Transmissibility of COVID-19 among vaccinated individuals

Targeted Literature Search

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Abbreviations and Definitions

Abbreviations

AZ	AstraZeneca ChAdOx1 nCoV-19 vaccine
CDC	Centres for Disease Control and Prevention
Ct	Cycle threshold
COVID-19	Coronavirus Disease 2019
IQR	Interquartile range
J and J	Janssen Ad26.COV2.S
mRNA	Messenger ribonucleic acid
NR	Not Reported
PCR	Polymerase chain reaction
PfBnT	Pfizer BioNTech's BNT162b2
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 efficacy and effectiveness of COVID-19 vaccination in reducing forward transmission from vaccinated people, and select studies examining the biological plausibility of vaccination induced transmission reduction. 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 efficacy and 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 March 11th, 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 17 studies were included in this review. Eleven studies were in humans and five were preclinical animal studies in macaques.

Asymptomatic and symptom unknown infection data were presented for only the UK component of the AstraZeneca ChAdOx1 nCoV-19 (AZ vaccine) vaccine studies. Participants were assessed by weekly self-administered nose and throat swabs for RT-PCR testing. The vaccine demonstrated efficacy against any PCR positive results compared with control in two studies, (67% 95% CI: 49-78)[1] and 46.3% (31.8-57.8)[2], from 21 days after the first dose. However, AZ vaccine standard dose was reported not to have significant efficacy against asymptomatic or unknown carriage with the wild type virus after 21 days of the first dose (7.8% (95% CI: -46.7-42.1) and after 14 days of the second dose 27.3% (95% CI: -17-54.9))[2] respectively. Similarly, two doses of the vaccine showed no significant efficacy against the asymptomatic carriage of the B.1.1.7 variant (26.5% (95% CI: -112-74.5))[3]. All the AZ vaccine studies were 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)[1] and 58.9% (95% CI: 1-82.9)[2] respective efficacies against asymptomatic and unknown infection 14 days after the second dose, although the higher efficacy in the low dose study results may have been partially explained a more extended interval before dose 2 in that subgroup, which has subsequently been shown to offer higher overall efficacy. A phase 2/3 RCT comparing the minimum cycle threshold (Ct) values in AZ vaccine vaccinated individuals with a comparator group of meningococcal vaccine, reported statistically significantly higher PCR Ct values in the AZ vaccinated group, suggesting lower viral loads in vaccine recipients.[3]

Tande et al. evaluated the effectiveness of at least one dose of either mRNA-1273 or BNT162b2 (PfBnT vaccine) in reducing the likelihood of a positive pre procedure or surgery screening COVID-19 test, with a significantly reduced relative risk for a positive test in vaccinated compared with unvaccinated people was significantly lower (0.44 (95% CI: 0.33-0.60)).[4]

Of the five PfBnT observational studies, two, involving Israeli participants reported vaccine effectiveness against asymptomatic infection.[5,6] Dagan et al., which did not establish baseline seronegativity, found one dose of PfBnT vaccine 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.[5] No routine SARSCoV2 assessment was performed. The vaccine was reported to have 90% efficacy (95% CI: 83-94) against asymptomatic infection seven days after the second dose.[5] Similarly, a press release by the vaccine manufacturer indicated that PfBnT vaccine was 94% effective against asymptomatic infection, 2 weeks after the second dose.[6]

The other three PfBnT vaccine studies involved healthcare workers (HCWs) and did not report effect estimates for vaccine protection against asymptomatic infection. Hall et al. in a study of HCWs with negative and positive baseline PCR or antibody in the UK, reported a higher incidence density of asymptomatic or unknown infections with unvaccinated HCWs than PfBnT or AZ vaccine recipients. The vaccine recipients were followed up for 396,318 person-days compared with 710,587 person days in unvaccinated group, with 35 and 218 asymptomatic or unknown infections reported, translating to 0.88 and 3 infections per 10,000 person-days respectively. No effect estimates were reported for asymptomatic infections.[7] In a second observational HCW study in Israel by Amit et al.,[8] asymptomatic test positive data was limited, and reasons for tests done without documented symptoms was not reported. The baseline RT-PCR status was not assessed; therefore, prolonged RT-PCR positivity after prior infection was not ruled out. Estimated asymptomatic infection prevalence in the vaccinated group was 1.7 per 10,000-person years between 15 and 28 days after vaccination, compared with 2.4 per 10,000 person-years in the unvaccinated group.[8] In a HCWs surveillance program after one dose of PfBnT vaccine by Matheson et al., 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).[9]

Two of the HCW studies measured Ct for PfBnT vaccine vaccinated and unvaccinated individuals. Levine- Tiefenbrun et al. found significantly higher Ct values (suggesting lower amounts of virus detected) in infected vaccinated individuals between 12 and 28 days after the first dose ($p<10^{-8}$).[10] In

the other study by Emary et al., an asymptomatic screening program among HCWs who were vaccinated with one dose of PfBnt vaccine, 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.[9]

Baden et al. showed that, among participants who received the first dose of the mRNA-1273 (Moderna) vaccine while negative for COVID-19 by RT-PCR or antibody testing at baseline, 0.1% had positive swabs but no symptoms at the time of their second dose, compared with 0.27% of the unvaccinated group, which is suggestive of 61.4% efficacy against asymptomatic carriage.[11]

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 (J and J vaccine), did not show efficacy against asymptomatic infection in the first 28 days of follow-up. However, the vaccine demonstrated 74% (95% CI: 46.8-88.4) efficacy 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.[12]

All the animal studies, although small numbers were included in challenge 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. The AZ vaccine reduced lower respiratory replication, but did not reduce nasal viral detection in vaccinated animals challenge studies;[13] whereas the Moderna[14] and Novavax[15] products reduced or eliminated nasal viral carriage versus controls.

Conclusion: Some studies, such as the AZ vaccine studies, included data on cross sectional prevalence of positive SARS-CoV-2 RT-PCR from routine swabbing, which suggested efficacy against asymptomatic infection, although this was not routinely assessed in a comparable way across studies. Limited evidence regarding the Ct values for AZ vaccine and the PfBnT 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 or effectiveness 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.[16] 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.[17] 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.

People who have started or finished COVID19 vaccine series have been documented to have detectable SARSCoV2 by RT-PCR at various time points after vaccinantion,[1] although cultivatable virus has not been assessed. It is not yet clear whether the current COVID-19 vaccines are as effective at reducing transmission as they are at reducing disease. Moreover, evaluating the ability of vaccinated individuals to transmit the virus after infection is challenging. Therefore, surrogates of transmission and transmissibility may be a helpful way around this challenge. Therefore, surrogates of transmission and transmissibility may be a helpful way around this challenge.

