Transmissibility of COVID-19 among vaccinated individuals

A Rapid Literature Review: Update #2

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Prepared By:
Charleen Salmon, Jordyn Flanagan, Brenlea Farkas, Liza Mastikhina, Oluwaseun Egunsola, Lynora Saxinger, Becky Skidmore, Fiona Clement, on behalf of the University of Calgary Health Technology Assessment Unit.

Contact:
Fiona Clement

Email: fclement@ucalgary.ca

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Project Contributors
Charleen Salmon[1,2]; Jordyn Flanagan[1,2]; Brenlea Farkas[1,2]; Liza Mastikhina[1,2]; Oluwaseun Egunsola[1,2]; Lynora Saxinger[3]; Becky Skidmore[4]; 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
3. Department of Medicine University of Alberta, Edmonton, Alberta, Canada
4. Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada

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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
mRNA-1273	Moderna's mRNA vaccine
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

KEY POINTS

- Forty-five studies, including six RCTs and 39 observational studies were included in this review.
- COVID-19 vaccination have been demonstrated to be associated with varied degrees of reduced household transmission of SARS-CoV-2, reduced incidence of asymptomatic infection, and a reduction in viral load, although data on the most recently emergent Delta VOC is required.
- Evidence from four large household surveillance studies from the Netherlands, Finland, and Israel suggests that full-dose of AZ, PfBnT, Moderna, or J&J vaccines may prevent significantly reduced household transmission of wild-type or the B.1.1.7 (Alpha) COVID-19 strain after 14 days of vaccination by at least 63%. No studies on vaccine effectiveness against infection transmission of the B.1.617.2 (Delta) strain were found.
- The AZ vaccine trial in the general population suggest that an initial low dose 1 followed with an extended interval standard dose 2 may provide up to 59% protection against asymptomatic or unknown infection. Efficacy against these outcomes was not demonstrated following two standard doses given at a short interval of ?1 mo. The higher efficacy in the low dose study results is felt to be partially explained by the extended interval before dose 2 in that subgroup, which has subsequently been shown to offer higher overall efficacy. A first dose of AZ vaccine was associated with significantly reduced odds (ORs between 0.39 and 0.45) of asymptomatic infection in another observational study.
- Asymptomatic infection is felt to be a risk for post-vaccination transmission, so reduction of asymptomatic infection is a useful end point.
- PfBnT vaccine observational studies in the general population suggest up to 90% effectiveness against asymptomatic infection after seven or more days of full-dose vaccination. For healthcare workers there was up to 75% effectiveness of asymptomatic infection against the wild-type strain after full-dose of the PfBNT vaccine.
- In the general population, vaccine effectiveness of a full dose of PfBNT was reported to be 35.9% effective at reducing asymptomatic infection against the B.1.617.2 (Delta) variant.
- Moderna vaccine observational studies in the general population suggest up to 57.4% effectiveness against asymptomatic infection of the B.1.617.2 (Delta) variant after 14 or more days of full-dose vaccination.
- In a community RCT assessing asymptomatic infection by collection of a RT-PCR swab at the dose 2 visit, a single dose of the Moderna vaccine showed efficacy of 61.4% against asymptomatic infection against wild-type SARS-CoV-2 in adults and 59.5% in adolescents aged 12-17 years. No vaccine efficacy for the full series was reported for adults but data from the adolescent trial of the Moderna vaccine showed two doses two weeks after vaccination had an efficacy of 39.2% against asymptomatic infection of the wild-type strain. The single dose protocol J&J vaccine had an efficacy

of 74% against asymptomatic infection after 28 days of vaccination for adults against the wild-type strain.

- Thirteen of the 20 studies reporting cycle threshold values found significantly increased cycle threshold, suggestive of a lower viral load, in PfBnT, Moderna, or AZ vaccinated individuals compared with unvaccinated. The two included studies reporting viral load found a significant reduction in the viral RNA load in mRNA-based vaccinated individuals.
- Further research is needed to evaluate post-vaccination infectivity and transmission of both the wild type COVID-19 virus and the variants of concern especially the B.1.617.2 (Delta) variant.

EXECUTIVE SUMMARY

Objectives: This is an update of a previous report with a literature search that ended May 4, 2021.[1] A total of 25 additional studies were included in this update for a total of 45 studies. The objective of this report is to identify comparative observational studies and randomized controlled trials (RCTs) evaluating the efficacy and effectiveness of COVID-19 vaccination in reducing forward transmission from vaccinated people, and studies examining the biological plausibility of vaccination induced transmission reduction. There is evolving data around the frequency of asymptomatic COVID-19 and whether 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. Since most COVID-19 vaccine trials use an endpoint of symptomatic infection, there is less data about whether asymptomatic infection and viral carriage can still occur after vaccination, and whether this incurs a risk for viral transmission from vaccinated persons.

Design: Rapid review with grey literature search.

Method: A search of databases, MEDLINE, Embase, L-OVE and the Cochrane Central Register of Controlled Trials was conducted to identify RCTs or comparative observational studies evaluating the efficacy and effectiveness of COVID-19 vaccination in the prevention of transmission, asymptomatic infections, and transmissibility of COVID-19 among vaccinated persons. An additional search of grey literature was conducted, including: Clinicaltrials.gov, McMaster Health Forum (COVID-END), MedRxiv, Google, regulatory submissions, and the websites of the Centres for Disease Control and Prevention (CDC) and World Health Organization (WHO). Abstracts were screened by a single reviewer and then reviewed in full text by two independent reviewers. This search is current to August 23, 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, seroprevalence, and all the reported outcomes of interest. Quality assessment was conducted based on study design: ROBINS-I for non-randomized studies and Cochrane Risk of Bias for human-subject RCTs. Data were extracted by one reviewer and verified by another. Animal studies were not included in this update.

Results: In this update, 25 additional studies were included. Therefore, this review has a total of 45 included studies. Four new studies on COVID-19 transmission to household contacts were included.

Reduction of household transmission: A retrospective cohort study in the Netherlands by de Gier et al. of 113,582 confirmed index cases of COVID-19 and 253,168 cohabitating household members or close contacts were assessed for vaccine effectiveness in preventing transmission to the household member or close contact and stratified by vaccination status, vaccine type, and days past date of inoculation.[2] At least one dose of PfBNT, Moderna, AZ, or J&J from past the 14th day of vaccination onwards was associated with the reduction of

transmission of COVID-19 to any household contact by 21% (95% CI: 12-28), 23% (95% CI: 14-32) to any unvaccinated household contact, 22% (95% CI: 9-33) to any other close contact, and 22% (95% CI: 8-34) to any unvaccinated close contact.[2] Fully vaccinated individuals with either PfBNT, Moderna, J&J, or AZ from past the 7th day of vaccination onwards, was associated with the reduction of transmission of COVID-19 to any household contact by 71% (95% CI: 63-77), 73% (95% CI: 65-79) to any unvaccinated household contact, 22% (95% CI: -5-43) to any other close contact, and 24% (95% CI: -5-43) to any unvaccinated close contact.[2] The low vaccine effectiveness of a fully vaccinated individual against transmission to any close contact or any close unvaccinated contact could be due to the studies being underpowered to detect differences due to the small number of events that occurred in vaccinated individuals compared to unvaccinated index cases.

A similar study was conducted in Finland by Salo et al. This retrospective cohort study investigated the vaccine effectiveness of 95,138 mRNA-based (PfBNT or Moderna) vaccinated healthcare workers against infection transmission to unvaccinated household members compared to unvaccinated healthcare workers and their unvaccinated household members.[3] At least one dose of an mRNA-based vaccine from the 14th day of vaccination onward reduced transmission to an unvaccinated spouse by 8.7% (95% CI: -28.9-35.4) and increased to 42.9% (95% CI: 22.3-58.1) reduction in transmission 10 weeks after the first dose.[3] At least one dose of an mRNA-based vaccine from the 14th day of vaccination onward increased transmission to an unvaccinated child living in the household between the ages of 3-18 years by 1.0% (95% CI: -53.9-33.7) and decreased transmission to the unvaccinated child by 32.9% (95% CI: 4.1-53.0) 10 weeks after the first dose.[3]

Two studies from Israel found that PfBNT fully vaccinated individuals from past the 7th day of vaccination onward had reduced infection transmission to their household contacts.[4,5] A retrospective cohort study using a nationally centralized database investigated the vaccine effectiveness of PfBNT against infection transmission of two-adult households only and one confirmed case of infection during the study period.[4] Of households with a fully vaccinated adult, the PfBNT vaccine was found to reduce infection transmission of the wild-type strain by 80.0% (95% CI: 73.0-85.1) compared to those who were unvaccinated and by 82.0% (95% CI: 75.5-86.7) compared to those who were recently vaccinated with one dose (between 0-7 days after vaccination).[4] A second Israeli study by Layan et al. conducted a case-control study of the PfBNT vaccine's effectiveness on reduction of infection transmission of the wild-type and B.1.1.7 (Alpha) strains in healthcare workers and their households.[5] The risk of transmission from vaccinated cases was 0.22 times (95% CI: 0.06-0.70) the risk of infection transmission compared to unvaccinated cases.[5]

The baseline serology and PCR of household contacts were not reported in any of the studies except for Salo et al. and Gazit et al. who only included seronegative participants.[3,4]

Reduction of asymptomatic test positive status after vaccination, various populations: Asymptomatic with lab documented infection data were presented in 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)[6] and 46.3% (31.8-57.8)[7], respectively, after 21 days following the first

dose. However, the 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)[7] respectively.

Several studies found that a full-dose of PfBNT or Moderna significantly reduced asymptomatic infection from the wild-type strain.[8-12] Tang et al. found a reduction in transmission of asymptomatic infection of fully vaccinated seronegative Qatari healthcare workers between 0-6 days past the date of vaccination (IRR: 0.35 [95% CI: 0.11-1.09]) and from more than 7 days past the date of vaccination (IRR: 0.10 [95% CI: 0.04-0.22]).[8] This finding was supported by Angel et al. who found similar significant reductions in asymptomatic infection.[9] A retrospective cohort study by Andrejko et al. of 525 seronegative California residents found that a full-dose of PfBNT had a 68.3% (95% CI: 27.9-85.7%) reduction of asymptomatic infection of the wild-type strain.[10]

Dagan et al. demonstrated 90% effectiveness (95% CI: 83-94) against asymptomatic infection seven days after the second dose from the wild-type or B.1.17 (Alpha) strain.[13] In an Israeli study, which utilized the national public health surveillance data, Haas et al. reported significantly higher vaccine effectiveness seven or more days after full-dose PfBnT vaccination, 90.4% (95% CI: 89.1-91.5).[14]

Tande et al. evaluated the effectiveness of at least one dose of either Moderna or PfBnT vaccine among people who underwent molecular tests prior to a procedure or surgery.[15] 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).[15] Lastly, Chemaitelly et al. found that a full-dose of Moderna was 92.5% effective (95% CI: 84.8-96.9) against asymptomatic carriage 14 days after full vaccination.[11]

There is limited evidence suggesting that mRNA-based vaccines have protection against asymptomatic carriage of the B.1.617.2 (Delta) variant. Tang et al. found that use of at least one dose of an mRNA-based vaccine past the 14th day onward from the date of vaccination, reduced asymptomatic infection by 44.3% (95% CI: 0-78.4) against the B.1.617.2 (Delta) variant.[12] The study conducted by Tang et al., stratified by vaccine manufacturer and found that a full dose of PfBNT past the 14th day onward from the date of vaccination was found to reduce asymptomatic infection by 35.9% (95% CI: 11.1-53.9) against the B.1.617.2 (Delta) variant[12] and that a full-dose of Moderna had 80.2% vaccine effectiveness (95% CI: 54.2-92.6) against asymptomatic carriage of the Delta strain 14 days after full vaccination[12]

Possible reduction of viral load / higher Ct values in vaccinated persons, population data: Twenty studies reported on Ct, an inverse proxy for viral load and two studies reported on viral load.

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.[16] 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).[16]

A longitudinal UK household survey by Pritchard el al. found statistically significant increase in the median Ct values of PfBnT or AZ single or full dose vaccinated individuals compared with unvaccinated individuals at any time point before or after 21 days post-vaccination (p<0.001).[17] Similarly, in another UK study by Shrotri et al., the mean Ct value of unvaccinated individuals within 27 days of vaccination was 26.6 (95% CI: 26-27.1) compared with 26·6 (95% CI: 25.19-26.62) with one dose of PfBnT or AZ, which was not significantly different (p=0.158).[18] However, after 28 days, there was a statistically significant decrease in the mean Ct between vaccinated and unvaccinated persons (mean Ct 26.6 (95% CI: 26-27.1) vs 31·3 (95% CI: 29.6-32.9), p<0·001).[18] Monthly routine PCR testing was conducted in these patients; however, the baseline serology was not reported.[18] In a longitudinal cohort study of HCWs who were offered voluntary nasal and oropharyngeal swab PCR testing every two weeks as well as serological testing, a small study of 49 people vaccinated with either PfBNT or AZ and 96 unvaccinated people in the USA by Mostafa et al. demonstrated non-significant differences in median Ct values (19.26 [Q1, Q3: 16.56-21.96] vs 19.6 [Q1, Q3: 16.28-22.66], respectively).[19] Similar non-significance in the median Ct values of PfBNT or AZ-vaccinated people vs unvaccinated was found in a UK study by Baltas et al. (Median=30.8 [IQR: 25.9-35.4] vs. Median=28.8 [IQR: 25.3-33.7], p=0.053).[20] Lastly, Lumley et al., found vaccination with either PfBnT or AZ to non-significantly increase Ct value by a mean of 2.7.[21]

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 three 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 three genes were significantly higher among infected vaccinated persons than controls ($p<10^{-8}$).[22] 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.[23] A study by McEllistrem et al. among community living centre residents reported five cases of asymptomatic infections (determined by surveillance nasal swabs every 2-5 days) among baseline PCR negative PfBnT vaccinated and unvaccinated residents. The median Ct values among unvaccinated residents (12.8, IQR: 12.4-14.9) were significantly lower (p=0.009) than vaccinated residents (19.4, IQR: 18.9-25.5).[24] Furthermore, viral load was -2.4 mean log10 lower among the vaccinated cohort (p=0.004).[24] In another large cohort study of HCWs at a large medical centre in Israel by Regev-Yochay et al, the mean Ct values among PfBNT fully vaccinated HCWs (27.3±2.2) was significantly higher (mean difference 5.09, 95% CI: 2.8-7.4, p<0.001) than unvaccinated HCWs (22.2±1.0).[25] A matched case-control study by Abu-Raddad et al. from Qatar, evaluating the Ct values of people with two doses of PfBNT with breakthrough infections compared to Ct values of infections in

unvaccinated individuals, found statistically significant higher median Ct values in vaccinated individuals (27.8; IQR: 21.1-32.7) than the median Ct value of unvaccinated individuals (25.8 (IQR: 19.5-31.4; p<0.001).[26] However, studies in France[27] and Greece[28] found no statistically significant differences between PfBNT vaccinated individuals' Ct values and the Ct values of those who were unvaccinated. Bailly et al. found that the Ct values of PfBNT fully vaccinated long-term care residents did not differ from the Ct values of unvaccinated residents (Median=21 [IQR:13-32] vs 15 [IQR: 12-17]; p=0.05).[27] Similarly, Ioannou et al.'s study of fully vaccinated healthcare workers in a Greek hospital amidst an outbreak found no significant differences between the median Ct values of those vaccinated and unvaccinated (18 [15.5-25.5] vs 18.5 [13.5-24]).[28]

A USA study investigating the Ct values of mRNA-based vaccinated healthcare workers (PfBNT or Moderna) from unvaccinated healthcare workers found that there was no statistically significant difference in mean Ct values in the early post-vaccination period defined as less than 14 days post vaccination (22.6±7 vs. 23±7.4) for partially-vaccinated healthcare workers more than 14 days past first dose but before the second dose (27.7±8.7 vs. 23±7.4), or for fully vaccinated healthcare workers at least 14 days past vaccination (28.5±7.4 vs. 23±7.4).[29] Another similar study by Duerr et al. reported Ct values for vaccinated individuals in the community but lumped all unvaccinated comparators as under a Ct value equal or less than 30 therefore, no effect size was presented.[30]

Two USA studies reported on viral load, one study is new to this updated version of the report. A prospective cohort study of baseline seronegative vaccinated and unvaccinated healthcare workers across Arizona had their mid-turbinate nasal swabs assessed for viral load.[31] Thompson et al. found that the mean viral RNA load for partially and fully vaccinated healthcare workers, with a mRNA-based vaccine, who were at least 14 days past the date of vaccination had lower presence of virus compared to their unvaccinated counterparts (2.3±1.7 Log_{10} copies/mL vs. 3.8±1.7 Log_{10} copies/mL).[31] This represented at least 40.2% lower viral RNA load after at least partial vaccination.[31]

A second retrospective cohort study of five vaccinated and five unvaccinated asymptomatic nursing home residents in a single nursing home evaluated the effectiveness of at least one dose of the PfBNT vaccine on attenuating viral load.[24] Viral load was -2.4 mean log10 lower among the vaccinated cohort (p=0.004).[24]

Data from vaccine efficacy trials where asymptomatic RT-PCR swabs were collected: Baden et al. showed that, among participants who received the first dose of the 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.[32]

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&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.[33]

Emerging Evidence: Variants of SARS-CoV-2 continue to surface, and the B.617.2 (Delta) variant is currently the one of most concern.[34,35] There has been emerging evidence that indicates that although a full vaccination series might reduce an individual's overall risk of becoming infected, there seems to be a limited difference in the Ct values between vaccinated and unvaccinated.[34,36] Certain outbreaks amongst vaccinated individuals in the USA have led to CDC recommendations for expanded prevention strategies such as universal masking in indoor spaces.[35]

Conclusion: Four months since the publication of the previous version of this report, 24 additional relevant studies have been published. Four of these were large household surveillance studies from the Netherlands, Finland, and Israel suggesting that a full dose of PfBNT, Moderna, AZ, or J&J vaccines may prevent household transmission after 14 days of vaccination. Twelve additional studies found that vaccines significantly reduce the risk of asymptomatic infection, with multiple studies finding that vaccines decreased the viral RNA load or increased the cycle threshold, suggestive of reduced viral load. Some studies, such as the RCTs investigating the AZ vaccine, 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. Evidence regarding the Ct values for the AZ, PfBnT, and Moderna vaccines suggest their potential to reduce viral load and possibly transmission. Further research is needed to evaluate post-vaccination infectivity and transmission of variants of concern especially the B.1.617.2 (Delta) strain from other jurisdictions.

