech (Ad26.COV2.S)	Janssen Biotech[13]	Multiple	Wild type	Negative	NA	1st	1-29	20% (-7-40.4)
	Janssen Biotech[13]	Multiple	Wild type	Negative	NA	1st	≥ 29	74% (46.8-88.4)
Pfizer, BioNTech (BNT162b2)	Amit et al.[9]	Israel	Wild type	Unknown	NA	1st	1-14	NR##
	Amit et al.[9]	Israel	Wild type	Unknown	NA	1st	15-28	NR###
	Dagan et al.[10]	Israel	Wild type and B.1.1.7	Unknown	NA	1st	14-20	29% (17-39)
	Dagan et al.[10]	Israel	Wild type and B.1.1.7	Unknown	NA	1st	21-27	52% (41-60)
	Dagan et al.[10]	Israel	Wild type and B.1.1.7	Unknown	NA	2nd	>7	90% (83-94)
	Hall et al.[11]	UK	Wild type	Unknown	NA	Both	21 and 7	NR
	Weekes et al.[15]	UK	Wild type and B.1.1.7	Unknown	NA	1	<12 and >12	NR
Moderna (mRNA-1273)	Baden et al.[14]	USA	Wild type	Negative	NA	1st	From day 1	NR#

* *Time PCR was conducted after first or second dose; LD: Low dose, SD: Standard dose(**Calculated from available data:** #0.1% and 0.27% of persons at risk had asymptomatic infection with vaccine and control respectively. ## 2.7 cases per 10000 person-days in vaccine vs 2.4 cases per 10000 person-days in control. ###1.9 cases per 10000 person-days in vaccine vs 2.4 cases per 10000 person-days).

Cycle threshold (Ct) Values

Three studies reported Ct values, an inverse proxy for viral load, in infected vaccinated and unvaccinated individuals.[6,12,15]

Results from Phase 2/3 vaccine efficacy studies of AstraZeneca's ChAdOx1 nCoV-19 vaccine compared with a comparator meningococcal vaccine in the United Kingdom, showed that the Ct values in infected vaccinated participants were statistically significantly higher than the comparator ($p<0.0001$), after 14 days of the second dose in baseline seronegative efficacy cohorts.[6] Furthermore, the vaccine recipients were PCR-positive for a significantly shorter period of time ($p<0.0001$). The Ct values in asymptomatic cases were also significantly higher among vaccine recipients than control ($p=0.0040$); however, this difference was not significant for primary symptomatic cases ($p=0.1534$). Vaccine recipients infected with the B.1.1.7 variant also showed significantly higher Ct values than control ($p=0.0113$).[6]

A retrospective study of Pfizer BioNTech's BNT162b2 mRNA vaccine recipients compared with demographically-matched control group of unvaccinated individuals in Israel, found no significant differences in the Ct values for any of the 3 genes (RdRp, N and E) measured less than 12 days after the first dose in infected persons. However, between 12 and 28 days after the first dose, the Ct values for the 3 genes were significantly higher among infected vaccinated persons than controls ($p<10^{-8}$).[12] In another UK study of one dose of BNT162b2 vaccine, the median Ct values of infected health care workers (HCWs) were reported to have shown a non-significant trend towards increase between unvaccinated (Median=20.3) and vaccinated HCWs after 12 days post-vaccination (Median=30.3), suggesting that samples from infected vaccinated individuals had lower viral loads.[15]

Animal Studies

All the animal studies estimated viral load by using viral genomic RNA (gRNA) and subgenomic RNA (sgRNA), from nasal or bronchoalveolar lavage (BAL) samples. None of the studies evaluated the animals for symptomatic infections.

van Doremalen et al. found that the ChAdOx1 nCoV-19 vaccine significantly reduced viral load in the bronchoalveolar lavage fluid of vaccinated rhesus macaques on the third, fifth and seventh day post viral challenge, compared with control animals.[16] In the BAL fluid obtained from control animals, viral genomic and subgenomic RNA were detected on all days; while two of the vaccinated animals had detectable viral gRNA three days after challenge. Viral gRNA was detected in nose swabs from all animals and no difference was found on any day between vaccinated and control animals.

Similarly, the mRNA-1273 vaccine showed significantly lower RNA and subgenomic RNA, in BAL and nasal swabs, in the 100-µg dose group compared with the control group.[18] Only one of the eight vaccinated had detectable subgenomic RNA in BAL fluid two days after challenge, while all the control animals had detectable RNA. Similarly, none of the eight animals administered the 100-µg dose had detectable subgenomic RNA detected in nasal swab compared with six of eight in the control.