Monoclonal antibody studies may provide useful insights into the pathophysiologic plausibility of vaccine induced transmission reduction, since they have been shown to result in circulating neutralizing antibody, with a significant decrease in quantitative viral load.[18] In one study, following quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing of nasopharyngeal swabs, an antibody cocktail was found to significantly reduce viral load compared with placebo.[18] The time-weighted average change in viral load in the first 7 days was −0.56 log10 copies per milliliter (95% CI, −1.02 to −0.11) among those who were serum antibody–negative at baseline.[18] Another study reported an elimination of more than 99.97% of viral RNA on day 11 after monoclonal antibody treatment.[19]

It is unclear if vaccines reduce the frequency of asymptomatic COVID-19 and if the viral load, and therefore infectiousness, is lower among people who develop COVID-19 post-vaccination compared with those who have not been vaccinated. Viral presence is an imperfect proxy of transmissibility although the quantity of virus present does appear to influence risk, as studies document transmission risk is higher with a higher viral load or lower Ct value.[20,21] Marks et al. found index viral load to be a major driver of transmission in a Spanish cohort.[21] Similarly, Bjorkman et al. found that index cases of university roommate transmission had an average viral load 6.5 log higher than those who did not. Transmission from asymptomatic students to roommates occurred in 20% of rooms with an infected student, with a lower mean Ct (E gene) of 26.2 in transmission index cases versus 28.9, (median 26.11 in transmission index cases versus 29.32).[22] However, risks related to viral presence by RT-PCR may be modulated by individual's immune status, as viral persistence after natural infection has been observed in individuals with neutralizing antibody responses after natural infection, without transmission to close contacts.[23] Although asymptomatic and especially presymptomatic transmission of SARSCoV-2 has been well documented, existing

studies suggest that transmission risk is lower from asymptomatic individuals than symptomatic individuals.[24]

The evidence for the transmissibility and transmission of COVID-19 infections in vaccinated individuals is rapidly evolving; therefore, the objective of this targeted literature search was to identify observational studies and randomized controlled trials (RCTs) evaluating the effectiveness or efficacy of COVID-19 vaccination in reducing asymptomatic viral carriage and other proxies of possible transmission, such as cycle threshold (Ct) values and viral load.

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 efficacy and 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 March 11th, 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 efficacy and 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,[25] Cochrane Risk of Bias (version 5.1.0) for human-subject RCTs,[26] and SYRCLE's Risk of Bias for animal studies.[27] Quality assessment was conducted by one reviewer and verified by a second reviewer.

Results

Study Characteristics

A total of 17 studies were included in this review. Twelve were human studies (Table 2 and 3)[1-12] and five were preclinical animal studies in macaques, with viral challenge 1-8 weeks post vaccination (Table 4).[13-15,28,29] Five of the human studies were randomized controlled trials,[1-3,11,12] two were prospective cohort studies[5,7] and five were retrospective cohort studies.[4,6,8-10] The studies were conducted across several countries including USA, UK, Israel, Brazil, South Africa and several South American countries. There were six studies evaluating Pfizer BioNTech's BNT162b2 vaccine (PfBnT vaccine),[5-10] three studies evaluated ChAdOx1 nCoV-19 by AstraZeneca (AZ vaccine),[1-3] one study each evaluated Janssen's Ad26.COV2.S vaccine (J and J vaccine),[12] and mRNA-1273 by Moderna,[11] and one evaluated both mRNA-1273 and PfBnT vaccine.[4] The five animals studies evaluated AZ vaccine,[13] Novavax's NVX-CoV2373,[15] mRNA-1273,[14] piCoVacc[28] and a DNA vaccine.[29]

Table 2: Characteristics of included RCTs

Author/Country/Design	Trial Information	Participant Inclusion/Exclusion Criteria	Vaccine Information	Efficacy/Effectiveness Outcomes
Author: Voysey 2021[2] **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[1] **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[3] **County**: UK **Date of Recruitment:** Oct-Jan 2021 **Trial Phase:** 2/3 **Design:** RCT **Funding:** UK Research and Innovation, National Institutes for Health Research	**Age:** NR **%Female:** NR **Type of comparator:** Meningococcal vaccine **Sample Vaccine:** 4236 **Sample Control:** 4270 **Total Sample:** 8506	Aged 18 and over; high-exposure populations eligible for vaccination under the government National Health Service coronavirus vaccine programme.	**Vaccine:** ChAdOx1 nCoV-19 **Manufacturer:** AstraZeneca **Dose:** Low or Standard Doses **Number of Doses**: 2	• Symptomatic Infection • Ct Values (weekly swabs processed. The minimum Ct value across the N and ORF1ab genes from each PCR test was computed)

Author/Country/Design	Trial Information	Participant Inclusion/Exclusion Criteria	Vaccine Information	Efficacy/Effectiveness Outcomes
(NIHR), Coalition for Epidemic Preparedness Innovations, NIHR Oxford Biomedical Research Centre, Thames Valley and South Midlands NIHR Clinical Research Network, and AstraZeneca.	**VOC:** B.1.1.7, Other			• 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[12] **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[11] **County**: USA **Date of Recruitment:** Jul-Nov, 2020 **Trial Phase:** 3 **Design:** Observer Blinded RCT **Funding:** Biomedical Advanced Research	**Age:** 51.4 **%Female:** 47.3 **Comparator:** saline **Sample Vaccine:** 14550 **Sample Control:** 14598 **Total Sample:** 29148	**Include:** Eligible participants were persons 18 years of age or older with no known history of SARS-CoV-2 infection and with locations or circumstances that put them at an appreciable risk	**Vaccine:** mRNA-1273 **Manufacturer:** Moderna **Dose:** 100mcg **Number of Doses**: 2	• Symptomatic infection • Severe cases • Any Positive PCR • Asymptomatic infection (Surveillance swab at the second dose visit)

Author/Country/Design	Trial Information	Participant Inclusion/Exclusion Criteria	Vaccine Information	Efficacy/Effectiveness Outcomes
and Development Authority and the National Institute of Allergy and Infectious Diseases		of SARSCoV-2 infection, a high risk of severe COVID-19, or both. **Exclude:** Pregnant women and children		

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 or Effectiveness Outcomes
Author: Hall, 2021[7] **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[8] **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[5] **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[10] **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:** Varied **Sample Control**: Varied	**Include:** All positive post-vaccination samples; **Exclude:** Patients who had a positive sample prior to	**Vaccine:** BNT162b2 **Manufacturer**: Pfizer BioNTech **Dose:** NR **Number of Doses**:1	• Ct values