Protocol/Topic Registration: PROSPERO-CRD42021252485.

Introduction

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of late September 2021, there have been more than 229,903,892 confirmed cases of COVID-19, which have resulted in more than 4,715,485 confirmed deaths worldwide.[37] Since the start of the pandemic, several clinical trials have been conducted to examine the safety and effectiveness of different vaccines to prevent COVID-19. Many of these have found the vaccines to be generally effective against symptomatic COVID-19 infection, with an average efficacy of 85% (95% CI: 71 - 93%) after a full course of vaccination.[38] However, recent evidence suggests that vaccine efficacy/effectiveness may be reduced against certain variants of COVID-19, notably the delta variant, which has been contributing to a recent surge of cases worldwide. Real-world effectiveness of the two-dose vaccine regimen against the delta variant has ranged from 67.0% (95% CI, 61.3 to 71.8) to 88.0% (95% CI, 85.3 to 90.1).[39]

People who have started or finished the COVID19 vaccine series have been documented to have detectable SARSCoV2 by RT-PCR at various time points after vaccination,[6] although demonstration of cultivatable virus and definitive evidence of transmission post vaccination 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, virologic surrogates of possible 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.[40] 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.[40] 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.[40] Another study reported an elimination of more than 99.97% of viral RNA on day 11 after monoclonal antibody treatment.[41]

There is evolving data around 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.[42,43] Marks et al. found index viral load to be a major driver of transmission in a Spanish cohort,[43] with only 32% of index cases responsible for transmission, and an attack rate of 12% in contacts of index cases with a viral load $<10^6$ and 25% in contacts of index cases with a viral load of 10^{10}. Similarly, Bjorkman et al. found that higher viral load increased SARS-CoV-2 transmission between asymptomatic residence hall roommates.[44] The index cases who transmitted infection 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).

However, the 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.[45] Although asymptomatic and especially pre-symptomatic transmission of SARSCoV-2 has been well documented, existing studies suggest that transmission risk is lower from asymptomatic individuals than symptomatic individuals.[46]

The evidence for the transmissibility and transmission of COVID-19 infections in vaccinated individuals is rapidly evolving; therefore, the objective of this rapid review was to identify comparative observational studies and randomized controlled trials (RCTs) evaluating the effectiveness or efficacy of COVID-19 vaccination in reducing infection transmission, asymptomatic viral carriage, and other proxies of possible transmission, such as cycle threshold (Ct) values and viral load. This is an update of a previous report with a literature search that ended May 4th, 2021.[1]

Methods

An experienced medical information specialist developed and tested the search strategies through an iterative process in consultation with the review team. The MEDLINE strategy was peer reviewed by another senior information specialist prior to execution using the PRESS Checklist.[47]

Using the multifile option and deduplication tool available on the OVID platform, we searched Ovid MEDLINE®, including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, and EBM Reviews - Cochrane Central Register of Controlled Trials. We also searched for primary studies on the Living Overviews of Evidence (L-OVE) platform. We performed all searches on August 23, 2021.

The strategies utilized a combination of controlled vocabulary (e.g., "COVID-19 Vaccines", "COVID-19/tm [Transmission]", "Disease Transmission, Infectious") and keywords (e.g., "mRNA vaccine", "unvaccinated", "infectiousness"). Vocabulary and syntax were adjusted across the databases. The search strategies are in Appendix 1. No language or date limits were applied. Results were downloaded and deduplicated using EndNote version 9.3.3 (Clarivate Analytics) and uploaded to Word.

A grey literature search was also conducted, including: 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). This search was limited to studies conducted since May 4, 2021, and current to August 23, 2021. There were no language limitations.

A screening form based on the eligibility criteria was prepared. Citations identified as potentially relevant from the literature search were screened by a reviewer, and subsequently

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 not included in this update.
Intervention	COVID-19 vaccination
Comparator	Non-vaccinated persons.
Outcome	Ct values, viral load, 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. Studies evaluating the transmissibility or infectivity of COVID-19 among vaccinated individuals were included.
Study Design	Comparative 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 were included. Studies eligible for inclusion had to have a control group of unvaccinated people.

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, seroprevalence, and all the reported outcomes of interest (e.g., asymptomatic infection, transmission). All reviewers completed a calibration exercise whereby data from two sample studies were extracted by all four reviewers and areas of disagreement were discussed. 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[48] and Cochrane Risk of Bias (version 5.1.0) for human-subject RCTs.[49] Quality assessment was conducted by one reviewer and verified by a second reviewer.

Results

Twenty-one studies were included in the previous version of this work published in May 2021.[1] This current search (May 4, 2021 – August 23 2021) yielded 3,340 unique citations, 3,189 of which were excluded after abstract review (Figure 1). A total of 151 studies identified from the database search proceeded to full-text review. An additional 24 studies identified through grey literature search were also reviewed. In total, 150 studies were excluded for the following reasons: outcomes not of interest (n=102), duplicate (n=18), comparator not of interest (n=15), study design not of interest (n=7), intervention not of interest (n=2), population not of interest (n=1), and other (n=5).

Twenty-five new studies were included resulting in a total of 45 studies (Figure 1; 20 studies from the May version and 25 new studies). One study[50] included in the May version was not included in this update because it was a press release from March that could not be linked to a published study and provided minimal information on the population and outcomes. The

update focused on human studies only; therefore, the 12 pre-clinical animal studies included in the March/May report were not included in this update.

Study Characteristics

Across the 45 studies, six were randomized controlled trials (five from the May version,[6,7,16,32,33] one newly identified[51]), 17 were retrospective cohort studies (six from the May version,[15,22-24,52,53] 11 newly identified[2-4,8-10,19,29,36,54,55], 13 were prospective cohort studies (eight from the May version,[13,14,17,18,21,25,56,57] five newly identified[27,28,31,58,59]), and nine were case control studies (one from the May version,[60] eight newly identified[5,11,12,20,26,30,61,62]).

Figure 1: Flowchart of Included Studies

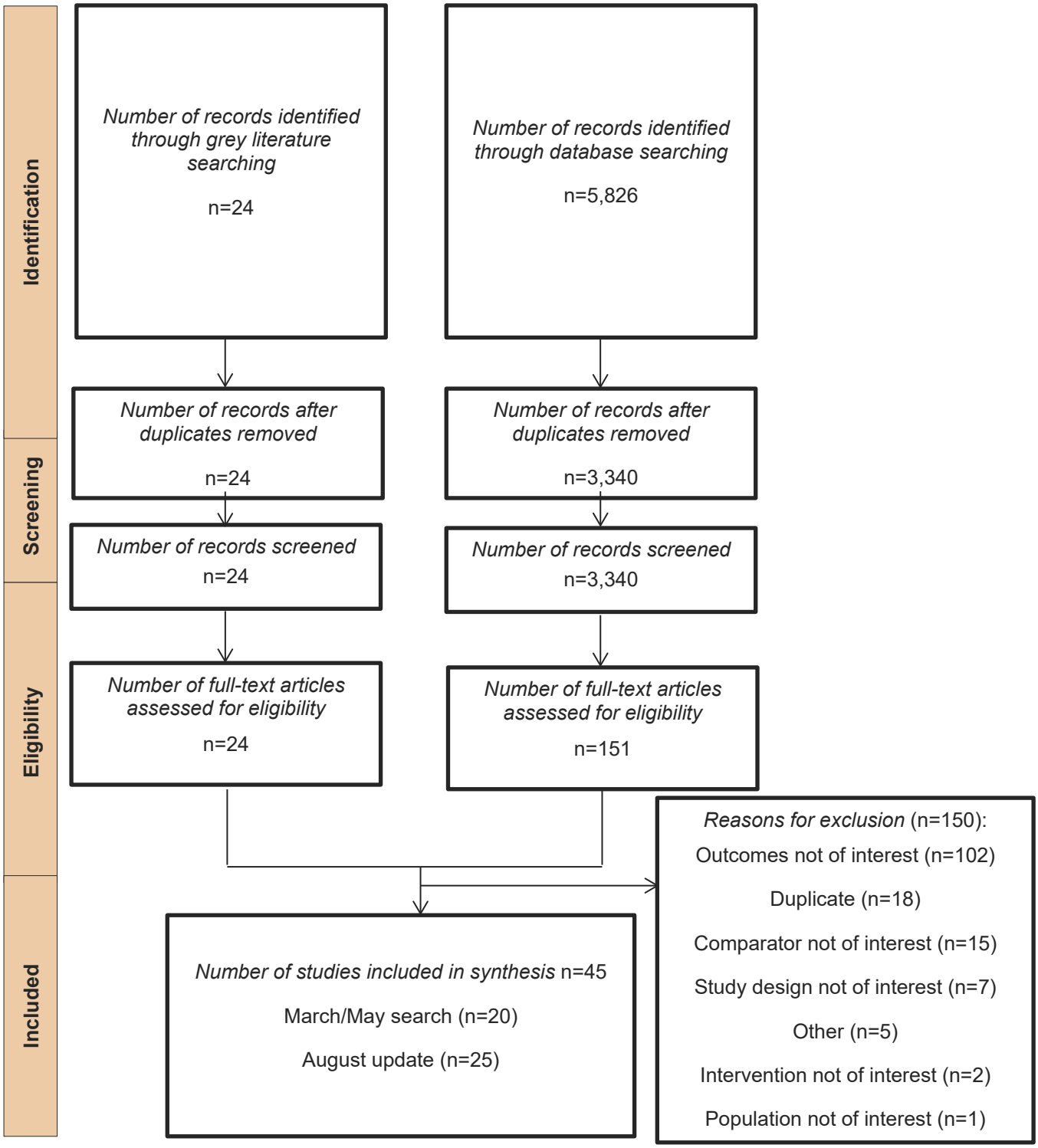

Table 2: Characteristics of Included RCTs

Author/Country/Design	Trial Information	Participant Inclusion/Exclusion Criteria	Vaccine Information	Efficacy/Effectiveness 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[6] **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[16] **County**: UK **Date of Recruitment:** Oct-Jan 2021 **Trial Phase:** 2/3 **Design:** RCT	**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
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.	**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[33] (Regulatory Submission) **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[32] **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:** Moderna **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		
Author: Ali, 2021[51] **County**: USA **Date of Recruitment:** 9 Dec 2020 - 28 Feb 2021 **Trial Phase:** Phase 2/3 **Design:** RCT **Funding:** Moderna and the Biomedical Advanced Research and Development Authority	**Age:** 14.3 ±1.6 **%Female:** 49% **Comparator:** placebo **Sample Vaccine:** 2139 **Sample Control:** 1042 **Total Sample:** 3181	**Include:** Male and female adolescents between the ages of 12 and 17 years were eligible for enrollment if they were considered to be in good general health by the 26 U.S. investigators **Exclude:** travel outside of the United States in the 28 days before screening, pregnancy or breast-feeding, acute illness or fever 24 hours before or at screening, previous administration of an investigational vaccine against SARS-CoV-2, or current treatment with investigational agents for prophylaxis against Covid-19	**Vaccine:** Moderna **Manufacturer:** Moderna **Dose:** 100ug **Number of Doses**: 2	• Asymptomatic

IQR: interquartile range, NR: Not Reported, PCR: Polymerase Chain Reaction, RCT: randomized controlled trial, VOC: Variant of Concern, Studies are peer reviewed publications except otherwise stated.

Newly identified RCT in this version is shaded in blue.

Table 3: Characteristics of Observational Studies

Author/Country/Design	Trial Information	Participant Inclusion/Exclusion Criteria	Vaccine Information	Effectiveness Outcomes
Author: Hall, 2021[56] **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[52] **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[13] **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[22] **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 **Total Sample:** Varied **VOC:** NR	**Include:** All positive post-vaccination samples **Exclude:** Patients who had a positive sample prior to vaccination; patients age 90 and above	**Vaccine:** BNT162b2 **Manufacturer**: Pfizer BioNTech **Dose:** NR **Number of Doses**:1	• Ct values

Author: Jones, 2021[23] **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[15] **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 Moderna **Manufacturers:** Pfizer BioNTech or Moderna **Number of Doses:** 1 or 2	• PCR+ among Asymptomatic (consecutive preprocedural molecular screening tests)
Author: McEllistrem, 2021[24] **Country:** USA **Date of recruitment:** December 8, 2020–February 2, 2021 **Trial Phase:** Post approval **Design:** Retrospective Cohort **Funding:** None	**Age:** NR **%Female:** NR **Comparator:** Unvaccinated **Sample vaccine:** 5 **Sample control:** 5 **Total sample:** 10 **VOC:** NR	**Include:** A negative baseline nasopharyngeal reverse transcription polymerase chain reaction test (RT-PCR, Palo Alto VA, CA) for SARS-CoV-2 on 12/2/20.	**Vaccine:** BNT162b2 **Manufacturers:** Pfizer BioNTech **Number of Doses:** 1	• Ct values • Viral load • Asymptomatic (surveillance nares testing for SARS-CoV-2 with the BD Veritor antigen every 2-5 days)
Author: Shah, 2021[53] (Pre-print) **Country:** UK **Date of recruitment:** December 8, 2020 – March 3, 2021 **Trial Phase:** Post approval **Design:** Retrospective Cohort **Funding:** British Heart Foundation through an intermediate clinical research fellowship	**Age:** 44.4(11.4) **%Female:** 78.7 **Comparator:** Unvaccinated **Sample vaccine:** 109,074 **Sample control:** 144,525 **Total sample:** **VOC:** NR	**Include:** Healthcare workers were included if they were employed by the National Health Service (NHS) in Scotland on or before the 1st of March 2020 (the first positive reported case of COVID-19 in Scotland) and still employed by the NHS on the	**Vaccine:** BNT162b2 or ChAdOx1 nCoV-19 **Manufacturers:** Pfizer BioNTech or Oxford AstraZeneca **Number of Doses:** 1	• Transmission to contact

(FS/19/17/34172); Wellcome Trust intermediate clinical fellowship and Beit fellowship (201492/Z/16/Z)		1st of November 2020; healthcare worker cohort was restricted to the working-age population (18-65 years of age). The household member cohort included all ages but was restricted to households with no more than one healthcare worker (4% of healthcare workers lived in multiple healthcare worker households)		
Author: Bouton, 2021[60] (Pre-print) **Country:** USA **Date of recruitment:** December 9, 2020-February 23, 2021 **Trial Phase:** Post approval **Design:** Case Control **Funding:**	**Age:** 40(13) **%Female:** NR **Comparator:** Unvaccinated **Sample vaccine:** 96 **Sample control:** 329 **Total sample:** 425 **VOC:** NR	**Include:** HCWs had been vaccinated prior to the vaccine initiative and were included in analyses. HCW who received a vaccination following their positive SARS-CoV-2 RT-PCR were included in the unvaccinated group.	**Vaccine:** BNT162b2 or Moderna **Manufacturers:** Pfizer BioNTech or Moderna **Number of Doses:** 1	• Asymptomatic (Asymptomatic testing is available to HCWs for workplace exposures, following out-of-state travel, and per request) • All PCR-positive (symptomatic and asymptomatic)
Author: Regev-Yochay, 2021[25] (Pre-print) **Country:** Israel **Date of recruitment:** December 19, 2020 – March 14, 2021 **Trial Phase:** Post approval **Design:** Cohort **Funding:** Sheba Medical Center, Israel	**Age:** NR **%Female:** NR **Comparator:** Unvaccinated **Sample vaccine:** **Sample control:** **Total sample:** 3578 **VOC:** NR	**Include:** HCW at Sheba Medical Center (Israel)	**Vaccine:** BNT162b2 or Moderna **Manufacturers:** Pfizer BioNTech or Moderna **Number of Doses:** 1 or 2	• Asymptomatic (Symptomatic or exposed to confirmed case) • Symptomatic • Severe cases
Author: Lumley, 2021[21] (Pre-print) **Country:** England **Date of recruitment:** Through to February 28, 2021 **Trial Phase:** Post approval **Design:** Longitudinal Cohort **Funding:** Supported by the UK Government's Department of Health and Social Care. Also supported by the National Institute for Health Research	**Age:** 39 (IQR:30-50) **%Female:** 74.0 **Comparator:** Unvaccinated seronegative **Sample vaccine:** NR **Sample control:** NR **Total sample:** 13,109 **VOC:** B.1.1.7	**Include:** Only those who participated in asymptomatic screening, symptomatic testing or vaccination from 01-September-2020 onwards were included. All staff working for the hospitals were eligible to participate.	**Vaccine:** BNT162b2 or ChAdOx1 nCoV-19 **Manufacturers:** Pfizer BioNTech or Oxford AstraZeneca **Number of Doses:** 1 or 2	• Ct values • Symptomatic • Asymptomatic Asymptomatic (voluntary nasal and oropharyngeal swab PCR testing every two weeks and serological testing every two months)

Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at Oxford University in partnership with Public Health England (PHE) (NIHR200915), the NIHR Biomedical Research Centre, Oxford, and benefactions from the Huo Family Foundation and Andrew Spokes.				
Author: Pritchard, 2021[17] (Pre-print) **Country:** UK **Date of recruitment:** December 1, 2020 – April 3, 2021 **Trial Phase:** Post approval **Design:** Prospective Cohort **Funding:** Department of Health and Social Care with in-kind support from the Welsh Government, the Department of Health on behalf of the Northern Ireland Government and the Scottish Government.	**Age:** NR **%Female:** NR **Comparator:** Unvaccinated **Sample vaccine:** **Sample control:** **Total sample:** 373,402 **VOC:** NR	**Include:** This analysis included participants aged 16 years or over (i.e. those who theoretically could have received vaccination), and all visits with positive or negative swab results from 1 December 2020 to 3 April 2021.	**Vaccine:** BNT162b2 or ChAdOx1 nCoV-19 **Manufacturers:** Pfizer BioNTech or Oxford AstraZeneca **Number of Doses:** 1 or 2	• Asymptomatic (Weekly nose and throat self-swab for first month, then monthly for 12 months from enrolment) • Ct values • Symptomatic
Author: Shrotri, 2021.[18] (Pre-print) **Country:** UK **Date of recruitment:** December 8, 2020 – March 15, 2021 **Trial Phase:** Post approval **Design:** Prospective Cohort **Funding:** UK Government Department of Health and Social Care.	**Age:** 86 (IQR: 80-91) **%Female:** 69.6 **Comparator:** Unvaccinated **Sample vaccine:** **Sample control:** **Total sample:** 10,412 **VOC:** NR	**Include:** At least two PCR test results in total, and ≥ 1 PCR result during the analysis period. Residents entered the risk period on 8 December 2020 if they had ≥ 1 valid PCR result on or prior to that date; or, if they had no PCR results before 8 December 2020, on the date of their first negative PCR test. Residents with a positive PCR result ≤ 90 days before 8 December entered the risk period 90 days after their positive test.	**Vaccine:** BNT162b2 or ChAdOx1 nCoV-19 **Manufacturers:** Pfizer BioNTech or Oxford AstraZeneca **Number of Doses:** 1 or 2	• Ct values • Symptomatic
Author: Haas, 2021[14] **Country:** Israel	**Age:** NR **%Female:** 50.8 **Comparator:** Unvaccinated	**Include:** unvaccinated and vaccinated individuals aged ≥16 years.	**Vaccine:** BNT162b2 **Manufacturers:** Pfizer BioNTech	• Asymptomatic (routine testing) • Severe cases

Date of recruitment: Jan 24, 2021–April 3, 2021 **Trial Phase:** Post approval **Design:** Prospective Cohort **Funding:** Israel MoH and Pfizer.	**Sample vaccine:** NR **Sample control:** NR **Total sample:** NR **VOC:** B.1.1.7		**Number of Doses:** 1 or 2	• Symptomatic
Author: Harris, 2021[57] (Pre-print) **Country:** UK **Date of recruitment:** January 4 – February 28, 2021 **Trial Phase:** Post approval **Design:** Prospective Cohort **Funding:** This work was undertaken as part of the core functions of Public Health England in relation to the surveillance of communicable diseases and outbreak response	**Age:** NR **%Female:** Unvaccinated index case: 47.6%, Index case vaccinated 21+ day before: 38.3%, Index case vaccinated <21 days before: 40.6% **Comparator:** Unvaccinated **Sample vaccine:** **Sample control:** **Total sample:** 1,018,842 **VOC:** NR	**Include:** Households with an index case occurring between 4 January 2021 to 28 February 2021, with 14 days observable follow up for all contacts; households with a single index case age 16+, and no co-primary cases.	**Vaccine:** BNT162b2 or ChAdOx1 nCoV-19 **Manufacturers:** Pfizer BioNTech or Oxford AstraZeneca **Number of Doses:** 1	• Transmission to contact
Author: Chemaitelly, 2021[11] **Country:** Qatar **Date of Recruitment:** 1 Feb 2021 - 10 May 2021 **Trial Phase:** NR **Design:** Test-negative case control **Funding:** NR	**Age:** NR **%Female:** NR **Comparator:** no vaccine **Sample Vaccine:** 1590 **Sample Control**: 154394 **Total Sample:** NR **VOC:** B.1.1.7; B.1.351; B.1.617	**Include:** This study was conducted in the resident population of Qatar, inclusion: a B.1.1.7 case, a B.1.351 case or a severe or critical or fatal COVID-19 disease case **Exclude:** All records of vaccination with one or two doses using a vaccine other than Moderna were excluded	**Vaccine:** Moderna **Manufacturer:** Moderna **Number of Doses**: NR	• Asymptomatic
Author: Ioannou, 2021[28] **Country:** Greece **Date of Recruitment:** 4 Jan 2021 - 14 Apr 2021 **Trial Phase:** Post Approval **Design:** Prospective cohort **Funding:** NR	**Age:** 42.3 ±9.9 **%Female:** 74.5% **Comparator:** no vaccine **Sample Vaccine:** 21 **Sample Control**: 31 **Total Sample:** 52 **VOC:** B.1.1.7	**Include:** Vaccinated (with BNT162b2) and non-vaccinated healthcare workers who tested positive for COVID-19 at a single centre in Greece **Exclude:** NR	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer **Number of Doses**: 2	• CT values
Author: Thompson, 2021[31] **Country:** USA **Date of Recruitment:** 14 Dec 2020- 10 Apr 2021	**Age:** NR **%Female:** 62% **Comparator:** no vaccine **Sample Vaccine:** 3179	**Include:** Eligible participants include Arizona residents aged 18–85 years who currently work at least 20 hours per week in an	**Vaccine:** mRNA vaccine **Manufacturer:** Moderna, Pfizer	• Asymptomatic • CT values

Trial Phase: NR **Design:** Prospective Cohort **Funding:** National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention under contract numbers 75D30120R68013 awarded to Marshfield Clinic Research Laboratory, 75D30120C08379 to University of Arizona, and 75D30120C08150 awarded to Abt Associates, Inc.	**Sample Control**: 796 **Total Sample:** 3975 **VOC:** B.1.429; B.1.1.7; B.1.427	occupation involving regular direct contact (within three feet) with others, assessed at the participant level **Exclude:** Exclusion criteria include receipt of a COVID-19 vaccine prior to enrolment, although we continue to follow participants who are vaccinated during the study.	**Number of Doses**: 1 or 2	
Author: Angel, 2021[9] **Country:** Israel **Date of Recruitment:** 20 Dec 2020- 25 Feb 2021 **Trial Phase:** Post Approval **Design:** Retrospective cohort **Funding:** None	**Age:** 44.3 ±12.5 **%Female:** 66.5% **Comparator:** Non vaccinated HCW **Sample Vaccine:** 5953 **Sample Control**: 757 **Total Sample:** 6710 **VOC:** NA	**Include:** HCWs who received at least 1 vaccine dose between December 20, 2020, and February 25, 2021, were as signed to the vaccinated group. The control group was composed of health care workers who did not receive any doses of the BNT162b2 vaccine during this period. **Exclude:** HCWs who did not undergo at least 1 PCR test during the study period, had incomplete data pertaining to vaccination dates, or contracted SARS CoV-2 infection prior to the study period were excluded from the analysis	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer **Number of Doses**: 1 or 2	• Asymptomatic cases >7 days and >28 days after first and second dose of vaccine
Author: Tang, 2021[8] **Country:** USA **Date of Recruitment:** 17 Dec 2020 - 20 Mar 2021 **Trial Phase:** Post Approval **Design:** Retrospective cohort **Funding:** American Lebanese Syrian Associated Charities	**Age:** NR **%Female:** Vaccinated: 66%, Control: 58.3% **Comparator:** Unvaccinated individuals **Sample Vaccine:** 3052 **Sample Control**: 2165	**Include:** Vaccine eligible workers that meet state vaccination guidelines **Exclude:** Individuals with prior COVID-19 exposure were excluded	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer **Number of Doses**: 1 or 2	• Asymptomatic cases 0-11 days and >12 days after first dose • Asymptomatic cases 0-6 days and >7 days after second dose

	Total Sample: 5217 **VOC:** NA			
Author: Andrejko, 2021[10] **Country:** USA **Date of Recruitment:** 24 Feb 2021- 29 Apr 2021 **Trial Phase:** Post Approval **Design:** Retrospective cohort **Funding:** California Department of Public Health, grant from the ELC program of the US CDC and NIH/NIAID grant	**Age:** NR **%Female:** 49.30% **Comparator:** unvaccinated **Sample Vaccine:** 20 **Sample Control**: 454 **Total Sample:** 525 **VOC:** NA	**Include:** California residents with molecular SARS-CoV-2 test results and a telephone number. Controls were persons with negative SARS-CoV-s molecular test results during the same period **Exclude:** participants who recalled receiving any previous positive test result for SARS-CoV-2 infection or seropositivity, prior to the reported test. Data was excluded from children aged 0-17 years, who were generally ineligible for COVID-19 vaccination over the study period; and particpants who reported receiving COVID-19 vaccinations other than BNT162b2 or Moderna (due to limited coverage of a third authorized vaccine. or receipt of COVID-19 vaccination without knowledge of vaccination dates	**Vaccine:** BNT162b2 or Moderna **Manufacturer:** Pfizer, Moderna **Number of Doses**: 1 or 2	• Asymptomatic cases >15 days after 2nd dose • Asymptomatic cases up to 14 days after 1st or second dose
Author: Jacobson, 2021[29] **Country:** USA **Date of Recruitment:** Dec 2020-Apr 2021 **Trial Phase:** Post Approval **Design:** Retrospective quality improvement **Funding:** NR	**Age:** 37.5 ±10.6 **%Female:** 69.8% **Comparator:** Unvaccinated HCP **Sample Vaccine:** NR **Sample Control**: NR **Total Sample:** 283 **VOC:** B.1.427/B.1.429	**Include:** include post vaccine SARS CoV-2 cases, defined as HCPs with positive SARS-CoV-2 nucleic acid amplification test after receiving one or more vaccine doses **Exclude:** NR	**Vaccine:** BNT162b2 or Moderna **Manufacturer:** Pfizer, Moderna **Number of Doses**: 1 or 2	• CT values ≤ 14 after first dose • CT values up to 14 days after 1st or 2nd dose • CT values over 14 days after 2nd dose
Author: Bailly, 2021[27] **Country:** France **Date of Recruitment:** 8 Mar 2021 - 29 Mar 2021	**Age:** Fully vaccinated residents: 87.0 ± 8.2 years **%Female:**	**Include:** Residents and staff from a nursing home unit with a positive COVID case	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer **Number of Doses**: 2 doses	• Asymptomatic cases after 2 doses • CT values after 2 doses

Trial Phase: Post Approval **Design:** Prospective cohort **Funding:** Ministry of Health	Fully vaccinated residents: 64.5% **Comparator:** Non-vaccinated residents **Sample Vaccine:** 13 **Sample Control**: 5 **Total Sample:** 18 **VOC:** 501Y.V2	**Exclude:** NR		
Author: Salo, 2021[3] (Pre-print) **Country:** Finland **Date of Recruitment:** 27 Dec 2020- 24 Mar 2021 **Trial Phase:** Post approval **Design:** Retrospective **Funding:** InFLAMES and INVEST Flagship Programmes of the Academy of Finland.	**Age:** Vaccinated: 47.1 ±13.1 Unvaccinated: 43.8 ±14.5 **%Female:** 86.5% **Comparator:** unvaccinated HCW **Sample Vaccine:** 95138; spouses of vaccinated HCW:52,766 **Sample Control**: 193000; spouses of control:111,000 **Total Sample:** 288138 **VOC:** NA	**Include:** Vaccinated and unvaccinated HCW. An individual was included in this sample if their spouse is a healthcare worker and they had not been vaccinated during the sample period. **Exclude:** NR	**Vaccine:** BNT162b2 or Moderna **Manufacturer:** Moderna, Pfizer **Number of Doses**: 1 or 2	• Transmission to unvaccinated spouse 14 days and 10 weeks after 1st dose • Transmission to unvaccinated child 3-18 years, 14 days and 10 weeks after 1st dose • Transmission to unvaccinated child 3-12 years, 6 weeks and 10 weeks after 1st dose • Transmission to unvaccinated child 13-18 years, 6 and 10 weeks after 1st dose
Author: Muhsen, 2021[58] (Pre-print) **Country:** Israel **Date of Recruitment:** Dec 2020-Jan 2021 **Trial Phase:** Post approval **Design:** Prospective cohort **Funding:** No external funding	**Age:** 46.2 ±11.8 **%Female:** 79.5% **Comparator:** Unvaccinated individuals **Sample Vaccine:** 20 **Sample Control**: 44 **Total Sample:** 9162 **VOC:** NA	**Include:** 1) adherence to routine screening for SARS-CoV-2 infection by RT-PCR testing. Specifically, they had 12 or more out of the 20 planned screening tests for the period September 2020 through January 2021; 2) working in LCTFs that vaccinated >75% of their employees collectively during three consecutive days; and 3) being RT-PCR negative for SARS-CoV-2 infection by the date of immunization with the second vaccine dose.	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer **Number of Doses**: 2	• CT values over 14 days after 2nd dose

		Unvaccinated HCWs at baseline, who were vaccinated later, were censored upon receiving their first vaccination dose **Exclude:** Excluded from the primary analysis were HCWs working at institutions that did not have a collective immunization period, partially vaccinated HCWs at baseline (i.e. received one vaccine dose), and those who had a RT-PCR-confirmed SARS-CoV-2 infection before immunization, or between immunization with the second dose until day seven or 14 days post immunization.		
Author: de Gier, 2021[2] (Pre-print) **Country:** Netherlands **Date of Recruitment:** 1 Feb 2021- 27 May 2021 **Trial Phase:** Post Approval **Design:** Retrospective cohort **Funding:** Ministry of Health, Welfare and Sports	**Age:** NR **%Female:** NR **Comparator:** Unvaccinated individuals **Sample Vaccine:** 2032 **Sample Control**: 139802 **Total Sample:** Index cases: 113582; contacts: 253168 **VOC:** B.1.1.7	**Include:** household members and other close contacts of confirmed cases **Exclude:** household contacts of an index were excluded if the most likely setting of infection of the index was 'at home' according to the source tracing interview	**Vaccine:** ChAdOx1-S, BNT162b2, Moderna, Janssen **Manufacturer:** Pfizer, Moderna, AstraZeneca, Janssen **Number of Doses**: 1 or 2	• Transmission to contact over 14 days after 1st dose: any household contact, unvaccinated household contacts, any other close contact, unvaccinated close contacts, AstraZeneca vaccinated household contact, Pfizer vaccinated household contact, Moderna vaccinated household contact • Transmission to contact over 7 days after 2nd dose in: any household contact, unvaccinated household contacts, any other close contact, unvaccinated close contacts,