Another study showed that PiCoVacc, a vaccine developed by Sinovac Biotech (China), significantly reduced viral load in the pharynx and lungs of all the vaccinated animals compared with control animals, on the third and seventh day post-viral challenge.[19]

Yu et al. evaluated the protective efficacy of DNA vaccines compared with controls.[20] The vaccines included, those with full-length deletion of the cytoplasmic tail (S.dCT), deletion of the transmembrane domain and cytoplasmic tail reflecting the soluble ectodomain (S.dTM), S1 domain with a foldon trimerization tag (S1), receptor-binding domain with a foldon trimerization tag (RBD), prefusion-stabilized soluble ectodomain with deletion of the furin cleavage site, two proline mutations, and a fold on trimerization tag (S.dTM.PP). The study

reported significantly lower levels of viral sgRNA in the BAL and nasal swabs of vaccinated animals compared with the control group on days one to four after challenge.[20]

In the Novavax's NVX-CoV2373 vaccine study, macaques administered placebo had elevated viral load two and four days post viral challenge, while all but one of the vaccinated animals had no detectable sgRNA in their BAL fluid.[17] Similarly, half of the placebo group had elevated viral RNA in their nasal swabs, while none was detectable in vaccinated animals.[17]

Discussion

All the vaccines included in this review were effective against symptomatic wild-type COVID-19 infections. Data are overall limited to address the likelihood of viral transmission from vaccine recipients, because most COVID-19 vaccine studies did not include asymptomatic carriage, and no studies included evidence of viral transmission after vaccination. Limited evidence suggests Pfizer BioNTech's BNT162b2 and AstraZeneca's ChAdOx1 nCoV-19 vaccines may also be effective against symptomatic infections with the B.1.1.7 variant. None of the approved vaccines have been assessed primarily on their ability to prevent transmission. However, some surrogates of transmissibility, including Ct values and asymptomatic infection have been reported in some clinical trials and real-world observational studies.

The ChAdOx1 nCoV-19 and BNT162b2 vaccines were found to be significantly associated with higher Ct values than their respective comparators, suggesting that these vaccines may potentially reduce viral load and consequently lower the risk of transmission. It is however noteworthy that the relationship between viral load, viral shedding, infectivity and the duration of infectivity are not well understood. Ct values are also subject to error.[21]

Asymptomatic infections resulting in viral transmission makes the containment of COVID-19 challenging.[22,23] This review suggests the effectiveness of some of the approved vaccines against asymptomatic infection. While the BNT162b2 vaccine and Janssen's Ad26.COV2.S were reported to have up to 90% and 74% effectiveness against asymptomatic infection respectively; two standard doses of AstraZeneca's ChAdOx1 nCoV-19 vaccine were shown to be ineffective against asymptomatic infection. However, an initial low dose of the vaccine, followed by a standard dose, was found to be about 50% effective.

Conclusion

There is some data from select vaccine studies on Pfizer BioNTech's BNT162b2 and Janssen's Ad26.COV2.S showing effectiveness against asymptomatic infection. Limited evidence regarding the Ct values for AstraZeneca's ChAdOx1 nCoV-19 and the BNT162b2 vaccines suggest their potential to reduce viral load and therefore possibly transmission. There are very few studies on the efficacy of the approved vaccines against the variants of concern. Further research is needed to evaluate post-vaccination infectivity and transmission of the wild type COVID-19 virus and the variants.

References

1. Johns Hopkins University. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). https://www.covidtracker.com/. Published 2021. Accessed 27 February 2021.
2. Byambasuren O, Cardona M, Bell K, Clark J, McLaws M-L, Glasziou P. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis. *Official Journal of the Association of Medical Microbiology and Infectious Disease Canada.* 2020;5(4):223-234.
3. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919.
4. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011;343.
5. Hooijmans CR, Rovers MM, De Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC medical research methodology.* 2014;14(1):1-9.
6. Emary KR, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B. 1.1. 7). 2021.
7. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet.* 2021;397(10269):99-111.
8. Voysey M, Clemens SAC, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *The Lancet.* 2021.
9. Amit S, Regev-Yochay G, Afek A, Kreiss Y, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *The Lancet.* 2021.
10. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *New England Journal of Medicine.* 2021.
11. Hall VJ, Foulkes S, Saei A, et al. Effectiveness of BNT162b2 mRNA Vaccine Against Infection and COVID-19 Vaccine Coverage in Healthcare Workers in England, Multicentre Prospective Cohort Study (the SIREN Study).
12. Levine-Tiefenbrun M, Yelin I, Katz R, et al. Decreased SARS-CoV-2 viral load following vaccination. *medRxiv.* 2021.
13. Janssen Biotech I. *Vaccines and Related Biological Products Advisory Committee Meeting February 26, 2021: FDA Briefing Document.* 26 February 2021 2021.
14. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England Journal of Medicine.* 2021;384(5):403-416.
15. Matheson NJ, Weekes MP. Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection. 2021.
16. van Doremalen N, Lambe T, Spencer A, et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. *Nature.* 2020;586(7830):578-582.
17. Guebre-Xabier M, Patel N, Tian J-H, et al. NVX-CoV2373 vaccine protects cynomolgus macaque upper and lower airways against SARS-CoV-2 challenge. *Vaccine.* 2020;38(50):7892-7896.
18. Corbett KS, Flynn B, Foulds KE, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. *New England Journal of Medicine.* 2020;383(16):1544-1555.
19. Gao Q, Bao L, Mao H, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. *Science.* 2020;369(6499):77-81.