	Total Sample: Varied **VOC:** NR	vaccination; patients age 90 and above		
Author: Weekes, 2021[9] **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)
Author: Tande, 2021[4] **Country:** USA **Date of recruitment:** December, 2020 to February, 2021 **Trial Phase:** Post approval **Design:** Retrospective Cohort **Funding:** Internal funding at the Mayo Clinic	**Age:** 54.2 (19.7) **%Female:** 52.5 **Comparator:** Unvaccinated **Sample vaccine:** 3006 **Sample control:** 45,327 **Total sample:** **VOC:** NR	**Include:** 18 or mor years old, underwent preprocedural/presurgical testing within 48-72 hours of procedure Exclude: Patients tested due to symptoms or a known exposure were tested using an alternative ordering process	**Vaccine:** BNT162b2 or mRNA-1273 **Manufactures:** Pfizer BioNTech or Moderna **Number of Doses:** 1 or 2	• PCR+ among Asymptomatic (consecutive preprocedural molecular screening tests)
Author: Pfizer BioNTech **Country:** Israel **Date of recruitment:** January 17 through March 6, 2021 **Trial Phase:** Post approval **Design:** Retrospective cohort	**Age:** NR **%Female:** NR **Sample vaccine:** NR **Sample control:** NR **Total sample:** NR	**NR**	**Vaccine:** BNT162b2 **Manufacturers:** Pfizer BioNtech	• Symptomatic • Asymptomatic (Surveillance method unclear)

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

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)[14] 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)[13] 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)[28] 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)[15] 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)[29] 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[1-3,11,12] were assessed with the Cochrane Risk of Bias Assessment Tool.[26] Two studies had some concerns regarding randomization,[3,12] two were of low risk[2,11] and one study had no sufficient information for assessment.[1] All but one low risk study[11] was assessed to have some concerns regarding deviation from intended intervention. Four studies were of some concerns for missing outcome data,[1,2,11,12] one was assessed to be of high risk of bias.[3] All the studies were of low risk of bias for the measurement of outcomes. All but one study with some concern [3] were of low risk for the selection of reported results [1-3,11,12] Overall, four of the RCTs were of some concerns for bias[1,2,11,12] and one had a high risk of bias[3] (Figure 1).

The six non-RCTs[4,5,7-10] were assessed using ROBINS-I tool.[25] All, but one study,[8] were of moderate risk of bias due to confounding. Two studies were of moderate[5,7] and four of low risks of bias[4,8-10] for participants' selection. All, but one moderate risk study,[8] were of low risk for the classification of intervention and the measurement of outcomes. There were four studies with low risk of bias[4,5,10,15] and one with moderate risk for deviation from intervention.[7] All, but two low risk of bias studies,[4,5] did not have sufficient information on missing data or the selection of reported results. Overall, five studies were considered to be of moderate risk,[4,5,7,9,10] while one study did not have enough information for risk assessment.[8] (Figure 2). The press release[6] was not assessed.

The five included animal studies[13-15,28,29] were assessed with the Systematic Review Centre for Laboratory animal Experimentation's (SYRCLE) risk of bias tool for animal studies.[27] All but one study[13] 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.[11]	Low	Low	Some concerns	Low	Low	Some concerns
Emary et al.[3]	Some concerns	Some concerns	High	Low	Some concerns	High
Janssen Biotech[12]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Voysey et al.[2]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Voysey et al.[1]	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.[7]	Moderate	Moderate	Low	Moderate	NI	Low	NI	Moderate
Levine-Tiefenbrun et al.[10]	Moderate	Low	Low	Low	NI	Low	NI	Moderate
Amit et al.[8]	NI	Low	Moderate	NI	NI	Moderate	NI	NI
Dagan et al.[5]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Weekes et al.[9]	Moderate	Low	Low	Low	NI	Low	NI	Moderate
Tande et al.[4]	Moderate	Low	Low	Low	Low	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.[14]	Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Van Doremalen et al.[13]	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Unclear
Gao et al.[28]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Yu et al.[29]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Guebre-Xabier et al.[15]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

All studies were published in 2020

Vaccine Efficacy and Effectiveness

Several RCTs have shown the efficacies of full-dose vaccination with ChAdOx1 nCoV-19 , BNT162b2, Ad26.COV2.S , mRNA-1273 and NVX-CoV2373 vaccines, against symptomatic COVID-19 infection, with efficacies ranging between 66.1% (95% CI: 55-74.8) and 94.8% (95% CI 89.8–97.6). These have been compiled and presented in details in Appendix 1 and Appendix 2. 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 or Effectiveness Against Asymptomatic Infection

Ten studies reported vaccine efficacy or effectiveness against asymptomatic COVID-19 infection (Table 5 and Table 6). Three of these involved AZ vaccine,[1-3] another four examined PfBnT vaccine[5-8] and one study each evaluated mRNA-1273[11] and J and J [12] vaccines and one evaluated both mRNA-1273 and BNT162b2.[4] The methods of assessing efficacy or effectiveness against asymptomatic infection used in some of these studies include RT-PCR nasopharyngeal swabs at time intervals.

All the AZ vaccine trials implemented weekly self-administered nose and throat swabs for testing on baseline seronegative participants. The PCR status of these participants were not established at baseline. Only two of the PfBnT vaccine studies documented a testing protocol; one utilized a fortnightly asymptomatic PCR testing;[7] while the other conducted weekly testing.[9] Neither of these two studies documented baseline serology or PCR. The mRNA-1273 trial conducted surveillance swabs at the second dose visit among participants who were PCR negative and seronegative at baseline;[11] 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).[12]

AstraZeneca Vaccine Efficacy In The General Population

First Dose AstraZeneca

Asymptomatic infection data were presented for only the UK component of the AZvaccine studies. Two AZ vaccine studies reported vaccine efficacy against asymptomatic or unknown infection of 7.8% (-46.7-42.1)[2] and 16% (-88-62)[1] respectively, after more than 21 days and 22 to 90 days of the first dose. However, vaccine efficacy among participants with positive results, irrespective of symptoms, were 46.3% (31.8-57.8)[2] and 67% (49-78)[1], respectively over the same period (Table 5).

Full Dose AstraZeneca

After 14 days of the second dose, two AZ vaccine studies did not demonstrate efficacy against asymptomatic or unknown infection with the wild type virus 22.2% (-9.9-45) and 27.3% (95% CI: -17-54.9)) respectively.[1,2] A third study did not show efficacy against asymptomatic infection with the B.1.1.7 variant (26.5% (95% CI: -112-74.5)), following low or standard dose vaccination.[3] All three studies involved 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)[1] and 58.9%(95% CI: 1-82.9)[2] respective efficacies against asymptomatic and unknown infection 14 days after the second dose (Table 6).

However, when participants who were PCR positive irrespective of symptoms were considered, two doses of AZ vaccine showed efficacies of 55.7% (41.1-66.7)[2] and 54.1% (44.7%, 61.9%)[1] after 14 days of second dose vaccination.

Pfizer BioNTech Vaccine Effectiveness In The General Population

First Dose Pfizer BioNTech Vaccine

Of the five PfBnT vaccine observational vaccine studies,[5-9] two, involving Israeli participants reported vaccine effectiveness against asymptomatic infection.[5] One of this studies, by Dagan et al., 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 (Table 5).