				AstraZeneca vaccinated household contact, Pfizer vaccinated household contact, Moderna vaccinated household contact, Janssen vaccinated household contact
Author: McEllistrem,2021[55] **Country:** USA **Date of Recruitment:** 2 Dec 2020 to 14 May 2021 **Trial Phase:** Post approval **Design:** Retrospective Cohort (observational) **Funding:** NR	**Age:** 74.5 years (IQR NR) **%Female:** 7.76% **Comparator:** unvaccinated **Sample Vaccine:** 97 **Sample Control**: 19 **Total Sample:** NR **VOC:** NA	**Include:** residing at the Community Living Center; without a prior history of COVID-19 who agreed to immunization **Exclude:** prior history of COVID-19; agreed to immunization after 12/16/21	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer-BioNTech **Number of Doses**: 2	• Asymptomatic cases 1 to 21 days following 1st vaccination • Asymptomatic cases 14-21 days following 1st vaccine • Asymptomatic cases 7 days following 2nd vaccine
Author: Souza, 2021[54] (Pre-print) **Country:** Brazil **Date of Recruitment:** 2021-03-01 **Trial Phase:** Post approval **Design:** Observational cohort **Funding:** Sao Paulo Research Foundation, MCTI	**Age:** 73 (IQR 50-83) **%Female:** 96.2% **Comparator:** unvaccinated **Sample Vaccine:** 23 **Sample Control**: 3 **Total Sample:** 26 **VOC:** B.1.1.7 (UK)	**Include:** Individuals at least 18 years of age exposed to residents infected with SARS-CoV-2 (from either the convent or LTC facility). Residents and employees from both locations were included in the study **Exclude:** N/a	**Vaccine:** ChAdIx01, 1 resident vaxxed with Ad26.COV2.S and CoronaVac, 1 employee vaxxed with ChAdOx1 **Manufacturer:** AstraZeneca and SinoVac BioTech **Number of Doses**: 1 or 2	• Asymptomatic cases in individuals >23 days following 1st dose • Viral load in individuals >23 days following 1st dose • Asymptomatic cases in individuals 5-27 days following 2nd dose • Viral load in individuals 5-27 days following 2nd dose
Author: Abu-Raddad, 2021[26] (Pre-print) **Country:** Qatar **Date of Recruitment:** 28 Feb 2020 - 11 July 2021 **Trial Phase:** Post approval **Design:** Matched Case-control 1:1 ratio **Funding:** NR	**Age:** 33-35 **%Female:** 14.90%-21.100% **Comparator:** Unvaccinated **Sample Vaccine:** 60-421 **Sample Control**: 60-421 **Total Sample:** 120-842 **VOC:** B.1.1.7 (Alpha/UK), B.1.351 (Beta/South Africa), B.1.617.2 (Delta/India)	**Include:** All records of RT-qPCR in Qatar but only samples of matched cohorts were included in the analysis. Only breakthrough infections in fully vaccinated individuals were included in the analysis. Being fully vaxxed was defined as >14 days after the second dose **Exclude:** Individuals with a record of a SARS-CoV-2	**Vaccine:** BNT162b2, Moderna **Manufacturer:** Pfizer-BioNTech, Moderna **Number of Doses**: 2	• CT value over 14 days following 2nd dose of vaccine

		antibody positive test before the first RT-qPCR positive test were excluded from analysis of those with primary infections. Individuals with a record of vaccination before the reinfection diagnosis were excluded from the analysis of those with reinfection.		
Author: Antonelli, 2021[61] **Country:** UK **Date of Recruitment:** 8 Dec 2020- 1 May 2021 **Trial Phase:** Post Approval **Design:** Case-control **Funding:** NR	**Age**: Dose 1 group: 52.0±14.2 Control 1 group: 51.5±14.2 Dose 2 group: 54.5±14.3 Control 2 group: 53.7±13.8 **%Female:** 69.5% **Comparator:** Unvaccinated **Sample Vaccine:** 4731 **Sample Control**: 4731 **Total Sample:** 9462 **VOC:** B.1.1.7 (Alpha/UK), B.1.617.2 (Delta/India)	**Include:** App of self-reported data. Inclusion: 1) age > 18 years, 2) living in the UK, 3) first dose of a COVID-19 vaccine between 8 Dec 2020-1 May 2021, 4) at least 14 days of app usage after vaccination, 5) a positive RT-PCR or lateral flow antigen (LFAT) at least 14 days after first vaccination but before second dose (if more than 1 test result reported, only the first positive test was selected), and 6) no positive SARS-CoV-2 prior to vaccination **Exclude:** NR	**Vaccine:** BNT162b2 or ChAdIx01 **Manufacturer:** Pfizer-BioNTech, AstraZeneca **Number of Doses**: 1 or 2	• Asymptomatic cases over 14 days after 1 or 2 doses
Author: Duerr, 2021[30] **Country:** USA **Date of Recruitment:** Feb 2021 - April 2021 **Trial Phase:** Post Approval **Design:** Case-control **Funding:** NYU Langone Institutional Funding	**Age:** NR **%Female:** NR **Comparator:** Unvaccinated **Sample Vaccine:** 101 **Sample Control**: 1046 **Total Sample:** 1147 **VOC:** B.1.1.7 (Alpha/UK), B.1.526 (Iota/NY), P1, and others	**Include:** Cases included individuals who tested positive by real-time RT-PCR for SARS-CoV-2 RNA regardless of Ct, any time after 14 days of inoculation with the second dose of Pfizer-BioNTech/Moderna or with single dose Janssen. Control group consisted of full-genome sequenced SARS-CoV-2 positive cases, had Ct<30, and were collected in the same time	**Vaccine:** BNT162b2, Moderna, or Janssen **Manufacturer:** Pfizer-BioNTech, Moderna, Johnson&Johnson **Number of Doses**: 1 or 2	• CT values over 14 days following 1st or 2nd dose in breakthrough infections

		period as the breakthrough infections **Exclude:** NR		
Author: Sansone, 2021[62] **Country:** Italy **Date of Recruitment:** 25 Jan 2021 - 13 Apr 2021 **Trial Phase:** NR **Design:** Case-control **Funding:** NR	**Age:** NR **%Female:** NR **Comparator:** Unvaccinated **Sample Vaccine:** 40 **Sample Control**: 52 **Total Sample:** 92 **VOC:** B.1.1.7 (Alpha/UK), B1.525	**Include:** Data from health and epidemiological surveillance at the workplaces performed on the ASST "Spedali Civili di Brescia" workforce. Mandatory character of such an activity therefore no ethics committee approval necessary. All workers gave wrwitten consent to the vaccination and data processing. Data was anonymysed. **Exclude:** NR	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer **Number of Doses**: 2	• Asymptomatic cases over 14 days following 2nd vaccine
Author: Layan, 2021[5] (Pre-print) **Country:** Israel **Date of Recruitment:** 31 Dec 2020 to 26 Apr 2021 **Trial Phase:** Post Approval **Design:** Case-control (Observational) **Funding:** Sheba Medical Center. SC acknowledges financial support from the Investissement d'Avenir program, the Laboratoire d'Excellence Integrative Biology of Emerging Infectious Diseases program (grant ANR-10-LABX-62-IBEID), HAS, the INCEPTION project (PIA/ANR-16 CONV-0005), the European Union's Horizon 2020 research and innovation program under grant 101003589 (RECOVER) and 874735 (VEO), AXA and Groupama.	**Age:** 32±16 **%Female:** 58% **Comparator:** unvaccinated **Sample Vaccine:** 15-124 **Sample Control**: 200-641 **Total Sample:** 215-687 **VOC:** alpha	**Include:** HCWs employed by Sheba Medical Center with a SARS-CoV-2 case **Exclude:** missing vaccination status, dates of PCR test and/or symptom onset	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer-BioNTech **Number of Doses**: 2	• Transmission to contact >7 days following 2nd dose • Infected contacts >7 days following 2nd dose
Author: Mostafa, 2021[19] (Pre-print) **Country:** USA **Date of Recruitment:** Jan 2021- May 2021	**Age:** 51 (IQR NR) **%Female:** 63.3% **Comparator:** unvaccinated	**Include:** specimens of SARS-CoV-2 positive patients who had received two doses of either	**Vaccine:** BNT162b2 or ChAdOx1 nCOV-19	• CT values 2-100 days following 2nd dose

Trial Phase: Post Approval **Design:** Retrospective cohort (Observational) **Funding:** National Institute of Health (The Johns Hopkins Center of Excellence in Influenza Research and Surveillance, HHSN272201400007C), Johns Hopkins University, Maryland Department of Health, Centers for Disease Control and Prevention.	**Sample Vaccine:** 49 **Sample Control**: 96 **Total Sample:** NR **VOC:** P.1, B.1.1.7, B.1.351, B.1.526, and B.1.526.1	Pfizer-BioNTech (BNT162b2) or Moderna (Moderna) vaccines; specimens of a control unvaccinated cohort from a matched time frame **Exclude:** samples that had failed sequencing and were thought of as very low viral load or false positives did not yield infectious virus	**Manufacturer:** Pfizer-BioNTech, Moderna **Number of Doses**: 2	
Author: Gazit, 2021[4] (Pre-print) **Country:** Israel **Date of Recruitment:** 20 Dec 2020 and 17 Mar 2021 **Trial Phase:** Post Approval **Design:** Observational cohort **Funding:** None	**Age:** index case: unvaccinated, 56 ±15, recently vaccinated once, 63±12, fully vaccinated 68±9 additional case: unvaccinated, 56 ±15, recently vaccinated once, 63±12, fully vaccinated, 67±9 **%Female:** 50% **Comparator:** unvaccinated **Sample Vaccine:** 381 **Sample Control**: 2975 **Total Sample:** 3627 **VOC:** NA	**Include:** a household was defined as having two adults. Only households with two adults were included **Exclude:** households of only one member, households with varying numbers of children, households in which an infection was recorded before December 20, 2020	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer-BioNTech **Number of Doses**: 1 and 2	• Transmission to contact 0-7 days following 1st dose • Transmsission to contact >7 days following 2nd dose
Author: Pouwels, 2021[59] (Pre-print) **Country:** UK **Date of Recruitment:** 1 Dec 2020 to 16 May 2021 **Trial Phase:** Post Approval **Design:** Prospective Cohort Observational **Funding:** Department of Health and Social Car, Welsh Government, the Department of Health on behalf of the Northern Ireland Government and the Scottish Government.	**Age:** 28-57 **%Female:** 53.6-55.8% **Comparator:** unvaccinated **Sample Vaccine:** NR **Sample Control**: 10853 **Total Sample:** NR **VOC:** Delta	**Include:** participants aged 18 years or over (i.e. those who were eligible for vaccination), and all visits with positive or negative swab results from 1 December 2020 to 1 August 2021. **Exclude:** A small number of visits after reported vaccination with either unknown or vaccines other than	**Vaccine:** BNT162b2, ChAdOx1, or Moderna **Manufacturer:** Pfizer-BioNTech, Moderna **Number of Doses**: 1 or 2	• CT values 0 to 20 days following 1st dose • CT values >21 days following 1st dose, or 0-13 days following 2nd dose • CT values >14 days following 2nd dose

		ChAdOx1, BNT162b2 or Moderna (for the latter we only included the first dose and only for the period ≥17 May) were excluded as these were too few to provide reliable estimates.		
Author: Tang, 2021[12] (Pre-print) **Country:** Qatar **Date of Recruitment:** 21 Dec 2020 and 21 Jul 2021 **Trial Phase:** Post Approval **Design:** matched test-negative, case-control **Funding:** Unclear	**Age:** 31-32 years **%Female:** 18.5-21.9% **Comparator:** unvaccinated **Sample Vaccine:** 48-532 **Sample Control**: 2194-2401 **Total Sample:** 2318-2862 **VOC:** Delta	**Include:** Every case that met the inclusion criteria (a Delta case) and that could be matched to a control **Exclude:** persons who received mixed vaccines, or who received a vaccine other than BNT162b2 or Moderna	**Vaccine:** BNT162b2, Moderna **Manufacturer:** Pfizer-BioNTech, Moderna **Number of Doses**: 1 or 2	• Asymptomatic cases >14 days following 1st and 2nd dose
Author: Baltas, 2021[20] **Country: UK** **Date of Recruitment:** 30th of September 2020 and 15th of March 2021 **Trial Phase:** Post Approval **Design:** case-control **Funding:** COG-UK Hospital-Onset COVID-19 Infections (HOCI) Wellcome Trust Study through grants from UK Research and Innovation (UKRI); the Wellcome Trust; and the John Black Charitable Foundation	**Age:** median 79, IQR 65 – 86 **%Female:** 42.9% **Comparator:** unvaccinated **Sample Vaccine:** 112 **Sample Control**: 399 **Total Sample:** 511 **VOC:** B.1.1.7, B.1.525	**Include:** All SARS CoV-2 first positive cases recruited into the COG-UK-HOCI study between the 30th of September 2020 and 15th of March 2021 **Exclude:** Positive patients, whose samples were not available for sequencing	**Vaccine:** BNT162b2 or ChAdOx1 nCOV-19 **Manufacturer:** Pfizer-BioNTech, Moderna **Number of Doses**: 1	• CT values <14 and >14 following 1st dose
Author: Riemersma, 2021[36] (Pre-print) **Country: USA** **Date of Recruitment:** 28 June–24 July 2021 **Trial Phase:** Post Approval **Design:** Retrospective cohort **Funding:** NR	**Age:** median NR **%Female:** NR **Comparator:** unvaccinated **Sample Vaccine:** 79 **Sample Control**: 212 **Total Sample:** 291 **VOC:** B.1.1.7	**Include:** All samples tested in a Wisconsin commercial laboratory who had **Exclude:** NR	**Vaccine:** NR **Manufacturer:** NR **Number of Doses**: 2	• CT values >14 following 2nd dose

IQR: interquartile range, NR: Not Reported, PCR: Polymerase Chain Reaction, RCT: randomized controlled trial, VOC: Variant of Concern, NR: Not Reported. Studies are peer-reviewed publications except otherwise stated.

Newly identified observational studies shaded in blue.

Risk of Bias Assessment

Across the six included RCTs, all scored “low” for bias on outcome measurement, and all except for one[16] scored “low” for bias on selection of reported results. For risk of bias on randomization, three scored low,[7,32,51] two were of some concern,[16,33] and one[6] did not report sufficient information. For bias stemming from intended intervention, two scored low,[32,51] and the rest were of some concern. With respect to bias stemming from missing outcome data, only one study was low,[51] one study was high,[16] and the rest were of some concern. On the overall risk of bias domain, only one study scored low,[51] one scored high,[16] and the rest were of some concern.

Across the 39 observational studies, 22 were rated as moderate on risk of bias due to confounding, with nine rated as low, seven rated as high, and one with no information. On risk of bias for participant selection, 19 were rated as low, 14 were rated as serious, and six were rated as moderate. On bias in classification of interventions, all studies were rated as low, with exception of three studies that were rated as moderate. With respect to bias due to deviations from intended interventions, 19 studies scored low, 18 scored moderate, and two were rated as no information. For bias due to missing data, 19 were low, 12 were moderate, three were serious, and five did not have sufficient information. Across the outcome measurement domain, six studies were of moderate risk of bias, one was serious, and the rest were low. On bias in selection of reported results, seven studies scored low, three scored moderate, and the rest did not have sufficient information. On the overall risk of bias domain, 20 studies were rated as moderate risk of bias, 14 were serious, three were critical, one was low, and one did not have sufficient information.

Table 4: Risk of Bias Assessment for RCTs

Author	Randomization	Deviation from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported results	Overall Bias
Ali et al.[51]	Low	Low	Low	Low	Low	Low
Baden et al.[32]	Low	Low	Some concerns	Low	Low	Some concerns
Emary et al.[16]	Some concerns	Some concerns	High	Low	Some concerns	High
Janssen Biotech[33]	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.[6]	NI	Some concerns	Some concerns	Low	Low	Some concerns

All studies were published in 2021

Table 5: ROBINS-I Risk of Bias for non-RCTs

Author	Bias due to confounding	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
Abu-Raddad et al.[26]	Low	Low	Low	Low	Low	Low	NI	Moderate
Amit et al.[52]	NI	Low	Moderate	NI	NI	Moderate	NI	NI
Angel et al.[9]	Moderate	Serious	Low	Moderate	Serious	Low	NI	Serious
Andrejko et al.[10]	Moderate	Low	Low	Low	Moderate	Moderate	NI	Moderate
Antonelli et al.[61]	Serious	Low	Low	Moderate	Serious	Low	NI	Critical
Baltas et al.[20]	Moderate	Serious	Low	Moderate	Low	Low	Low	Serious
Bailly et al.[27]	Serious	Moderate	Low	Moderate	Moderate	Moderate	NI	Serious
Bouton et al.[60]	Low	Low	Low	Low	Low	Low	Low	Low
Chemaitelly et al.[11]	Low	Low	Low	Moderate	Low	Low	NI	Moderate

Dagan et al.[13]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
De Gier et al.[2]	Serious	Serious	Low	Low	Low	Moderate	NI	Serious
Duerr et al.[30]	Low	Low	Low	Low	Serious	Serious	NI	Critical
Gazit et al.[4]	Moderate	Serious	Low	Moderate	Low	Low	NI	Serious
Haas et al.[14]	Moderate	Low	Low	Low	Moderate	Low	NI	Moderate
Hall et al. [56]	Moderate	Moderate	Low	Moderate	NI	Low	NI	Moderate
Harris et al.[57]	Moderate	Low	Low	Low	Moderate	Low	NI	Moderate
Ioannou et al.[28]	Moderate	Moderate	Low	Moderate	Low	Low	NI	Moderate
Jacobson et al.[29]	Moderate	Serious	Low	Moderate	Moderate	Moderate	Low	Serious
Jones et al.[23]	Moderate	Low	Low	Low	NI	Low	NI	Moderate
Layan et al.[5]	Serious	Serious	Low	Moderate	Low	Low	NI	Serious
Levine-Tiefenbrun et al.[22]	Moderate	Low	Low	Low	NI	Low	NI	Moderate
Lumley et al.[21]	Low	Low	Low	Low	Moderate	Low	Moderate	Moderate
McEllistrem et al.[24]	Moderate	Low	Low	Low	Low	Low	NI	Moderate
McEllisrem et al.[55]	Serious	Serious	Low	Moderate	Low	Low	NI	Serious
Mostafa et al.[19]	Moderate	Serious	Low	NI	Low	Low	NI	Serious
Muhsen et al.[58]	Moderate	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
Pouwels et al.[59]	Moderate	Serious	Low	Moderate	Low	Low	Low	Serious
Pritchard et al.[17]	Low	Low	Low	Low	Moderate	Low	Moderate	Moderate
Regev-Yochay et al.[25]	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Riemersma et al.[36]	Serious	Serious	Low	Moderate	Moderate	Low	NI	Critical
Salo et al.[3]	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	NI	Serious
Sansone et al.[62]	Low	Low	Low	Low	Low	Low	NI	Moderate
Shah et al. [53]	Moderate	Moderate	Low	Low	Low	Low	NI	Moderate
Shrotri et al.[18]	Moderate	Low	Low	Low	Moderate	Low	NI	Moderate
Souza et al.[54]	Low	Low	Low	Low	Low	Low	NI	Moderate

Tande et al.[15]	Moderate	Low	Low	Low	Low	Low	NI	Moderate
Tang et al.[8]	Moderate	Serious	Low	Moderate	Moderate	Low	NI	Serious
Tang et al.[12]	Moderate	Serious	Low	Moderate	NI	Low	NI	Serious
Thompson et al.[31]	Serious	Serious	Moderate	Moderate	Low	Low	Low	Serious

All studies conducted in 2021, NI, No information

Vaccine Effectiveness against Infection Transmission

Six studies reported on the effectiveness of the PfBNT, Moderna, J&J, and AZ vaccines against disease transmission; four new studies were included in this update (Table 6). Studies included examined vaccine effectiveness against the wild-type or B.1.1.7 (Alpha) strain; none of the studies evaluated vaccine effectiveness against infection transmission against the B.1.617.2 (Delta) strain.