20. Yu J, Tostanoski LH, Peter L, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. *Science.* 2020;369(6505):806-811.
21. Pollock AM, Lancaster J. Asymptomatic transmission of covid-19. *BMJ.* 2020;371:m4851.
22. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic transmission, the Achilles' heel of current strategies to control Covid-19. In: Mass Medical Soc; 2020.
23. Yu X, Yang R. COVID-19 transmission through asymptomatic carriers is a challenge to containment. *Influenza and other respiratory viruses.* 2020;14(4):474-475.
24. Madhi SA, Baillie VL, Cutland CL, et al. Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B. 1.351 variant in South Africa. *medRxiv.* 2021.
25. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *The Lancet.* 2021.
26. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial [press release]. 28 January 2021 2021.
27. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *New England Journal of Medicine.* 2020;383(27):2603-2615.

Appendix 1: Vaccine Efficacy against Symptomatic Infection

Vaccine	Author	Country	Strain	Dose	Follow-Up days	Vaccine Efficacy (95% CI)
AstraZeneca (ChAdOx1 nCoV-19)	Voysey et al.[7]	UK/Brazil	Wild type	2nd	>14	70.4% (54.8-80.6) ‡
	Voysey et al.[8]	UK/Brazil/S.Africa	Wild type	2nd	>14	66.7% (57.4-74.0) ‡
	Voysey et al.[8]	UK/Brazil/S.Africa	Wild type	2nd	>14	63.1% (51.8-71.7)
	Voysey et al[8]	UK/Brazil/S.Africa	Wild type	2nd	>14	80.7% (62.1-90.2) †
	Madhi et al.[24]	South Africa	Wild type	2nd	>14	21.9% (-49.9 -59.8)
	Madhi et al.[24]	South Africa	B.1.351	2nd	>14	10.4% (-76.8-54.8)
	Emary et al.[6]	UK	Wild type, B.1.1.7, others	2nd	>14	74.2% (65-81.0)
	Emary et al.[6]	UK	B.1.1.7	2nd	>14	74.6% (41.6-88.9)
Gamaleya (Gam-COVID-Vac)	Logunov et al.[25]	Russia	Wild type	2nd	NR	91·1% (83·8–95·1)
Janssen Biotech (Ad26.COV2.S)	Janssen[13]	Multiple	Wild type	1st	>14	66.9 (59-73.4)
	Janssen[13]	Multiple	Wild type	1st	>28	66.1 (55-74.8)
Moderna (mRNA-1273)	Baden et al.[14]	USA	Wild type	2nd	>14	94% (89.3-96.8)
Novavax (NVX-CoV2373)	Novavax[26]	UK	Wild type	2nd	>7	89.3% (75.2 – 95.4)
	Novavax[26]	South Africa	Wild type	NR	NR	49.4% (6.1 – 72.8)
Pfizer BioNTech (BNT162b2)	Hall et al.[11]	UK	Wild type	2nd	7	85% (74-96)
	Hall et al.[11]	UK	Wild type	1st	21	70% (53-87)
	Polack et al.[27]	Multiple	Wild type	2nd	>7	94.8% (89.8–97.6)
	Amit et al.[9]	Israel	Wild type	1st	15-28	75% (52 -87)
	Dagan et al.[10]	Israel	Wild type, B.1.1.7	1st	14-20	57% (50-63)
	Dagan et al.[10]	Israel	Wild type, B.1.1.7	1st	21-27	66% (57-73)
	Dagan et al.[10]	Israel	Wild type, B.1.1.7	2nd	>7	94% (87-98)

‡Low Dose (LD) or Standard Dose (SD) vs SD;† LD vs SD