Full Dose Pfizer BioNTech Vaccine

Dagan et al also demonstrated 90% efficacy (95% CI: 83-94) against asymptomatic infection seven days after the second dose.[5] A press release by the vaccine manufacturer reported two weeks post-second dose effectiveness of 94% against asymptomatic infection in Israel.[6] The study utilized de-identified aggregate Israel Ministry of Health public health surveillance data. The analysis was conducted when more than 80% of tested specimens in Israel were variant B.1.1.7.[6] The other three studies involved health care workers and will be discussed in a separate section (Table 6).

mRNA (Pfizer BioNTech and Moderna) Vaccines Effectiveness In The General Population

First or second dose of mRNA vaccine

Tande et al. evaluated the effectiveness of at least one dose of either mRNA-1273 or PfBnT vaccine among people who underwent molecular tests prior to a procedure or surgery.[4] The relative risk for a positive test during asymptomatic pre-procedure screening in vaccinated compared with unvaccinated was significantly lower (0.44 (95% CI: 0.33-0.60)). Ten or more days after the 1st dose, the risk of a positive test was also significantly lower among the vaccinated (0.28 (95% CI: 0.16-0.49; p<.0001)). The risk of test positivity was similarly lower among the vaccinated, after the second dose 0.27 (95% CI: 0.12-0.60).[4]

Moderna Vaccine Efficacy In The General Population

First Dose Moderna Vaccine

A study of the mRNA-1273 reported that 0.1% of the participants receiving the first dose developed asymptomatic infection compared with 0.27% of the unvaccinated group, 21 days after the first dose; which is suggestive of 61.4% efficacy against asymptomatic carriage. Participants in this trial were negative for COVID-19 by RT-PCR or antibody testing at baseline.[11] There was no data on asymptomatic infection after full dose (Table 5).

Janssen Vaccine efficacy in the general population

Full Dose Janssen vaccine

This is a single dose vaccine. The J and J vaccine did not show statistically significant efficacy against asymptomatic infection in the first 29 days of follow-up. However, after 29 days post-vaccination, asymptomatic infection was significantly lower among vaccinated participants (74%, 95% CI: 46.8-88.4%).[12] 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. Furthermore, efficacy as demonstrated by seroconversion in previously asymptomatic participants was 74.2% compared with placebo (95% CI: 47.1; 88.6).[12]

Effectiveness of Vaccines in Health Care Workers (HCWs)

Three studies involving HCWs reported findings regarding asymptomatic infections among recipients of PfBnT vaccine. Two of these studies were one dose studies,[8,9] while a third study was a mix of one and two doses.[7]

Hall et al. in a study of HCWs with negative and positive baseline PCR or antibody in the UK, reported a higher incidence density of asymptomatic or unknown infections with unvaccinated HCWs than PfBnT or AZ vaccine recipients. The vaccine recipients were followed up for 396,318 person-days compared with 710,587 person days in unvaccinated group, with 35 and 218 asymptomatic or unknown infections reported, translating to 0.88 and 3 infections per 10,000 person-days respectively. No effect estimates were reported for asymptomatic infections.[7]

Matheson et al. in an asymptomatic weekly screening study among HCWs who were vaccinated with one dose of PfBnT vaccine 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).[9]

In a third observational HCW study in Israel by Amit et al, asymptomatic test positive data was limited as it was not an active surveillance study. The reason for asymptomatic testing was not reported. The baseline status was not assessed; therefore, prolonged RT-PCR positivity post-infection was not ruled out. Estimated asymptomatic infection prevalence in the vaccinated group was 1.7 per 10,000-person years between 15 and 28 days after vaccination, compared with 2.4 per 10,000 person-years in the unvaccinated group.[8]

Table 5: First-dose Vaccine efficacy or effectiveness against asymptomatic infection

Vaccine	Author	Country	Strain targeted by PCR	Baseline Serology	Dosing Schedule	Follow-up days*	Outcomes	Vaccine Efficacy (95%CI)+
	Voysey et al.[2]	UK	Wild type	Negative	LD or SD	>21	Asymptomatic or unknown	7.8% (-46.7-42.1)
	Voysey et al.[2]	UK	Wild type	Negative	LD or SD	>21	Any PCR+	46.3% (31.8-57.8)
	Voysey et al.[1]	UK/Brazil/S.Afrca	Wild type	Negative	LD or SD	22-90	Any PCR+	67% (49-78)
	Voysey et al.[1]	UK/Brazil/S.Afrca	Wild type	Negative	SD	22-30	Asymptomatic or Unknown	0.2 (-209-68)
	Voysey et al.[1]	UK/Brazil/S.Afrca	Wild type	Negative	SD	31-60	Asymptomatic or Unknown	17 (-172-75)
	Voysey et al.[1]	UK/Brazil/S.Afrca	Wild type	Negative	SD	22-90	Asymptomatic or unknown	16% (-88-62)
Janssen Biotech (Ad26.COV2.S)	Janssen Biotech[12]	Multiple	Wild type	Negative	NA	1-29	Asymptomatic	20% (-7-40.4)
	Janssen Biotech[12]	Multiple	Wild type	Negative	NA	≥ 29	Asymptomatic	74% (46.8-88.4)
Pfizer, BioNTech (BNT162b2)	Amit et al.[8]	Israel	Wild type	Unknown	NA	1-14	Asymptomatic or unknown	NR##
	Amit et al.[8]	Israel	Wild type	Unknown	NA	15-28	Asymptomatic or unknown	NR###
	Dagan et al.[5]	Israel	Wild type and B.1.1.7	Unknown	NA	14-20	Asymptomatic	29% (17-39)
	Dagan et al.[5]	Israel	Wild type and B.1.1.7	Unknown	NA	21-27	Asymptomatic	52% (41-60)
	Hall et al.[7]	UK	Wild type	Unknown	NA	21 days after 1st dose and 7 days after 2nd	Asymptomatic or unknown	97.2%#
	Weekes et al.[9]	UK	Wild type and B.1.1.7	Unknown	NA	<12 and >12	Asymptomatic	NR
Moderna (mRNA-1273)	Baden et al.[11]	USA	Wild type	Negative	NA	From day 1	Asymptomatic	61.4%#
mRNA vaccines (BNT162b2 or mRNA-1273)	Tande et al.[4]	USA		Unknown	NA	From day 1, at least one dose	PCR+ in asymptomatic	RR: 0.44 (0.33-0.60)

* Time PCR was conducted after first or second dose; LD: Low dose, SD: Standard dose, #Calculated from raw values. ## 2.7 cases per 10000 person-days in vaccine vs 2.4 cases per 10000 person-days in control. ###1.7 cases per 10000 person-days in vaccine vs 2.4 cases per 10000 person-days, Calculated from raw values).+ Efficacy reported for RCTs and Effectiveness for observational studies. All Pfizer BioNtech's studies except Dagan et al. involved healthcare workers. 0.44 (95% CI: 0.33-0.60)