A retrospective cohort study in the Netherlands by de Gier et al. of 113,582 confirmed index cases of COVID-19 and 253,168 cohabitating household members or close contacts were assessed for vaccine effectiveness in preventing transmission to the household member or close contact and stratified by vaccination status, vaccine type, and days past date of inoculation.[2] At least one dose of PfBNT, Moderna, AZ, or J&J from past the 14th day of vaccination onwards, was associated with the reduction of transmission of COVID-19 to any household contact by 21% (95% CI: 12-28), 23% (95% CI: 14-32) to any unvaccinated household contact, 22% (95% CI: 9-33) to any other close contact, and 22% (95% CI: 8-34) to any unvaccinated close contact.[2] Fully vaccinated individuals with either PfBNT, Moderna, J&J, or AZ from past the 7th day of vaccination onwards, was associated with the reduction of transmission of COVID-19 to any household contact by 71% (95% CI: 63-77), 73% (95% CI: 65-79) to any unvaccinated household contact, 22% (95% CI: -5-43) to any other close contact, and 24% (95% CI: -5-43) to any unvaccinated close contact.[2] The low vaccine effectiveness of a fully vaccinated individual against transmission to any close contact or any close unvaccinated contact could be due to the studies being underpowered to detect differences due to the small number of events that occurred in vaccinated individuals compared to unvaccinated index cases.

de Gier et al. also stratified vaccine effectiveness by vaccine type and found that at least one dose of PfBNT from the 14th day of vaccination onward, reduced transmission to any household contact by 26% (95% CI: 12-37) and fully vaccinated individuals reduced transmission to any household contact by 70% (95% CI: 61-77).[2] At least one dose of Moderna from the 14th day of vaccination onward, reduced transmission to any household contact by 51% (95% CI: 8-74) and fully vaccinated individuals reduced transmission to any household contact by 88% (95% CI: 50-97).[2] At least one dose of AZ from the 14th day of vaccination onward, reduced transmission to any household contact by 15% (95% CI: 4-26) and fully vaccinated individuals reduced transmission to any household contact by 58% (95% CI: 12-84).[2] Fully vaccinated individuals with the J&J vaccine reduced transmission to household contact by 77% (95% CI: 6-94).[2]

A similar study was conducted in Finland by Salo et al. This retrospective cohort study investigated the vaccine effectiveness of 95, 138 mRNA-based (PfBNT or Moderna) vaccinated healthcare workers against infection transmission to unvaccinated household members compared to unvaccinated healthcare workers and their unvaccinated household members.[3] At least one dose of an mRNA-based vaccine from the 14th day of vaccination onward, reduced transmission to an unvaccinated spouse by 8.7% (95% CI: -28.9-35.4) and increased to 42.9% (95% CI: 22.3-58.1) reduction in transmission, 10 weeks after the first

dose.[3] At least one dose of an mRNA-based vaccine from the 14th day of vaccination onward, increased transmission to an unvaccinated child living in the household between the ages of 3-18 years by 1.0% (95% CI: -53.9-33.7) and decreased transmission to the unvaccinated child by 32.9% (95% CI: 4.1-53.0), 10 weeks after the first dose.[3]

Two studies from Israel found that PfBNT fully vaccinated individuals from past the 7th day of vaccination onward, had reduced infection transmission to their household contacts.[4] [5] A retrospective cohort study using a nationally centralized database investigated the vaccine effectiveness of PfBNT against infection transmission of two-adult households only one confirmed case of infection during the study period.[4] Of households with a fully vaccinated adult, the PfBNT vaccine was found to reduce infection transmission of the wild-type strain by 80.0% (95% CI: 73.0-85.1) compared to those who were unvaccinated and by 82.0% (95% CI: 75.5-86.7) compared to those who were recently vaccinated with one dose (between 0-7 days after vaccination).[4] A second Israeli study by Layan et al. conducted a case-control study of the PfBNT vaccine's effectiveness on reduction of infection transmission of the wild-type and B.1.1.7 (Alpha) strains in healthcare workers and their households.[5] The risk of transmission from vaccinated cases was 0.22 times (95% CI: 0.06-0.70) the risk of infection transmission compared to unvaccinated cases.[5]

Shah et al. in a retrospective study of 194,362 household members of 144,525 healthcare workers, who had received at least one dose of the PfBnT or AZ, found that from the 14th post-vaccination day onwards, vaccinating a co-habiting healthcare worker was associated with a significantly reduced risk of documented COVID-19 among household members (rate per 100 person-years: 9.40 versus 5.93; HR: 0.70, (95% CI: 0.63-0.78)).[53] The risk of hospitalization was also significantly lower among household contacts of vaccinated HCWs (rate per 100 person-years: 0.51 versus 0.31; HR: 0.77, (95% CI: 0.53-1.10)).[53] Following a second dose, the risks of infection and hospitalization involving a household member were significantly lower, rate per 100 person-years of 9.40 versus 2.98, HR: 0.46 (95% CI: 0.30-0.70) and 0.51 versus 0.22 per 100 person-years, HR: 0.68 (95% CI: 0.17-2.83), respectively).[53] The baseline serology and PCR of household contacts were not reported (Table 6).

A study by Harris et al. evaluated the risks of transmission of COVID-19 after one dose of PfBnT and AZ vaccination to unvaccinated household contacts using a retrospective design and a matched case-control method.[57] In the retrospective cohort analysis, there were 96,898 secondary cases among 960,765 household contacts of unvaccinated individuals (10.1%). There were 196 secondary cases in 3,424 contacts (5.72%) where the index case received AZ vaccine more than 21 days before PCR positivity, and 371 secondary cases in 5,939 contacts (6.25%) where the index case received the PfBnT vaccine. Adjusted odds ratio of transmission were 0.53 (95% CI: 0.43-0.63) and 0.51 (95% CI: 0.44-0.59), respectively, which were significantly lower.[57] In the matched case-control method, the odds of secondary infection among contacts of AZ and PfBnT vaccinated individuals were also significantly lower, 0.62 (95% CI: 0.48-0.79) and 0.51 (95% CI: 0.42-0.62) respectively.[57]

The baseline serology and PCR of household contacts were not reported in any of the studies except for Salo et al. and Gazit et al. whom only included seronegative participants (Table 6).[3,4]

Vaccine Efficacy or Effectiveness Against Asymptomatic Infection

Twenty-five studies reported vaccine efficacy or effectiveness against asymptomatic COVID-19 infection, including 11 new observational studies and one new randomized control trial for this update (Table 7 and Table 8). Of the six RCTs included, three studied the AZ vaccine,[6,7,16] one evaluated the J&J vaccine,[33] and two studied the vaccine efficacy of the Moderna vaccine.[32,51]

Of the observational studies included, 12 examined the PfBNT vaccine,[8,9,14,23-25,27,52,55,56,62,63] two studied the AZ vaccine,[21,54] one evaluated the Moderna vaccine,[11] four studies evaluated both Moderna and PfBNT,[10,12,31,60] and two evaluated PfBNT and AZ vaccines.[17,61]

The methods of assessing efficacy or effectiveness against asymptomatic infection used in some of these studies included RT-PCR nasopharyngeal swabs at different time intervals.

AstraZeneca Vaccine Efficacy in the General Population

No new additional studies investigating vaccine efficacy or effectiveness of the AZ vaccine against asymptomatic infections were included in this update.

First Dose AstraZeneca

Wild type

Asymptomatic infection data were presented for only the UK component of the AZ vaccine studies. Two AZ vaccine studies reported vaccine efficacy against asymptomatic or unknown infection of 7.8% (-46.7-42.1)[7] and 16% (-88-62)[6], 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, was 46.3% (31.8-57.8)[7] and 67% (49-78)[6], respectively, over the same periods (Table 7). These trials implemented weekly self-administered nose and throat swabs for testing on baseline seronegative participants. The PCR status of these participants was not established at baseline.

Full Dose AstraZeneca

Wild type

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.[6,7] 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.[16] 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)[6] and 58.9%(95% CI: 1-82.9)[7] respective efficacies against asymptomatic and unknown infection 14 days after the second dose (Table 8).

AstraZeneca Vaccine Effectiveness in the General Population

Wild type

First Dose AstraZeneca

In a large UK household survey with longitudinal follow-up among seronegative or seropositive individuals, Pritchard et al. reported significant reductions in the odds of asymptomatic infections following AZ vaccine 0-7 days, 8-20 days and 21 or more days after the first dose (ORs: 0.45 (95% CI: 0.35-0.57), 0.47 (95% CI: 0.37-0.6) and 0.39 (95% CI: 0.3 -0.51), respectively).[17] Nose and throat self-swabs were conducted every week for a month, and subsequently monthly for 12 months from enrolment.[17]

Pfizer BioNTech Vaccine Effectiveness in the General Population

Of the 11 studies reporting PfBNT vaccine efficacy or effectiveness, five new additional studies investigating effectiveness of the Pfizer BioNTech vaccine against asymptomatic infections were included in this update.

First Dose Pfizer BioNTech Vaccine

Wild type

An Israeli observational study by Dagan et al., which did not establish baseline seronegativity, showed that one dose of PfBNT 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 7). In a large UK household survey with longitudinal follow-up involving participants with unknown baseline serology status, Pritchard et al. reported significant reductions in the odds of asymptomatic infections following PfBNT vaccine 0-7 days, 8-20 days and 21 or more days after the first dose, ORs: 0.48 (95% CI: 0.39-0.6) and 0.54 (95% CI: 0.45-0.65) respectively, compared with unvaccinated previously PCR negative individuals.[17] Nose and throat self-swabs were conducted every week for a month, and subsequently monthly for 12 months from enrolment.[17]

A retrospective study in Qatar by Tang et al. showed that seronegative healthcare workers with at least one dose of PfBNT were 0.58 times (95% CI: 0.3-1.12) less likely than unvaccinated healthcare workers to have an asymptomatic infection of the wild-type virus between 0-11 days past the date of vaccination and 0.58 times (95% CI: 0.3-1.13) less likely than unvaccinated healthcare workers to have an asymptomatic infection between ≥12 days after the first dose and second dose.[8] This was a similar nonsignificant finding to an Israeli study by Angel et al. showing that seronegative healthcare workers that were inoculated with at least one dose of PfBNT were 0.48 times (95% CI: 0.19-1.26; p=0.12) less likely than unvaccinated healthcare workers to develop asymptomatic infection against the wild-type of the virus between 7 to 28 days past the vaccination date.[9]

Variants of Concern

A study conducted by Tang et al., which did not establish baseline seronegativity nor had a routine swabbing protocol, used a matched test-negative case-control method to investigate the effectiveness of at least one dose of PfBNT against the B.1.617.2 (Delta) variant at

preventing asymptomatic infection.[12] One dose of PfBNT past the 14th day onward from the date of vaccination was found to reduce asymptomatic infection by 25.2% (95% CI: 0.0-78.7).[12]

Full Dose Pfizer BioNTech Vaccine

Wild Type

Several studies found that a full-dose of PfBNT significantly reduced asymptomatic infection from the wild-type strain.[8-10] Tang et al. found a reduction in transmission of asymptomatic infection of fully vaccinated seronegative Qatari healthcare workers between 0-6 days past the date of vaccination (IRR: 0.35 [95% CI: 0.11-1.09]) and from more than 7 days past the date of vaccination of the second dose (IRR: 0.10 [95% CI: 0.04-0.22]).[8] This finding was supported by Angel et al. who found similar significant reductions in asymptomatic infection. PfBNT fully vaccinated individuals were 0.09 times (95% CI: 0.03-0.25; p<0.01) less likely as unvaccinated individuals to have asymptomatic infection after at least 7 days from full vaccination and 0.09 times (95% CI:0.01-0.35; p=0.002) times as likely to have asymptomatic infection 21 days after full vaccination compared to unvaccinated individuals.[9] A retrospective cohort study by Andrejko et al. of 525 seronegative California residents found that a full-dose of PfBNT had a 68.3% (95% CI: 27.9-85.7%) reduction of asymptomatic infection of the wild-type strain.[10]

Dagan et al. also demonstrated 90% effectiveness (95% CI: 83-94) against asymptomatic infection seven days after the second dose from the wild-type or B.1.17 (Alpha) strain. In an Israeli study, which utilized the national public health surveillance data, Haas et al. reported significantly higher vaccine effectiveness seven or more days after full dose PfBnT vaccination, 90.4% (95% CI: 89.1-91.5).[14] The incidence rate per 100 000 person-days among unvaccinated individuals was 54.6 compared with 3.2 in those vaccinated. Vaccine effectiveness after 14 or more days was 93.8% (95% CI: 93.3-94.2).[14] Pritchard et al. also found full dose vaccination with PfBnT vaccine to significantly reduce the odds of asymptomatic infection compared with unvaccinated previously PCR negative UK residents, 0.48 (95% CI: 0.36-0.66).[17]

Variants of Concern

The study conducted by Tang et al. found that a full-dose of PfBNT past the 14th day onward from the date of vaccination was found to reduce asymptomatic infection by 35.9% (95% CI: 11.1-53.9) against the B.1.617.2 (Delta) variant.[12]

mRNA (Pfizer BioNTech and Moderna) Vaccines Effectiveness in the General Population

One new study was included in this update that examined the effectiveness of the Pfizer BioNTech or Moderna vaccine against asymptomatic infection.

First or second dose of mRNA vaccine

Wild type

Tande et al. evaluated the effectiveness of at least one dose of either Moderna or PfBnT vaccine among people who underwent molecular tests prior to a procedure or surgery.[15] 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).[15]

Variants of Concern

Similar to the studies by Tande et al. and Bouton et al., Tang et al. found that use of at least one dose of an mRNA-based vaccine past the 14th day onward from the date of vaccination reduced asymptomatic infection by 44.3% (95% CI: 0-78.4) against the B.1.617.2 (Delta) variant.[12]

Moderna Vaccine Efficacy in the General Population

Of the four included studies reporting on Moderna, three new additional studies investigating vaccine efficacy (n= 1) or effectiveness (n=2) of the Moderna vaccine against asymptomatic infections were included in this update.

First and/or Full Dose Moderna Vaccine

Wild type

A study of the Moderna vaccine by Baden et al. reported that 0.1% of the participants receiving the first dose developed asymptomatic infection, assessed at the time of second dose with nasal swabs, compared with 0.27% of the unvaccinated group 21 days after the first dose, which is suggestive of 61.4% efficacy against asymptomatic carriage of the wild-type strain. Participants in this trial were negative for COVID-19 by RT-PCR or antibody testing at baseline.[32]

A phase 2/3 randomized-control trial by Ali et al. in 3732 seronegative adolescents (age 12-17 years) in the USA evaluating the vaccine efficacy of the Moderna vaccine is ongoing.[51] Participants were randomly assigned in a 2:1 ratio to receive two injections of either the Moderna vaccine (n=2139), each containing 100 µg or placebo (n=1042), 28 days apart. The study reported 0.97% of participants with an asymptomatic infection of those with a PCR-positive swab with no respiratory symptoms present 14 days after the first dose compared to 2.70% of unvaccinated adolescents with asymptomatic infection; this is suggestive of 59.5% (95% CI: 28.4-77.3) vaccine efficacy against asymptomatic carriage of the wild-type strain.[51] Fourteen days after the second dose, 1.17% of adolescents were had an asymptomatic infection as confirmed by the presence of a PCR-positive swab compared to 1.54% of unvaccinated adolescents with asymptomatic carriage of wild-type strain.[51] Full vaccination of Moderna is suggestive of 39.2% (95% CI: -24.7-69.7) vaccine efficacy against asymptomatic carriage of the wild-type strain.[51]

Moderna Vaccine Effectiveness in the General Population

First Dose Moderna Vaccine

Wild Type

A test-negative case-control study by Chemaitelly et al. in Qatar suggested a vaccine efficacy of 47.3% (95% CI: 36.7-55.5) against asymptomatic infection, defined as a PCR-positive test conducted with no reported symptoms compatible with a respiratory tract infection, at least 14 days after a first dose.[11]

Variants of Concern

Another Qatari study by Tang et al. found that use of at least one dose of the Moderna vaccine past the 14th day from the date of vaccination reduced asymptomatic infection by 57.4% (95% CI: 0-92.9) against the B.1.617.2 (Delta) variant.[12]

Full Dose Moderna Vaccine

Wild type

Chemaitelly et al. found that a full dose of Moderna was 92.5% effective (95% CI: 84.8-96.9) against asymptomatic carriage 14 days after full vaccination.[11]

Variants of Concern

Tang et al. found 80.2% vaccine effectiveness (95% CI: 54.2-92.6) against asymptomatic carriage of the Delta strain 14 days after full vaccination.[12]

Janssen Vaccine Efficacy in the General Population

No new additional studies investigating vaccine efficacy or effectiveness of the J&J vaccine against asymptomatic infections were included in this update.