Table 6: Full-dose vaccine efficacy or effectiveness against asymptomatic infection

Vaccine	Author	Country	Strain targeted by PCR	Baseline Serology	Dosing Schedule	Follow-up days*	Outcomes	Vaccine Efficacy (95%CI)+
	Voysey et al.[2]	UK	Wild type	Negative	LD or SD and SD	>14	Asymptomatic or unknown	27.3% (-17-54.9)
	Voysey et al.[2]	UK	Wild type	Negative	LD and SD	>14	Asymptomatic or unknown	58.9% (1-82.9)
	Voysey et al.[2]	UK	Wild type	Negative	SD and SD	>14	Asymptomatic or unknown	3.8% (-72.4-46.3)
	Voysey et al.[2]	UK	Wild type	Negative	LD or SD and SD	>14	Any PCR+	55.7% (41.1-66.7)
	Voysey et al.[1]	UK	Wild type	Negative	LD or SD and SD	>14	Any PCR+	54.1% (44.7%, 61.9%)
	Voysey et al.[1]	UK	Wild type	Negative	LD or SD and SD	>14	Asymptomatic or unknown	22.2% (-9.9-45)
	Voysey et al.[1]	UK	Wild type	Negative	SD and SD	>14	Asymptomatic or unknown	2.0% (-50.7-36.2)
	Voysey et al.[1]	UK	Wild type	Negative	LD and SD	>14	Asymptomatic or unknown	49.3% (7.4-72.2)
	Emary et al.[3]	UK	Wild type, B.1.1.7, Other	Negative	LD or SD and SD	>14	Asymptomatic	15.7% (-10.7-35.8)
AstraZeneca (ChAdOx1 nCoV-19)	Emary et al.[3]	UK	B.1.1.7	Negative	LD or SD and SD	>14	Asymptomatic	26.5% (-112-74.5)
	Emary et al.[3]	UK	Variants not B.1.1.7	Negative	LD or SD and SD	>14	Asymptomatic	75.4% (39.9-89.9)
Janssen Biotech (Ad26.COV2.S)	Janssen Biotech[12]	Multiple	Wild type	Negative	NA	1-29	Asymptomatic	20% (-7-40.4)
	Janssen Biotech[12]	Multiple	Wild type	Negative	NA	≥ 29	Asymptomatic	74% (46.8-88.4)
	Dagan et al.[5]	Israel	Wild type and B.1.1.7	Unknown	NA	>7	Asymptomatic	90% (83-94)
	Hall et al.[7]	UK	Wild type	Unknown	NA	21 days after 1st dose and 7 days after 2nd	Asymptomatic or unknown	
Pfizer BioNTech (BNT162b2)	Pfizer [Press Release][6]	Israel	Wild type and B.1.1.7	Unknown	NA	>14	Asymptomatic	94%

* Time PCR was conducted after first or second dose; LD: Low dose, SD: Standard dose, #Calculated from raw values.+ Efficacy reported for RCTs and Effectiveness for observational studies. Hall et al. was the only full-dose study healthcare workers' data

Risk of Vaccinated HCW developing COVID-19

Table 7 to Table 9 utilized estimates from the current HCW specific literature on likelihood of asymptomatic, symptomatic or any infection over a range of attack rates (to encompass a range of exposure risk) to describe the risk of vaccinated HCW developing COVID-19 after a potential exposure to support decision makers in policy design. The risk reduction values used are from an evolving body of literature and a range of study designs, with reduction of risk noted by weeks from first dose as extracted from the studies. Vaccine related risk reduction ranges are based on available HCW study data, from the following time points: 3 weeks post dose 1 mRNA; 3 weeks to 12 weeks post dose 1 nonreplicating adenovirus. Vaccination protection following first dose was selected both based on available data and because this is relevant as the dosing schedules are currently based on an extended interval for many vaccinees. These data should be considered within the context of current uncertainties including long-term follow up data beyond three months after vaccination.

As an example, interpretation from Table 7, the risk of a HCW developing an asymptomatic COVID-19 infection (estimated to be 20% of all infections) following a low-risk exposure (0.5%) after receiving first dose of vaccine would be between 1/757 (3 weeks post vaccination) and 1/1,136 (12 weeks post vaccination) for adenovirus vector vaccines and 1/833 to 1/5,000 3 weeks post vaccination for mRNA vaccines.

Table 7: Risk of first dose vaccinated HCW developing asymptomatic COVID-19 (approximately 20% of all cases) after a potential exposure (data estimates from wild type SARS-CoV-2)[1]

Attack Rate based on Exposure Risk[2] ***A***	**Risk of Developing COVID-19 based on Proportion of Type of COVID-19 Infection x Exposure Risk** ***B*** ***(A x 20%)***	**Vaccination Type** **Nonreplicating adenovirus vaccine or mRNA vaccine**	**Vaccine Risk Reduction (assuming risk reduction [protection] remains the same regardless of exposure risk)[3]** ***C***	**Risk of developing COVID-19 following vaccination regimen** ***D*** ***(B x C)***
Low risk 0.5%	0.1%	mRNA vaccine	0.39 - 0.03 (61%-97% 3 weeks after first dose)	**1/2,564 – 1/33,333**
		Nonreplicating adenovirus vaccine	0.25 (75% 12 weeks after first dose)	**1/4,000**
Medium risk 1%	0.2%	mRNA vaccine	0.39 - 0.03 (61%-97% 3 weeks after first dose)	**1/1,282 - 1/16,666**
		Nonreplicating adenovirus vaccine	0.25 (75% 12 weeks after first dose)	**1/2,000**
High risk 5%	1%	mRNA vaccine	0.39 - 0.03 (61%-97% 3 weeks after first dose)	**1/256 - 1/3,333**
		Nonreplicating adenovirus vaccine	0.25 (75% 12 weeks after first dose)	**1/400**
Superspreader event 10%	2%	mRNA vaccine	0.39 - 0.03 (61%-97% 3 weeks after first dose)	**1/128 - 1/1,666**
		Nonreplicating adenovirus vaccine	0.25 (75% 12 weeks after first dose)	**1/200**

2 Estimates for attack rate derived from study data and stratified to estimate range from low risk to superspreader event risk. from Abbas et al. which identified HCW risk to range from ~2-8%. Abbas, M., Robalo Nunes, T., Martischang, R. et al. Nosocomial transmission and outbreaks of coronavirus disease 2019: the need to protect both patients and healthcare workers. Antimicrob Resist Infect Control 10, 7 (2021). https://doi.org/10.1186/s13756-020-00875-7

3 Study data applied to all infections and asymptomatic infections: nonreplicating adenovirus vaccines - AZ: 16% after 3 weeks, (25-60% after 12 weeks, NS); Janssen: 75% after 12 weeks (PCR and/or serology without previous symptoms). mRNA vaccines - Moderna: 61% from 3 weeks after dose 1; Pfizer BioNTech (Hall et al): 97% 21 days after dose 1; Pfizer BioNTech (Daagen et al): 29% effectiveness 15 days after dose 1 in HCW

Table 8: Risk of vaccinated HCW developing symptomatic COVID-19 (80% of all cases) after a potential exposure (data estimates from wild type SARS-CoV-2) compared with no vaccination[1]

Attack Rate based on Exposure Risk[2] ***A***	**Risk of Developing COVID-19 based on Proportion of Type of COVID-19 Infection x Exposure Risk** ***B (A x 80%)***	**Vaccination Type** **Nonreplicating adenovirus vaccine or mRNA vaccine**	**Vaccine Risk Reduction, time after first dose by vaccine type (assuming risk reduction [protection] remains the same regardless of exposure risk)[3]** ***C***	**Risk of vaccinated person developing COVID-19 by regimen** ***D (B x C)***
Low risk 0.5%	0.4%	Nonreplicating adenovirus vaccine effectiveness range across studies (67% 3w post dose 1 to -75% 12 w post dose 1)	0.22 to 0.66	**1/757** **to** **1/1,136**
		mRNA vaccine effectiveness range (70% 3 w post dose 1 to 95% 2 wks post dose 1)	0.3 to 0.05	**1/833** **to** **1/5,000**
Medium risk 1%	0.8%	Nonreplicating adenovirus vaccine effectiveness range	0.33 (67% effectiveness 3 weeks post first dose)	**1/378**
			0.22 (75% maximum reduction from 12 weeks onwards)	**1/568**
		mRNA vaccine effectiveness range	0.3 (70% reduction 3 weeks after first dose)	**1/416**
			0.05 (95% reduction 2 weeks after first dose)	**1/2,500**
High risk 5%	4%	Nonreplicating adenovirus vaccine effectiveness range	0.33 (67% effectiveness 3 weeks post first dose)	**1/75**
			0.22	**1/113**

			(75% maximum reduction from 12 weeks onwards)	
		mRNA vaccine effectiveness range	0.3 (70% reduction 3 weeks after first dose)	**1/83**
			0.05 (95% reduction 2 weeks after first dose)	**1/500**
Superspreader event 10%	8%	Nonreplicating adenovirus vaccine effectiveness range	0.33 (67% effectiveness 3 weeks post first dose)	**1/37**
			0.22 (75% maximum reduction from 12 weeks onwards)	**1/56**
		mRNA vaccine effectiveness range	0.3 (70% reduction 3 weeks after first dose)	**1/41**
			0.05 (95% reduction 2 weeks after first dose)	**1/250**

[1] Estimate of type of COVID-19 cases (symptomatic ~80%) is a conservative estimate derived from a meta-analysis on the proportion of asymptomatic case and potential range for community transmission. 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. https://jammi.utpjournals.press/doi/pdf/10.3138/jammi-2020-0030

[2] Estimates for attack rate derived from study data and stratified to estimate range from low risk to superspreader event risk. from Abbas et al. which identified HCW risk to range from ~2-8%. Abbas, M., Robalo Nunes, T., Martischang, R. et al. Nosocomial transmission and outbreaks of coronavirus disease 2019: the need to protect both patients and healthcare workers. Antimicrob Resist Infect Control 10, 7 (2021). https://doi.org/10.1186/s13756-020-00875-7

[3] Study data applied to all infections and asymptomatic infections: nonreplicating adenovirus vaccines - AZ: 16% after 3 weeks, (25-60% after 12 weeks, NS); Janssen: 75% after 12 weeks (PCR and/or serology without previous symptoms). mRNA vaccines - Moderna: 61% from 3 weeks after dose 1; Pfizer BioNTech (Hall et al): 97% 21 days after dose 1; Pfizer BioNTech (Dagen et al): 29% effectiveness 15 days after dose 1 in HCW

Table 9: Estimated Risk of vaccinated developing symptomatic or asymptomatic COVID-19 after varied risk exposures (current data estimates from wild type SARS-CoV-2 and are evolving - will require frequent updates) compared with no vaccination[1]

Attack Rate based on Exposure Risk[2] ***A***	**Risk of Developing COVID-19 based on Proportion of Type of COVID-19 Infection x Exposure Risk** ***B (A x 100%)***	**Vaccination Type** **Nonreplicating adenovirus vaccine or mRNA vaccine**	**Vaccine Risk Reduction (assuming risk reduction [protection] remains the same regardless of exposure risk)[3,4]** **C**	**Risk of developing COVID-19 following vaccination regimen** ***D (B x C)***
Low risk 0.5%	0.5%	Nonreplicating adenovirus vaccine effectiveness range	0.84 (16% effectiveness 3 weeks post first dose)	**1/250**
			0.25 (75% maximum reduction from 12 weeks onwards)	**1/800**
		mRNA vaccine effectiveness range	0.39 (61% reduction 3 weeks after first dose)	**1/512**
			0.03 (97% reduction 3 weeks after first dose)	**1/6,666**
Medium risk 1%	1%	Nonreplicating adenovirus vaccine effectiveness range	0.84 (16% effectiveness 3 weeks post first dose)	**1/119**
			0.25 (75% maximum reduction from 12 weeks onwards)	**1/400**
		mRNA vaccine effectiveness range	0.39 (61% reduction 3 weeks after first dose)	**1/256**
			0.03 (97% reduction 3 weeks after first dose)	**1/3,333**
High risk 5%	5%	Nonreplicating adenovirus vaccine effectiveness range	0.84 (16% effectiveness 3 weeks post first dose)	**1/23**
			0.25	**1/80**

			(75% maximum reduction from 12 weeks onwards)	
		mRNA vaccine effectiveness range	0.39 (61% reduction 3 weeks after first dose)	**1/51**
			0.03 (97% reduction 3 weeks after first dose)	**1/666**
Superspreader event 10%	10%	Nonreplicating adenovirus vaccine effectiveness range	0.84 (16% effectiveness 3 weeks post first dose)	**1/11**
			0.25 (75% maximum reduction from 12 weeks onwards)	**1/40**
		mRNA vaccine effectiveness range	0.39 (61% reduction 3 weeks after first dose)	**1/25**
			0.03 (97% reduction 3 weeks after first dose)	**1/333**

1 Estimate of type of COVID-19 cases (symptomatic ~80%) is a conservative estimate derived from a meta-analysis on the proportion of asymptomatic case and potential range for community transmission. 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. https://jammi.utpjournals.press/doi/pdf/10.3138/jammi-2020-0030