Full Dose Janssen vaccine

This is a single dose vaccine. The J&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, assessed via surveillance swabs at unspecified intervals among baseline seronegative participants, was significantly lower among vaccinated participants (74%, 95% CI: 46.8-88.4%).[33] 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).[33]

Table 6: Observational Studies of Vaccine Effectiveness Against Transmission to Household Contacts

Vaccine	Author	Country	Dose	Follow-up days*	Outcomes*	Vaccine Effectiveness (95%CI)[+]
Pfizer, BioNTech (BNT162b2)	Harris et al.[57]	England	1	14-16	Transmission to household contact	OR: 0.73 (0.62-0.83) [Estimated VE: 25%]
	Harris et al.[57]	England	1	≥21	Transmission to household contact	aOR: 0.51 (0.44, 0.59) [Estimated VE: 46%]
	Harris et al.[57]	England	1	28-34	Transmission to household contact	OR: 0.62 (0.52-0.74) [Estimated VE:35%]
	de Gier et al.[2]	Netherlands	1	>14	Transmission to household contact	Adjusted VE 26% (95%CI: 12-37)
	de Gier et al.[2]	Netherlands	2	>7	Transmission to household contact	Adjusted VE 70% (95% CI: 61-77)
	Gazit et al.[4]	Israel	1	0-7	Transmission to vaccinated household contact	94% (95% CI: 90.8-95.7)
	Gazit et al.[4]	Israel	2	>7	Transmission to vaccinated household contact	70.1% (95% CI: 61.3-76.9)
	Layan et al.[5]	Israel	2	>7	HCW transmission to household contact	78% (95% CI: 30-94)
Moderna (mRNA-1273)	de Gier et al.[2]	Netherlands	1	>14	Transmission to household contact	Adjusted VE 51% (95%CI: 8-74)
	de Gier et al.[2]	Netherlands	2	>7	Transmission to household contact	Adjusted VE 88% (95% CI: 50-97)
Janssen (Ad26.COV2.S)	de Gier et al.[2]	Netherlands	1	>14	Transmission to household contact	Adjusted VE 77% (95% CI: 6-94)
AstraZeneca (ChAdOx1 nCoV-19)	Harris et al.[57]	England	1	14-16	Transmission to household contact	OR: 0.78 (0.66-0.92) [Estimated VE: 21%]
	Harris et al.[57]	England	1	≥21	Transmission to household contact	aOR: 0.53 (95% CI 0.43-0.63) [Estimated aVE: 44%]
	Harris et al.[57]	England	1	28-34	Transmission to household contact	OR: 0.44 (0.34-0.58) [Estimated VE: 54%]
	de Gier et al.[2]	Netherlands	1	>14	Transmission to household contact	Adjusted VE 15% (95%CI: 4-26)
	de Gier et al.[2]	Netherlands	2	>7	Transmission to household contact	Adjusted VE 58% (95% CI: -12-84)
BNT162b2 or ChAdOx1 nCoV-19	Shah et al.[53]	Scotland	1	7-13	HCW Transmission to household	-8% (95% CI: -25 - 6)
	Shah et al.[53]	Scotland	1	14-20	HCW Transmission to household	15% (95%CI:1-27)

	Shah et al.[53]	Scotland	1	>28	HCW Transmission to household	36% (95% CI: 27-44)
	Shah et al.[53]	UK	2	>14	HCW Transmission to household	54%(95% CI: 30-70)
Pfizer, BioNTech or Moderna, mRNA-1273	Salo et al.[3‡]	Finland	1	14	Transmission to household contact (unvaccinated spouse)	8.7% (95% CI: -28.9-35.4)
	Salo et al.[3‡]	Finland	1	70	Transmission to household contact (unvaccinated spouse)	42.9% (95% CI: 22.3-58.1)
	Salo et al.[3‡]	Finland	1	14	Transmission to household contact (unvaccinated child 3-18 years)	-1% (95% CI: -53.9-33.7)
	Salo et al.[3‡]	Finland	1	70	Transmission to household contact (unvaccinated child 3-18 years)	32.9% (95% CI: 4.1-53.0)
	Salo et al.[3‡]	Finland	1	42	Transmission to household contact (unvaccinated child 3-12 years)	12.3% (95% CI: -37.4-44.0)
	Salo et al.[3‡]	Finland	1	70	Transmission to household contact (unvaccinated child 3-12 years)	22.3% (95%CI: -34.4-55.2)
	Salo et al.[3‡]	Finland	1	42	Transmission to household contact (unvaccinated child 13-18 years)	16.7% (95% CI: -17.7-41.0)
	Salo et al.[3‡]	Finland	1	70	Transmission to household contact (unvaccinated child 13-18 years)	38% (95% CI: 1.2-61.1)
Pfizer, BioNTech or Moderna, mRNA-1273 or AstraZeneca, ChAdOx1 nCoV-19 or Janssen, Ad26.COV2.S	de Gier et al.[2]	Netherlands	1	>14	Transmission to household contact	Adjusted VE 21% (95% CI: 12-28)
	de Gier et al.[2]	Netherlands	1	>14	Transmission to unvaccinated household contact	Adjusted VE 23% (95% CI: 14-32)
	de Gier et al.[2]	Netherlands	1	>14	Transmission to any other close contact	Adjusted VE 22% (95% CI: 9-33)
	de Gier et al.[2]	Netherlands	1	>14	Transmission to any unvaccinated close contact	Adjusted VE 22% (95% CI: 8-34)
	de Gier et al.[2]	Netherlands	2	>7	Transmission to household contact	Adjusted VE 71% (95% CI: 63-77)
	de Gier et al.[2]	Netherlands	2	>7	Transmission to unvaccinated household contact	Adjusted VE 73% (95% CI: 65-79)
	de Gier et al.[2]	Netherlands	2	>7	Transmission to any other close contact	Adjusted VE 22% (95% CI: -5-43)

	de Gier et al.[2]	Netherlands	2	>7	Transmission to any unvaccinated close contact	Adjusted VE 24% (95% CI: -5-43)

*None of the studies excluded other sources of exposure. VE: Vaccine Effectiveness, OR: Odds Ratio, ⁺ VE =1-RR (or HR) x100%, where RR is the reported relative risk or Hazard ratio; or derived from reported baseline prevalence in unvaccinated group and OR[64].

‡All studies included participants with unknown baseline serology except for Salo et al. whom included participants who were seronegative

Table 7: 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 or Effectiveness (95%CI)+
AstraZeneca (ChAdOx1 nCoV-19)	Voysey et al.[7] (RCT)	UK	Wild type	Negative	LD or SD	>21	Asymptomatic or unknown	7.8% (-46.7-42.1)
	Voysey et al.[7] (RCT)	UK	Wild type	Negative	LD or SD	>21	Any PCR+	46.3% (31.8-57.8)
	Voysey et al.[6] (RCT)	UK/Brazil/South. Afrca	Wild type	Negative	LD or SD	22-90	Any PCR+	67% (49-78)
	Voysey et al.[6] (RCT)	UK/Brazil/South. Afrca	Wild type	Negative	SD	22-30	Asymptomatic or Unknown	0.2 (-209-68)
	Voysey et al.[6] (RCT)	UK/Brazil/South. Afrca	Wild type	Negative	SD	31-60	Asymptomatic or Unknown	17% (-172-75)
	Voysey et al.[6] (RCT)	UK/Brazil/South. Afrca	Wild type	Negative	SD	22-90	Asymptomatic or unknown	16% (-88-62)
	Pritchard et al.[17]	UK	Wild type and B.1.1.7	Both	NA	0-7	Asymptomatic	OR: 0.45(0.35 to 0.57)
	Pritchard et al.[17]	UK	Wild type and B.1.1.7	Both	NA	8-20	Asymptomatic	OR: 0.47(0.37 to 0.6)
	Pritchard et al.[17]	UK	Wild type and B.117	Both	NA	≥ 29	Asymptomatic	OR: 0.39(0.3 to 0.51)
	Souza et al.[54]	Brazil	B.1.1.7 (UK)	NR	NA	>23 days	asymptomatic	NR
Janssen Biotech (Ad26.COV2.S)	Janssen Biotech[33] (RCT)	Multiple	Wild type	Negative	NA	1-29	Asymptomatic	20% (-7-40.4)
	Janssen Biotech[33] (RCT)	Multiple	Wild type	Negative	NA	≥ 29	Asymptomatic	74% (46.8-88.4)
Pfizer, BioNTech (BNT162b2)	Amit et al.[52]	Israel	Wild type	Unknown	NA	1-14	Asymptomatic or unknown	NR##
	Amit et al.[52]	Israel	Wild type	Unknown	NA	15-28	Asymptomatic or unknown	NR###
	Dagan et al.[13]	Israel	Wild type and B.1.1.7	Unknown	NA	14-20	Asymptomatic	29% (17-39)
	Dagan et al.[13]	Israel	Wild type and B.1.1.7	Unknown	NA	21-27	Asymptomatic	52% (41-60)
	Hall et al.[56]	UK	Wild type	Unknown	NA	21 days after 1st dose and 7 days after 2nd	Asymptomatic or unknown	97.2%#
	Haas et al.[14]	Israel	Wild type and B.1.1.7	Unknown	NA	14-21 days	Asymptomatic	52% (48·9–55·0)
	Pritchard et al.[17]	UK	Wild type and B.117	Both	NA	0-7	Asymptomatic	OR: 0.48(0.39 to 0.6)
	Pritchard et al.[17]	UK	Wild type and B.117	Both	NA	8-20	Asymptomatic	OR:0.54(0.45 to 0.65)
	Pritchard et al.[17]	UK	Wild type and B.1.1.7	Both	NA	≥ 29	Asymptomatic	OR: 0.44(0.36 to 0.55)

Vaccine	Author	Country	Strain targeted by PCR	Baseline Serology	Dosing Schedule	Follow-up days*	Outcomes	Vaccine Efficacy or Effectiveness (95%CI)+
	Regev-Yochay et al.[25]	Israel	Wild type	Both	NA	4-10	Asymptomatic at first test	28(-18 to 57)
	Regev-Yochay et al.[25]	Israel	Wild type	Both	NA	4-10	Asymptomatic (who never became symptomatic)	27(-38 to 61)
	McEllistrem et al.[55]	USA	Wild Type	Unknown	NA	12-15 days	Asymptomatic	NR
	Jones et al.[23]	UK	Wild type and B.1.1.7	Unknown	NA	<12 and >12	Asymptomatic	NR
	Tang et al.[12]	Qatar	VOC delta	NR	NA	≥ 14	Asymptomatic	25.2 (0.0-78.7)
	Angel et al.[9]	Israel	Wild type	Seronegative	NA	7-28	Asymptomatic	adjusted IRR (95%CI): 0.48(0.19-1.26); p=0.12
	Tang et al.[8]	USA	Wild type	Seronegative	NA	0-11	Asymptomatic	IRR(95%CI): 0.58 (0.3-1.12)
	Tang et al.[8]	USA	Wild type	Seronegative	NA	>12	Asymptomatic	IRR(95%CI): 0.58 (0.3-1.13)
	McEllistrem el al.[24]	USA	Wild type	Unclear	NA	1-21	Asymptomatic	NR
	McEllistrem el al.[24]	USA	Wild type	Unclear	NA	14-21	Asymptomatic	NR
Moderna (mRNA-1273)	Baden et al.[32] (RCT)	USA	Wild type	Negative	NA	From day 1	Asymptomatic	61.4%#
	Ali et al.[51] (RCT)	USA	Wild type	Negative	NA	>14	Asymptomatic	59.5%(28.4 to 77.3)
	Tang et al.[12]	Qatar	VOC delta	NR	NA	≥ 14	Asymptomatic	57.4 (0.0-92.9)
	Chemaitelly et al.[11]	Qatar	Wild type and VOC B.1.1.7; B.1.351; B.1.617	Unknown	NA	14	Asymptomatic	47.3%(37.6-55.5%)
mRNA vaccines (BNT162b2 or Moderna mRNA-1273)	Tande et al.[15]	USA		Unknown	NA	From day 1, at least one dose	PCR+ in asymptomatic	56% (40-67)
	Bouton et al.[60]	USA	Wild type	Unknown	NA	From day 1, 1 dose	Asymptomatic	RR calculated: -1% (-57-35)
	Tang et al.[12]	Qatar	VOC delta	NR	NA	≥ 14	Asymptomatic	44.3 (0.0-78.4)

* 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). Studies are observational except otherwise stated. , + VE =1-RR (or HR) x100%

Table 8: 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 or Effectiveness (95%CI)+
AstraZeneca (ChAdOx1 nCoV-19)	Voysey et al.[7] (RCT)	UK	Wild type	Negative	LD or SD and SD	>14	Asymptomatic or unknown	27.3% (-17-54.9)
	Voysey et al.[7] (RCT)	UK	Wild type	Negative	LD and SD	>14	Asymptomatic or unknown	58.9% (1-82.9)
	Voysey et al.[7] (RCT)	UK	Wild type	Negative	SD and SD	>14	Asymptomatic or unknown	3.8% (-72.4-46.3)
	Voysey et al.[7] (RCT)	UK	Wild type	Negative	LD or SD and SD	>14	Any PCR+	55.7% (41.1-66.7)
	Voysey et al.[6] (RCT)	UK	Wild type	Negative	LD or SD and SD	>14	Any PCR+	54.1% (44.7%, 61.9%)
	Voysey et al.[6] (RCT)	UK	Wild type	Negative	LD or SD and SD	>14	Asymptomatic or unknown	22.2% (-9.9-45)
	Voysey et al.[6] (RCT)	UK	Wild type	Negative	SD and SD	>14	Asymptomatic or unknown	2.0% (-50.7-36.2)
	Voysey et al.[6] (RCT)	UK	Wild type	Negative	LD and SD	>14	Asymptomatic or unknown	49.3% (7.4-72.2)
	Emary et al.[16] (RCT)	UK	Wild type, B.1.1.7, Other	Negative	LD or SD and SD	>14	Asymptomatic	15.7% (-10.7-35.8)
	Emary et al.[16]	UK	B.1.1.7	Negative	LD or SD and SD	>14	Asymptomatic	26.5% (-112-74.5)
	Emary et al.[16]	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[33] (RCT)	Multiple	Wild type	Negative	NA	1-29	Asymptomatic	20% (-7-40.4)
	Janssen Biotech[33] (RCT)	Multiple	Wild type	Negative	NA	≥ 29	Asymptomatic	74% (46.8-88.4)
Pfizer BioNTech (BNT162b2)	Dagan et al.[13]	Israel	Wild type and B.1.1.7	Unknown	NA	>7	Asymptomatic	90% (83-94)
	Hall et al.[56]	UK	Wild type	Unknown	NA	21 days after 1st dose and 7 days after 2nd	Asymptomatic or unknown	NR
	Haas et al.[14]	Israel	Wild type and B.1.1.7	Unknown	NA	≥7	Asymptomatic	91·5% (90·7–92·2)
	Haas et al.[14]	Israel	Wild type and B.1.1.7	Unknown	NA	≥14	Asymptomatic	93·8% (93·3–94·2)
	Regev-Yochay et al.[25]	Israel	Wild	Both	NA	>10	Asymptomatic at first testing	65% (45 to 79)
	Regev-Yochay et al.[25]	Israel	Wild	Both	NA	>10	Asymptomatic (who never	72%(48-86%).