2 Estimates for attack rate derived from study data and stratified to estimate range from low risk to superspreader event risk. from Abbas et al. which identified HCW risk to range from ~2-8%. Abbas, M., Robalo Nunes, T., Martischang, R. et al. Nosocomial transmission and outbreaks of coronavirus disease 2019: the need to protect both patients and healthcare workers. Antimicrob Resist Infect Control 10, 7 (2021). https://doi.org/10.1186/s13756-020-00875-7

3 Study data applied to all infections and asymptomatic infections: nonreplicating adenovirus vaccines - AZ: 16% after 3 weeks, (25-60% after 12 weeks, NS); Janssen: 75% after 12 weeks (PCR and/or serology without previous symptoms). mRNA vaccines - Moderna: 61% from 3 weeks after dose 1; Pfizer BioNTech (Hall et al): 97% 21 days after dose 1; Pfizer BioNTech (Dagen et al): 29% effectiveness 15 days after dose 1 in HCW

Cycle threshold (Ct) Values

Three studies reported Ct values, an inverse proxy for viral load, in infected vaccinated and unvaccinated individuals.[3,9,10]

Results from Phase 2/3 vaccine efficacy studies of AZ 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.[3] 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 ($p=0.0113$).[3]

A retrospective study of PfBnT 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 ($p<10^{-8}$).[10] In another UK study of one dose of BNT162b2 vaccine, the median Ct values of infected 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.[9]

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 AZ 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.[13] 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.[14] 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.[28]

Yu et al. evaluated the protective efficacy of DNA vaccines compared with controls.[29] 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.[29]

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.[15] Similarly, half of the placebo group had elevated viral RNA in their nasal swabs, while none was detectable in vaccinated animals.[15]

Discussion

The majority of the vaccines included in this review demonstrated efficacy and effectiveness against asymptomatic wild-type COVID-19 infections. The PfBnT, and J and J vaccines were reported to have up to 90%[5] and 74%[12] efficacies against asymptomatic infection respectively. Data were 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. None of the approved vaccines have been assessed primarily on their ability to prevent transmission.

The AZ and PfBnT 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.[30]

Preclinical primate studies showed that vaccinated animals receiving the Moderna mRNA (8 weeks prior)[14] or Novavax protein vaccine (35 days prior),[15] were less likely to have the virus recovered from nasal or lower respiratory samples than unvaccinated animals. The AZ vaccine was more protective against lower respiratory replication, while showing no difference in nasal virus replication.[13]

Studies suggesting the plausibility of vaccine-induced reduction of transmission, including monoclonal antibody therapeutics trials and epidemiologic evidence of transmission from individuals who were persistently RT-PCR positive after natural infection, with evidence of an immunologic response, indicated that viral load can be reduced by circulating antibodies, and that a lower viral load or higher Ct on RT-PCR was associated with a reduced risk of transmission.[18,19] However, RT-PCR positivity in the presence of neutralizing antibody and or

correlates of cell mediated immunity should not be considered to necessarily represent transmissible infection.

There were significant limitations to many of the included studies. The primary endpoint of the vaccine randomized controlled trials were detection of test positive symptomatic COVID-19, however some studies presented data, which suggest a reduction in the likelihood of testing positive for SARS-CoV-2 RT-PCR in the absence of documented symptoms after vaccination. Furthermore, it was not possible to directly compare findings across studies owing to variations in the assessment of symptom status, and the testing used and timing of these assessments. Also, the possibility of persistent PCR positivity after COVID-19 infection[31] could not be excluded in some of the studies without baseline PCR assessment. Few studies included surveillance nasal swabs for PCR positivity. Most of the current data were around viral detection, rather than evidence of cultivatable virus and epidemiologic evidence of transmission. Therefore, there was limited data to evaluate the efficacy or effectiveness of COVID-19 vaccines in decreasing viral loads. In addition, there is presently no available epidemiologic data addressing evidence of forward transmission after vaccination.

Based on the current evidence, we suggest the following:

1) all vaccinees should self-isolate and seek testing after the development of COVID-19 compatible symptoms

2) Following exposure, the risk of contracting COVID-19 and subsequent forward transmission from asymptomatic or paucisymptomatic viral carriage should be considered in light of whether the exposed individual was immunized, the time elapsed since immunization and the consequent expected degree of protection on, a case-by-case basis for those in vulnerable setting. When possible, a case-by-case consideration for whether exposed persons are immunized, is necessary. Low-moderate risk exposures could potentially be managed with careful use of personal protective equipment (PPE), and self-monitoring.

3) If a vaccinated HCW is assessed as having a significant exposure before the period of expected robust immunity, high risk exposures may be managed as for unimmunized persons.

4) All immunized persons should continue to use recommended PPE when in close contact with unimmunized persons.

5) Population and public health data being collected on positive COVID-19 tests occurring after vaccination should be combined with laboratory data on Ct values, identification of variant strain infections, and epidemiologic contact tracing data to prospectively monitor for evidence of forward transmission of infection from vaccinated persons.

Conclusion

Some studies, such as the AZ vaccine studies, included data on cross sectional prevalence of positive SARS-CoV-2 RT-PCR from routine swabbing, which suggested efficacy against asymptomatic infection, although this was not routinely assessed in a comparable way across studies. Limited evidence regarding the Ct values for AZ vaccine and the PfBnT 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 or effectiveness 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.

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Appendix 1: Vaccine Efficacy or Effectiveness Against Symptomatic Infection

Vaccine	Author	Country	Strain	Dose	Days after Dose	Vaccine Efficacy (95% CI)
AstraZeneca (ChAdOx1 nCoV-19)	Voysey et al.[2]	UK/Brazil	Wild type	2nd	>14	70.4% (54.8-80.6) ‡
	Voysey et al.[1]	UK/Brazil/S.Africa		1st	22-30	77% (47-90)
	Voysey et al.[1]	UK/Brazil/S.Africa		1st	31-60	73% (33-89)
	Voysey et al.[1]	UK/Brazil/S.Africa		1st	61-90	78% (36-93)
	Voysey et al.[1]	UK/Brazil/S.Africa		1st	90-120	32% (-142-81)
	Voysey et al.[1]	UK/Brazil/S.Africa	Wild type	2nd	>14	66.7% (57.4-74.0) ‡
	Voysey et al.[1]	UK/Brazil/S.Africa	Wild type	2nd	>14	63.1% (51.8-71.7)
	Voysey et al[1]	UK/Brazil/S.Africa	Wild type	2nd	>14	80.7% (62.1-90.2) †
	Madhi et al.[32]	South Africa	Wild type	2nd	>14	21.9% (-49.9 -59.8)
	Madhi et al.[32]	South Africa	B.1.351	2nd	>14	10.4% (-76.8-54.8)
	Emary et al.[3]	UK	Wild type, B.1.1.7, others	2nd	>14	74.2% (65-81.0)
	Emary et al.[3]	UK	B.1.1.7	2nd	>14	74.6% (41.6-88.9)
Gamaleya (Gam-COVID-Vac)	Logunov et al.[33]	Russia	Wild type	2nd	NR	91·1% (83·8–95·1)
Janssen Biotech (Ad26.COV2.S)	Janssen[12]	Multiple	Wild type	1st	>14	66.9 (59-73.4)
	Janssen[12]	Multiple	Wild type	1st	>28	66.1 (55-74.8)
Moderna (mRNA-1273)	Baden et al.[11]	USA	Wild type	2nd	>14	94% (89.3-96.8)
Novavax (NVX-CoV2373)	Novavax[34]	UK	Wild type	2nd	>7	89.3% (75.2 – 95.4)
	Novavax[34]	South Africa	Wild type	NR	NR	49.4% (6.1 – 72.8)
Pfizer BioNTech (BNT162b2)	Hall et al.[7]	UK	Wild type	2nd	7	85% (74-96)
	Hall et al.[7]	UK	Wild type	1st	21	70% (53-87)
	Polack et al.[35]	Multiple	Wild type	2nd	>7	94.8% (89.8–97.6)
	Amit et al.[8]	Israel	Wild type	1st	15-28	75% (52 -87)
	Dagan et al.[5]	Israel	Wild type, B.1.1.7	1st	14-20	57% (50-63)
	Dagan et al.[5]	Israel	Wild type, B.1.1.7	1st	21-27	66% (57-73)
	Dagan et al.[5]	Israel	Wild type, B.1.1.7	2nd	>7	94% (87-98)

‡Low Dose (LD) or Standard Dose (SD) vs SD;† LD vs SD. NB: Efficacy reported for RCTs and effectiveness for observational studies

Appendix 2: Vaccine Efficacy or Effectiveness Against Symptomatic Infection (includes all doses and reported timing)

Vaccine	Author	Trial name/NCT	Country	Virus type	Dosing	1st or 2nd dose	Post-vaccination day	Effect size/p.values
AstraZeneca	Voysey et al	COV002	UK	Wild type	LD and SD	2nd	>14	90% (67.4-97)
		COV002	UK		SD and SD	2nd	>14	60.3% (28-78.2)
		COV003	Brazil	Wild type	SD and SD	2nd	>14	64.2% (30.7-81.5)
		COV002/003	UK/Brazil	Wild type	LD/SD and SD	2nd	>14	67.1% (52.3-77.3)
		COV002	UK	Wild type	SD	1st	>21	55% (29.7%-71.1%)
		COV003	Brazil	Wild type	SD	1st	>21	71.2% (54.2-81.9)
		COV002/003	UK/Brazil	Wild type	LD/SD	1st	>21	58.3% (44-68.9)
	Voysey et al	COV001/002/003/005	UK/Brazil/S.Africa	Wild type	LD and SD	2nd	>14	66.7% (57.4%, 74.0%)
		COV001/002/003/005	UK/Brazil/S.Africa	Wild type	SD and SD	2nd	>14	63.1% (51.8%, 71.7%)
		COV001/002/003/005	UK/Brazil/S.Africa	Wild type	LD and SD	2nd	>14	80.7% (62.1%, 90.2%)
		COV001/002/003/005	UK/Brazil/S.Africa	Wild type	LD/SD SD	1st	>21	76% (59%, 86%)
	Madhi et al.	NCT04444674	South Africa	Wild type	SD and SD	2nd	>14	21.9% (-49.9 to 59.8)
				B.1.351		2nd	>14	10.4% (-76.8; 54.8)
	Emary et al.	NCT04400838/ISRCTN 15281137.	UK	Wild type and VOC	LD/ SD and SD	2nd	>14	74.2% (65.0%, 81.0%)
			UK	Variants of Concern	LD/ SD and SD	2nd	>14	74.6% (41.6%, 88.9%)
			UK	Variants of Concern	LD/ SD and SD	2nd	>14	84.1% (70.7%, 91.4%)
			UK	Wild type and VOC	LD/SD and SD	2nd	>14	75.4% (34.3%, 90.8%)
			UK	Wild type and VOC	LD/ SD and SD	2nd	>14	64.3% (44.9%, 76.8%)
Moderna	Baden et al.	NCT04470427	USA	Wild type	NA	1st	<14	
				Wild type	NA	1st	>14	
				Wild type	NA	2nd	<14	

Vaccine	Author	Trial name/NCT	Country	Virus type	Dosing	1st or 2nd dose	Post-vaccination day	Effect size/p.values
				Wild type	NA	2nd	>14	
				Wild type	NA	1st	NR	
				Wild type	NA	2nd	>14	94% (89.3-96.8)
Sputnik	Logunov et al	NCT04530396	Russia	Wild type	NA	1st	>21	91.6% (85.6-95.2, p<0.0001)
				Wild type	NA	1st	>14	87.6% (81.1-91.8, p<0.0001)
				Wild type	NA	2nd	anytime	91·1% (83·8–95·1, p<0.0001)
Novavax	Novavax	NR	UK	Wild type	NA	2nd	>7	89.3% (95% CI: 75.2 – 95.4)
		NR	South Africa	Wild type	NA	NR	NR	49.4% (95% CI: 6.1 – 72.8)
Pfizer BioNTech	Polack et al	NCT04368728	USA, Argentina, Brazil, South Africa, Germany, Turkey	Wild type	NA	2nd	>7	95.0 (90.3–97.6)
				Wild type	NA	1st	NR	82.0 (75.6–86.9)
				Wild type	NA	1st	12	52% (95% CI, 29.5 to 68.4)
				Wild type	NA	2nd	<7	90.5 (61.0–98.9)
		NCT04368728	USA, Argentina, Brazil, South Africa, Germany, Turkey	Wild type	NA	2nd	>7	94.8 (89.8–97.6)
	Amit et al.	NR	Israel	Wild type	NA	1st	1-14	rate reduction: 44% (12 to 64); adjusted rate reduction: 47% (17 to 66)
		NR	Israel	NR	NA	1st	15-28	rate reduction: 75% (52 to 87); adjusted rate reduction: 85% (71 to 92)
				NR	NA	2nd	NR	
	Dagan et al.		Israel	Wild type and VOC		1st	14-20	57% (95% CI, 50 to 63)
			Israel	Wild type and B.1.1.7		1st	21-27	66% (95% CI, 57 to 73)

Vaccine	Author	Trial name/NCT	Country	Virus type	Dosing	1st or 2nd dose	Post-vaccination day	Effect size/p.values
			Israel	Wild type and B.1.1.7		2nd	>7	94% (95% CI, 87 to 98)
	Hall et al.		UK			1st and second	21 and 7	

LD: Low Dose, SD: Standard Do