Vaccine	Author	Country	Strain targeted by PCR	Baseline Serology	Dosing Schedule	Follow-up days*	Outcomes	Vaccine Efficacy or Effectiveness (95%CI)+
							became symptomatic)	
	Pritchard et al.[17]	UK	Wild type and B.117	Both	NA	NR	Asymptomatic	OR:0.48(0.36 to 0.66)
	Pfizer [Press Release][50]	Israel	Wild type and B.1.1.7	Unknown	NA	>14	Asymptomatic	94%
	Tang et al.[12]	Qatar	VOC Delta	NR	NA	≥14	Asymptomatic	35.9 (11.1-53.9)
	Sansone et al.[62]	Italy	Wild type and VOC B.1.1.7 (Alpha/UK), B1.525	NR	NA	>14	Asymptomatic	OR: 0.38 (0.16-0.88)
	McEllistrem et al.[24]	USA	Wild type	Unclear	NA	7	Asymptomatic	NR
	Bailly et al.[27]	France	VOC 501Y.V2	Both	NA	NR	Asymptomatic	NR
	Andrejko et al.[10]	USA	Wild type	Seronegative	NA	>15	Asymptomatic	68.3% (27.9-85.7%)
	Tang et al.[8]	USA	Wild type	Seronegative	NA	0-6	Asymptomatic	IRR: 0.35 (0.11-1.09)
	Tang et al.[8]	USA	Wild type	Seronegative	NA	>7	Asymptomatic	IRR: 0.10 (0.04-0.22)
	Angel et al.[9]	Israel	Wild type	Seronegative	NA	>7	Asymptomatic	adjusted IRR: Vax 0.09(0.03-0.25); p<0.001
	Angel et al.[9]	Israel	Wild type	Seronegative	NA	>21	Asymptomatic	adjusted IRR: Vax 0.09(0.01-0.35); p=0.002
Moderna (mRNA-1273)	Ali et al.[51] (RCT)	USA	Wild type	Seronegative	NA	>14	Asymptomatic	39.2% (-24.7 to 69.7)
	Chemaitelly et al.[11]	Qatar	Wild type and VOC B.1.1.7; B.1.351; B.1.617	NR	NA	>14	Asymptomatic	92.5%(84.8-96.9%)
	Tang et al.[12]	Qatar	VOC Delta	NR	NA	≥14	Asymptomatic	80.2 (54.2-92.6)
BNT162b2 and ChAdOx1 nCoV-19	Shah et al.[53]	UK	Wild type	Unknown	NA	>14	HCW Transmission to household	HR=0.46 (95% CI: 0.30-0.70)
	Tang et al.[12]	Qatar	VOC Delta	NR	NA	≥14	Asymptomatic	40.0 (18.2-56.1)

* 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. Studies are observational, except otherwise state

Table 9: Ct Values

Vaccine	Author	Country	Virus type	Baseline Serology	1st or 2nd dose	Follow-up days	Sub-population	Ct Values (Vaccinated), Median (IQR), unless otherwise specified	Ct Values (Unvaccinated), Median (IQR), unless otherwise specified	Effect size/p-values
BNT162b2	Abu-Raddad[26]	Qatar	Wild type and B.1.1.7, B.1.351, B.1.617.2	Unknown	2	≥14	Breakthrough infection vs primary infection in unvaccinated	27.8 (21.1-32.7)	25.8 (19.5-31.4)	p <0.001
								Mean=26.8 (95% CI: 26.5-27.2)	Mean=25.5 (95% CI: 25.2-25.8)	Mean difference (95% CI): 1.3 (0.9-1.8), p<0.001
					2	≥14	Breakthrough infection vs reinfection in unvaccinated	28.2 (21.1-33.1)	31.2 (24.3-33.9)	p <0.001
								Mean=27 (95% CI: 26.3-27.6)	Mean=28.9 (95% CI: 28.3-29.5)	Mean difference (95% CI): 2.0 (1.1-2.8), p <0.001
	Bailly[27]	France	501Y.V2	Both	2	NR		21 (13-32)	15 (12-17)	p=0.05
	Ioannou[28]	Greece	B.1.1.7		2	>14		18 (15.5-25.5)	18.5 (13.5-24)	ns
	Jones[23]	UK	Wild-type and B.1.1.7	Unknown	1	≥12		30.3 (25.5-35.1)	23.3 (13.5-33)	ns
	Levine-Tiefenbrun[22]	Israel	Wild type	Unknown	1	<12		NR	NR	no significant differences in the Ct values for any of the 3 genes (RdRp, N and E)
					1	12-28		NR	NR	the Ct values for the 3 genes were significantly higher among infected vaccinated persons than controls ($p<10^{-8}$)
	McEllistrem[24]	USA	Wild type	Unknown	1	NR	Asymptomatic COVID-19	19.4 (18.9-22.5)	12.8 (12.4-14.9)	p=0.009
	Muhsen[58]	Israel	Wild type	Seronegative	2	>14		32 (14.5)	26.7 (8.8)	p=0.008
	Regev-Yochay[25]	Israel	Wild type	Both	2	≥11		Mean=27.3 (SD=2.2)	Mean=22.2 (SD=1.0)	Mean difference (95% CI): 5.09 (2.8-7.4), p<0.001

Vaccine	Author	Country	Virus type	Baseline Serology	1st or 2nd dose	Follow-up days	Sub-population	Ct Values (Vaccinated), Median (IQR), unless otherwise specified	Ct Values (Unvaccinated), Median (IQR), unless otherwise specified	Effect size/p-values
BNT162b2 or ChAdOx1	Baltas[20]	UK	Wild type and B.1.1.7	Unknown	1	9-24		30.8 (25.9-35.4)	28.8 (25.3-33.7)	P=0.053
	Lumley[21]	England	Wild type and B.1.1.7 (35% of unvaccinated seronegative; 65% vaccinated)	Seronegative	NR	NR		Change in median: 2.7 (-0.5 to 6.7)		NR
		England	Wild type and VOC	Seronegative	NR	NR		Mean=19.66 (95% CI: 15.01-27.53)	Mean=18.39 (95% CI: 14.00-25.57)	p=0.19
	Mostafa[19]	USA	Wild type, P.1, B.1.1.7 (61%), B.1.351, B.1.526 (9%), and B.1.526.1 (4.5%)	Unknown	2	2 to 100		19.26 (Q1, Q3: 16.56 to 21.96)	19.6 (Q1, Q3: 16.28 to 22.66)	ns
	Pritchard[17]	UK	Wild type	Both	1	0-7		31.2 (20.6-33.7)	28.4 (20.1-32.9)	p<0.001
					1	8-20		31 (23.5 to 33.8)	28.4 (20.1 to 32.9)	p<0.001
					1	≥21		31.7 (26.9 to 33.7)	28.4 (20.1 to 32.9)	p<0.001
					2	NR		33.1 (30.5 to 34.2)	28.4 (20.1 to 32.9)	p<0.001
	Shrotri[18]	UK	Wild type	Determined (adjusted for in analysis)	1	0-27		26.9 (25.19-26.62)	26.6 (26-27.1)	0.158
BNT162b2, ChAdOx1, or Moderna mRNA-1273	Pouwels[59]	UK	Alpha, Delta	Both	1	0 to 20	Alpha (1 Dec 2020 to 16 May 2021)	30.93 (Q1, Q3: 22.93 to 33.71)	28.7 (Q1, Q3: 20.4, 32.9) for not previously PCR positive; 32.8 (Q1, Q3: 30.9-34.2) for previously PCR positive	ns from unvaccinated but previously PCR/antibody-positive (age/sex-adjusted p=0.72), but significantly higher than in those unvaccinated and not previously PCR/antibody-positive, age/sex-adjusted p=0.02).
					1 or 2	>21 for dose 1 or 0-13 for dose 2		31.71(Q1, Q3: 26.64 to 33.57)		
					2	>14		33.3 (Q1, Q3: 31.6 to 34.0)		

Vaccine	Author	Country	Virus type	Baseline Serology	1st or 2nd dose	Follow-up days	Sub-population	Ct Values (Vaccinated), Median (IQR), unless otherwise specified	Ct Values (Unvaccinated), Median (IQR), unless otherwise specified	Effect size/p-values
					1	0 to 20	Delta (17 May 2021 to 13 Jun 2021)	29.93 (Q1, Q3: 22 to 34.21)	21.5 (Q1, Q3: 16.5 to 31.64) for not previously PCR positive; 30.86 (Q1, Q3: 29.5 to 34.28) for previously PCR positive	NR
					1 or 2	>21 for dose 1 or 0-13 for dose 2		30.07 (Q1, Q3: 18.64 to 33.64)		
					2	>14		32.29 (Q1, Q3: 26.07 to 33.93)		
					1	0 to 20	Delta (14 Jun 2021 to 1 Aug 2021)	25.64 (Q1, Q3: 21.64 to 30.79)	25.71 (Q1, Q3: 19.07 to 30.71) for not previously PCR positive; 22.29 (Q1, Q3: 16.57 to 30.29) for previously PCR positive	NR
					1 or 2	>21 for dose 1 or 0-13 for dose 2		24.64 (Q1, Q3: 18.86 to 31.29		
					2	>14		25.29 (Q1, Q3: 19.21 to 31.29)		
BNT162b2 or Moderna mRNA-1273	Jacobson[29]	USA	Wild type and B.1.427/B.1.429 (34.3%)	Both	1	≤ 14	Early post vaccination vs. unvaccinated	Mean=22.6 (SD=7)	Mean=23 (SD=7.4)	NR
					1 or 2	up to 14 after 2nd dose	Partially vaccinated vs unvaccinated	Mean=27.7 (SD=8.7)	Mean=23 (SD=7.4)	NR
					2	>14	Fully vaccinated vs unvaccinated	Mean=28.5 (SD=7.4)	Mean=23 (SD=7.4)	NR
BNT162b2, Moderna, or Janssen	Duerr[30]	USA	Wild type, B.1.1.7, B.1.526, P1, and others	Unknown	1 or 2	≥14	Vaccination breakthrough infections	27 (13-42)	≤30	NR
					1 or 2	≥14	Vaccination breakthrough infections that passed quality control	24 (13-36)	≤30	NR
ChAdOx1	Emary[16]	UK	Wild type and B.1.1.7	Unknown	2	≥14	Asymptomatic	30.25 (24.81-34.20)	28.15 (19.51-32.35)	p=0.0040

Vaccine	Author	Country	Virus type	Baseline Serology	1st or 2nd dose	Follow-up days	Sub-population	Ct Values (Vaccinated), Median (IQR), unless otherwise specified	Ct Values (Unvaccinated), Median (IQR), unless otherwise specified	Effect size/p-values
					2	≥14	Symptomatic	20.49 (15.43-24.44)	17.9 (15.06-25.06)	p=0.1534
					2	≥14	Symptomatic and asymptomatic B1.1.7	19.34 (15.39-21.62)	15.03 (12.51-16.59)	p=0.0113
					2	≥14	Symptomatic and asymptomatic not sequenced	29.52 (23.29-33.59)	25.57 (19.22-31.44)	p=0.0164
					2	≥14	Symptomatic and asymptomatic non-B.1.1.7 only	22.93 (17.54-29.4)	18.26 (15.15-25.57)	p=0.0201
Moderna (mRNA-1273)	Abu-Raddad[26]	Qatar	Wild type and B.1.1.7, B.1.351, B.1.617.2	Unknown	2	≥14	Breakthrough infection vs primary infection in unvaccinated	33.3 (29.6-34.8)	30.5 (23.5-33.7)	p<0.001
								Mean=31.2 (95% CI: 30.4-32.1)	Mean=28 (95% CI: 27-29.1)	Mean difference (95% CI): 3.2 (1.8-4.5), p<0.001
					2	≥14	Breakthrough infection vs reinfection in unvaccinated	33.1 (26.5-34.8)	33.1 (31.1-34.6)	p=0.104
								Mean=30 (95% CI: 28.3-31.7)	Mean=31.7 (95% CI: 30.5-32.9)	Mean difference: (95% CI): 1.7 (-0.4-3.8), p=0.104
NR	Riemersma[36]	USA	Wild type and B.1.617.2	NR	2	≥14		NR	NR	p=0.84
					2	≥14		NR	NR	p=0.99
					2	≥14		NR	NR	p=0.85
					2	≥14		NR	NR	p=0.61

Newly identified observational studies shaded in blue.

Cycle Threshold (Ct) Values

Twenty studies reported on Ct values, which is an inverse proxy for viral load. Eleven of these are new to the updated version of this report (Table 9).

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.[16] 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 ($p=0.0113$).[16]

A longitudinal UK household survey by Pritchard el al. found statistically significant increase in the median Ct values of PfBnT or AZ single or full dose vaccinated individuals compared with unvaccinated individuals at any time point before or after 21 days post-vaccination ($p<0.001$).[17] Similarly, in another UK study by Shrotri et al., the mean Ct value of unvaccinated individuals within 27 days of vaccination was 26.6 (95% CI: 26-27.1) compared with 26·6 (95% CI: 25.19-26.62) with one dose of PfBnT or AZ, which was not significantly different ($p=0.158$).[18] However, after 28 days, there was a statistically significant decrease in the mean Ct between vaccinated and unvaccinated persons (mean Ct 26.6 (95% CI: 26-27.1) vs 31·3 (95% CI: 29.6-32.9), $p<0·001$).[18] Monthly routine PCR testing was conducted in these patients; however, the baseline serology was not reported.[18] In a longitudinal cohort study of HCWs who were offered voluntary nasal and oropharyngeal swab PCR testing every two weeks as well as serological testing, a small study of 49 people vaccinated with either PfBNT or AZ and 96 unvaccinated people in the USA by Mostafa et al. demonstrated non-significant differences in median Ct values (19.26 [Q1, Q3: 16.56-21.96] vs 19.6 [Q1, Q3: 16.28-22.66], respectively).[19] Similar non-significance in the median Ct values of PfBNT or AerZ-vaccinated people vs unvaccinated was found in a UK study by Baltas et al. (Median=30.8 [IQR: 25.9-35.4] vs. Median=28.8 [IQR: 25.3-33.7], $p=0.053$).[20] Lumley et al., found vaccination with either PfBnT or AZ to non-significantly increase Ct value by a mean of 2.7.[21]

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 three 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 three genes were significantly higher among infected vaccinated persons than controls ($p<10^{-8}$).[22] 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.[23] A study by McEllistrem et al. among community living centre residents reported five cases of asymptomatic infections (determined by surveillance nasal swabs every 2-5 days) among baseline PCR negative PfBnT vaccinated and unvaccinated residents. The

median Ct values among unvaccinated residents (12.8, IQR: 12.4-14.9) were significantly lower (p=0.009) than vaccinated residents (19.4, IQR: 18.9-25.5).[24] Furthermore, viral load was -2.4 mean log10 lower among the vaccinated cohort (p=0.004).[24] In another large cohort study of HCWs at a large medical centre in Israel by Regev-Yochay et al, the mean Ct values among PfBNT fully vaccinated HCWs (27.3±2.2) was significantly higher (mean difference 5.09, 95% CI: 2.8-7.4, p<0.001) than unvaccinated HCWs (22.2±1.0).[25] A matched case-control study by Abu-Raddad et al. from Qatar, evaluating the Ct values of people with two doses of PfBNT with breakthrough infections compared to Ct values of infections in unvaccinated individuals, found statistically significant higher median Ct values in vaccinated individuals (27.8; IQR: 21.1-32.7) than the median Ct value of unvaccinated individuals (25.8 (IQR: 19.5-31.4; p<0.001).[26] However, studies in France[27] and Greece[28] found no statistically significant differences between PfBNT vaccinated individuals' Ct values and the Ct values of those who were unvaccinated. Bailly et al. found that the Ct values of PfBNT fully vaccinated long-term care residents did not differ from the Ct values of unvaccinated residents (Median=21 [IQR:13-32] vs 15 [IQR: 12-17]; p=0.05).[27] Similarly, Ioannou et al.'s study of fully vaccinated healthcare workers in a Greek hospital amidst an outbreak found no significant differences between the median Ct values of those vaccinated and unvaccinated (18 [15.5-25.5] vs 18.5 [13.5-24]).[28]

A USA study investigating the Ct values of mRNA-based vaccinated healthcare workers (PfBNT or Moderna) compared to unvaccinated healthcare workers found that there was no statistically significant difference in mean Ct values in the early post-vaccination period defined as less than 14 days post vaccination (22.6±7 vs. 23±7.4) for partially-vaccinated healthcare workers more than 14 days past first dose but before the second dose (27.7±8.7 vs. 23±7.4) or for fully vaccinated healthcare workers at least 14 days past vaccination (28.5±7.4 vs. 23±7.4).[29] Another similar study by Duerr et al. reported Ct values for vaccinated individuals in the community but lumped all unvaccinated comparators as under a Ct value equal or less than 30 therefore, no effect size was presented[30] (Table 9).

A longitudinal UK study from December 2020 to August 2021 found significant differences in Ct values in individuals vaccinated with either one or two doses of PfBNT, AZ, or Moderna[59]. From 1st December 2020 to 16th May 2021, Pouwels et al. assessed Ct values of people vaccinated with either PfBNT, Moderna, or AZ against the B.1.1.7 (Alpha) variant compared to their unvaccinated counterparts. Individuals with at least one dose of a vaccine had significantly higher Ct values (median=31.71) compared to the seronegative unvaccinated (median=28.7; p=0.02) or seropositive unvaccinated individuals (median=32.8, p=0.72) (Table 9).[59] From the 17th of May 2021 to 1st August 2021, Ct values of vaccinated individuals were assessed for the B.1.617.2 (Delta) variant compared to unvaccinated individuals and on average found that there appeared to be a higher cycle threshold among vaccinated people. However, there were no reported effect sizes or p-values for these periods.[59]

The study by Abu-Raddad et al. from Qatar also evaluated the median Ct values of people with breakthrough infections those with two doses of Moderna and found that there was statistically significantly higher median Ct values in the vaccinated (33.3; IQR: 29.6-34.8) than the median Ct value of unvaccinated individuals (30.5 (IQR: 23.5-33.7; p<0.001).[26]

In a pre-print by Riemersma et al., the authors included the Ct values of RT-PCR SARS-CoV-2 positive people from a single Wisconsin commercial laboratory with self-reported vaccination status between June 28 through July 24, 2021.[36] There were 291 specimens positive for SARS-CoV-2, with 79 people indicating that they were fully vaccinated and 212 unvaccinated individuals. The authors reported no significant differences in Ct values of vaccinated and unvaccinated people (p=0.85); the mean or median values or the previous serology of the sample were not reported. Of the 42 people identified with a Delta infection it was reported that there was no difference in Ct values (p=0.61).[36]

Viral Load

Two USA studies reported on viral load; one study is new to this updated version of the report. A prospective cohort study of baseline seronegative vaccinated and unvaccinated healthcare workers across Arizona had their mid-turbinate nasal swabs assessed for viral load.[31] Thompson et al. found that the mean viral RNA load for partially and fully vaccinated healthcare workers, with a mRNA-based vaccine, who were at least 14 days past the date of vaccination had lower presence of virus compared to their unvaccinated counterparts (2.3 ± 1.7 Log_{10} copies/mL vs. 3.8 ± 1.7 Log_{10} copies/mL).[31] This represented at least 40.2% lower viral RNA load after at least partial vaccination.[31]

A second retrospective cohort study of five vaccinated and five unvaccinated asymptomatic nursing home residents in a single nursing home evaluated the effectiveness of at least one dose of the PfBNT vaccine on attenuating viral load.[24] Viral load was -2.4 mean log10 lower among the vaccinated cohort (p=0.004).[24]

Discussion

In this update, 25 additional studies were included. Therefore, this review has a total of 45 included studies. Four new studies from the Netherlands, Finland, and Israel evaluating household transmission following vaccination found that PfBNT, Moderna, AZ, and J&J vaccines significantly reduce the risk of household transmission.[2-5] The majority of the vaccines included in this review demonstrated efficacy and effectiveness against asymptomatic wild-type COVID-19 infections. There is some limited evidence that there is moderate efficacy and effectiveness of vaccines against the B.1.617.2 (Delta) strain of the virus.

The AZ, PfBnT, and Moderna 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.[65] Furthermore, although there were statistically significant differences in median Ct values between vaccinated and unvaccinated individuals, most of the Ct values for both the vaccinated and unvaccinated individuals were ≤ 29, which clinically both indicate that the cycle thresholds were strongly positive indicative of an abundance of target viral nucleic acid in the samples.[66,67] A couple of studies found that vaccination with an mRNA-based vaccine reduced the viral load.[31,55]

There were significant limitations to many of the included studies. It was not possible to directly compare findings across studies owing to variations in the assessment of asymptomatic status, the testing used, and timing of these assessments. Also, the possibility of persistent PCR positivity after COVID-19 infection[68] 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. Therefore, there was limited data to evaluate the efficacy or effectiveness of COVID-19 vaccines in decreasing viral loads. In addition, there are only a limited number of epidemiologic data addressing evidence of forward transmission after vaccination.

Emerging Evidence

Variants of SARS-CoV-2 continue to surface, and the B.617.2 (Delta) variant is currently the one of most concern.[34,35] There has been emerging evidence that indicates that although a full vaccination series might reduce an individual's overall risk of becoming infected, there seems to be a limited difference in the Ct values between those vaccinated and unvaccinated.[34,36] Furthermore, certain outbreaks amongst vaccinated individuals in the USA have led to expanded prevention strategies, such as universal masking in indoor spaces.[35]

Comparisons of the proxy viral load measurement, Ct value, have found that, regardless of vaccination status, there was no difference in Ct values once an individual was infected with the B.1.617.2 (Delta) variant.[34,36] Public Health England (PHE) released a technical report on the NHS Test and Trace case data of the median and mean Ct values for all cases in the country. They reported that since May 2021 to July 2021, the median Ct value for unvaccinated individuals was 17.8 compared to the median of 18.0 in those who were vaccinated.[34] PHE suggested that there was limited difference in infectiousness due to the similarity in Ct values; the case data was not age stratified.[34]

The CDC reported in the Morbidity and Mortality Weekly Report on an outbreak of SARS-CoV-2 infections in vaccinated individuals in Barnstable County, Massachusetts.[35] During July 2021, 469 cases were associated with multiple summer and large public gathering events, with 74% (n=346) of cases occurring in fully vaccinated persons who had completed a 2-dose course of an mRNA vaccine (PfBNT or Moderna) or received the single-dose J&J vaccine. Genomic sequencing of specimens from 133 patients identified the B.1.617.2 (Delta) variant in 90% of cases. Of the 346 identified breakthrough infections, 274 (79%) had symptoms, and among the five who were hospitalized, four were fully vaccinated.[35] Ct values in specimens from 127 vaccinated persons with breakthrough cases were similar to those from 84 persons who were unvaccinated, not fully vaccinated, or whose vaccination status was unknown (median = 22.77 vs median=21.54, respectively).[35] Persons with COVID-19 reported attending densely packed indoor and outdoor events at venues that included bars, restaurants, guest houses, and rental homes. After the events of Barnstable County, the CDC recommended that all persons, including fully vaccinated individuals wear masks indoors in public settings especially in attendance of large public gatherings.

This emerging evidence suggests that the B.1.617.2 (Delta) variant is highly transmissible and that there may not be a difference between the viral load of those vaccinated compared

to those unvaccinated. However, more studies need to be conducted to fully understand the protection gleaned from vaccination. Until then, expanded prevention strategies, such as universal indoor masking, may help prevent the spread of the Delta variant.

Recommendations

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 pauci-symptomatic viral carriage should be considered in light of whether the exposed individual was vaccinated, 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 unvaccinated persons.

4) All vaccinated persons should continue to use recommended PPE when in close contact with unvaccinated 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

Four months since the publication of the previous version of this report, 24 additional relevant studies have been conducted. Four of these were large household surveillance studies from the Netherlands, Finland, and Israel suggesting that a full dose of PfBNT, Moderna, AZ, or J&J vaccines may prevent household transmission after 14 days of vaccination. Twelve additional studies found that vaccines significantly reduce the risk of asymptomatic infection, with multiple studies finding that vaccines decreased the viral RNA load or increased the cycle threshold, suggestive of reduced viral load. Some studies, such as the AZ vaccine RCTs, 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. Evidence regarding the Ct values for the AZ, PfBnT, and Moderna vaccine suggest their potential to reduce viral load and possibly transmission. Further research is needed to evaluate post-vaccination infectivity and transmission of variants of concern especially the B.1.617.2 (Delta) strain from other jurisdictions.

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Appendix 1: Search Strategy

Ovid Multifile

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <July 2021>, Embase <1974 to 2021 August 20> , Ovid MEDLINE(R) and Epub Ahead of Print, In-

Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to August 20, 2021>
Search Strategy:
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1 exp COVID-19 Vaccines/ (4322)
2 ((COVID-19 or COVID19) adj5 (immun* or inoculat* or vaccin*)).tw,kf. (19693)
3 ((coronavirus* or corona virus*) adj5 (immun* or inoculat* or vaccin*)).tw,kf. (4818)
4 ((2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2) adj5 (immun* or inoculat* or vaccin*)).tw,kf. (11949)
5 (((BNT162 or BNT162-01 or BNT162a1 or BNT162b1 or BNT162b2 or BNT162c2) and vaccin*) or N38TVC63NU).tw,kf. (1144)
6 (((AZD1222 or ChAdOx1) and vaccin*) or Covishield$2 or B5S3K2V0G8).tw,kf. (766)
7 ((Moderna and vaccin*) or EPK39PL4R4).tw,kf. (454)
8 ((mRNA adj3 vaccin*) and (COVID-19 or COVID19 or coronavirus* or corona virus* or 2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2)).tw,kf. (1795)
9 ((messenger RNA adj3 vaccin*) and (COVID-19 or COVID19 or coronavirus* or corona virus* or 2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2)).tw,kf. (158)
10 (LV-SMENP-DC and vaccin*).tw,kf. (5)
11 ((Ad5-nCoV and vaccin*) or hAdOx1 nCoV-19).tw,kf. (37)
12 (("Ad26.COV2.S" or Ad26COVS1 or JNJ 78436735 or JNJ-78436735 or JT2NS6183B) and vaccin*).tw,kf. (158)
13 Viral Vaccines/ and (Coronavirus/ or Betacoronavirus/ or Coronavirus Infections/) (1906)
14 or/1-13 [COVID-19 VACCINES] (33065)
15 COVID-19/pc [prevention & control] (8859)
16 Coronavirus Infections/pc [prevention & control] (10743)
17 Pandemics/pc [prevention & control] (14512)
18 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 (COVID-19 or COVID19)).tw,kf. (27144)
19 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 (coronavirus* or corona virus*)).tw,kf. (3792)
20 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 (2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2)).tw,kf. (6889)
21 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 spread*).tw,kf. (52770)
22 COVID-19/ep [Epidemiology] (17717)
23 COVID-19/tm [Transmission] (3563)
24 COVID-19/vi [Virology] (6344)
25 Coronavirus Infections/ep [Epidemiology] (23509)
26 Coronavirus Infections/tm [Transmission] (4703)
27 Coronavirus Infections/vi [Virology] (7690)
28 exp Disease Transmission, Infectious/ (352747)
29 (transmit* or transmissi* or infectiousness* or infectivit*).tw,kf. (1235632)
30 ((COVID-19 or COVID19) adj5 (caus* or pass or passed or passes or passing or spread*)).tw,kf. (32763)
31 ((coronavirus* or corona virus*) adj5 (caus* or pass or passed or passes or passing or spread*)).tw,kf. (17810)
32 ((virus* or infection*) adj5 (caus* or pass or passed or passes or passing or spread*)).tw,kf. (386113)

33 ((2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARSCoV2 or SARSCoV-2 or SARSCoV2 or SARS2) adj5 spread*).tw,kf. (5291)
34 (unvaccinat* or nonvaccinat* or non-vaccinat* or "not vaccinat*").tw,kf. (42643)
35 or/15-34 [TRANSMISSION] (1923307)
36 14 and 35 [COVID-19 VACCINES - DISEASE TRANSMISSION] (16076)
37 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial or equivalence trial).pt. (1248935)
38 "Clinical Trials as Topic"/ (314700)
39 exp "Controlled Clinical Trials as Topic"/ (382216)
40 (randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kf. (3721675)
41 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf. (731366)
42 trial.ti. (939819)
43 or/37-42 [RCT FILTER] (4670500)
44 36 and 43 [RCTs] (1647)
45 controlled clinical trial.pt. (186646)
46 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (573850)
47 (control* adj2 trial).tw,kf. (691363)
48 Non-Randomized Controlled Trials as Topic/ (12839)
49 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kf. (157674)
50 (nRCT or non-RCT).tw,kf. (1028)
51 Controlled Before-After Studies/ (210357)
52 (control* adj3 ("before and after" or "before after")).tw,kf. (825048)
53 Interrupted Time Series Analysis/ (203342)
54 time series.tw,kf. (77728)
55 (pre- adj3 post-).tw,kf. (294878)
56 (pretest adj3 posttest).tw,kf. (16682)
57 Historically Controlled Study/ (220764)
58 (control* adj2 study).tw,kf. (556350)
59 Control Groups/ (111904)
60 (control* adj2 group?).tw,kf. (1573730)
61 trial.ti. (939819)
62 or/45-61 [nRCT FILTER] (4350878)
63 36 and 62 [nRCTs] (1075)
64 exp Cohort Studies/ (3093661)
65 cohort?.tw,kf. (1911901)
66 Retrospective Studies/ (1784445)
67 (longitudinal or prospective or retrospective).tw,kf. (3831913)
68 ((followup or follow-up) adj (study or studies)).tw,kf. (130616)
69 Observational study.pt. (107979)
70 (observation$2 adj (study or studies)).tw,kf. (341258)
71 ((population or population-based) adj (study or studies or analys#s)).tw,kf. (47080)
72 ((multidimensional or multi-dimensional) adj (study or studies)).tw,kf. (276)
73 Comparative Study.pt. (2066781)
74 ((comparative or comparison) adj (study or studies)).tw,kf. (285012)
75 exp Case-Control Studies/ (1423752)
76 ((case-control* or case-based or case-comparison) adj (study or studies)).tw,kf. (272319)
77 Cross-Sectional Studies/ (690149)
78 (crosssection* or cross-section*).tw,kf. (1054262)
79 or/64-78 [OBSERVATIONAL STUDY FILTER] (9827573)
80 36 and 79 [OBSERVATIONAL STUDIES] (2568)
81 44 or 63 or 80 [ALL STUDY DESIGNS] (4117)

82 exp Animals/ not Humans/ (16123202)
83 81 not 82 [ANIMAL-ONLY REMOVED] (3982)
84 (202105* or 202106* or 202107* or 202108*).dt. (478611)
85 83 and 84 [UPDATE PERIOD] (576)
86 85 use ppez [MEDLINE RECORDS] (576)
87 SARS-CoV-2 vaccine/ (8936)
88 ((COVID-19 or COVID19) adj5 (immun* or inoculat* or vaccin*)).tw,kw. (22548)
89 ((coronavirus* or corona virus*) adj5 (immun* or inoculat* or vaccin*)).tw,kw. (5596)
90 ((2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2) adj5 (immun* or inoculat* or vaccin*)).tw,kw. (13897)
91 (((BNT162 or BNT162-01 or BNT162a1 or BNT162b1 or BNT162b2 or BNT162c2) and vaccin*) or N38TVC63NU).tw,kw. (1157)
92 (((AZD1222 or ChAdOx1) and vaccin*) or Covishield$2 or B5S3K2V0G8).tw,kw. (772)
93 ((Moderna and vaccin*) or EPK39PL4R4).tw,kw. (459)
94 ((mRNA adj3 vaccin*) and (COVID-19 or COVID19 or coronavirus* or corona virus* or 2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2)).tw,kw. (1814)
95 ((messenger RNA adj3 vaccin*) and (COVID-19 or COVID19 or coronavirus* or corona virus* or 2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2)).tw,kw. (161)
96 (LV-SMENP-DC and vaccin*).tw,kw. (5)
97 ((Ad5-nCoV and vaccin*) or hAdOx1 nCoV-19).tw,kw. (37)
98 (("Ad26.COV2.S" or Ad26COVS1 or JNJ 78436735 or JNJ-78436735 or JT2NS6183B) and vaccin*).tw,kw. (158)
99 (severe acute respiratory syndrome vaccine/ or virus vaccine/) and (coronavirinae/ or betacoronavirus/ or exp SARS-related coronavirus/ or coronavirus infection/) (1111)
100 or/87-99 [COVID-19 VACCINES] (36579)
101 coronavirus disease 2019/pc [prevention] (16383)
102 coronavirus infection/pc [prevention] (10779)
103 pandemic/pc [prevention] (14596)
104 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 (COVID-19 or COVID19)).tw,kw. (27702)
105 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 (coronavirus* or corona virus*)).tw,kw. (5416)
106 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 (2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2)).tw,kw. (7180)
107 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 spread*).tw,kw. (52807)
108 coronavirus disease 2019/ep [epidemiology] (29877)
109 coronavirus infection/ep [epidemiology] (23549)
110 virus transmission/ (72848)
111 (transmit* or transmissi* or infectiousness* or infectivit*).tw,kw. (1241266)
112 ((COVID-19 or COVID19) adj5 (caus* or pass or passed or passes or passing or spread*)).tw,kw. (32798)
113 ((coronavirus* or corona virus*) adj5 (caus* or pass or passed or passes or passing or spread*)).tw,kw. (17833)
114 ((virus* or infection*) adj5 (caus* or pass or passed or passes or passing or spread*)).tw,kw. (386369)
115 ((2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2) adj5 spread*).tw,kw. (5298)
116 (unvaccinat* or nonvaccinat* or non-vaccinat* or "not vaccinat*").tw,kw. (42646)

117 or/101-116 [TRANSMISSION] (1771114)
118 100 and 117 [COVID-19 VACCINES - DISEASE TRANSMISSION] (18078)
119 exp randomized controlled trial/ or controlled clinical trial/ (1492681)
120 clinical trial/ (1541965)
121 exp "controlled clinical trial (topic)"/ (217360)
122 (randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kw. (3785088)
123 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (760770)
124 trial.ti. (939819)
125 or/119-124 [RCT FILTER] (5250210)
126 118 and 125 [RCTs] (1545)
127 controlled clinical trial/ (558033)
128 "controlled clinical trial (topic)"/ (11831)
129 (control* adj2 trial).tw,kw. (1058875)
130 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kw. (158708)
131 (nRCT or non-RCT).tw,kw. (1030)
132 (control* adj3 ("before and after" or "before after")).tw,kw. (825052)
133 time series analysis/ (29877)
134 time series.tw,kw. (78764)
135 pretest posttest control group design/ (564)
136 (pre- adj3 post-).tw,kw. (294927)
137 (pretest adj3 posttest).tw,kw. (20506)
138 controlled study/ (8321938)
139 (control* adj2 study).tw,kw. (985693)
140 control group/ (111799)
141 (control* adj2 group?).tw,kw. (1574940)
142 trial.ti. (939819)
143 or/127-142 [nRCT FILTER] (11387363)
144 118 and 143 [nRCTs] (2998)
145 cohort analysis/ (1033210)
146 cohort?.tw,kw. (1917721)
147 retrospective study/ (2052657)
148 longitudinal study/ (308271)
149 prospective study/ (1296159)
150 (longitudinal or prospective or retrospective).tw,kw. (3853020)
151 follow up/ (1723966)
152 ((followup or follow-up) adj (study or studies)).tw,kw. (132434)
153 observational study/ (349424)
154 (observation$2 adj (study or studies)).tw,kw. (343991)
155 population research/ (116549)
156 ((population or population-based) adj (study or studies or analys#s)).tw,kw. (55167)
157 ((multidimensional or multi-dimensional) adj (study or studies)).tw,kw. (277)
158 exp comparative study/ (3392659)
159 ((comparative or comparison) adj (study or studies)).tw,kw. (302872)
160 exp case control study/ (1423752)
161 ((case-control* or case-based or case-comparison) adj (study or studies)).tw,kw. (275780)
162 cross-sectional study/ (817603)
163 (crosssection* or cross-section*).tw,kw. (1058104)
164 major clinical study/ (4204970)
165 or/145-164 [OBSERVATIONAL STUDY FILTER] (13849196)
166 118 and 165 [OBSERVATIONAL STUDIES] (3519)

167 126 or 144 or 166 [ALL STUDY DESIGNS] (5730)
168 exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (54468436)
169 exp human/ or exp human experimentation/ or exp human experiment/ (42855732)
170 168 not 169 (11614435)
171 167 not 170 [ANIMAL-ONLY REMOVED] (5365)
172 (202105* or 202106* or 202107* or 202108*).dc. (933210)
173 171 and 172 [UPDATE PERIOD] (1560)
174 173 use oemezd [EMBASE RECORDS] (1560)
175 exp COVID-19 Vaccines/ (4322)
176 ((COVID-19 or COVID19) adj5 (immun* or inoculat* or vaccin*)).ti,ab,kw. (22546)
177 ((coronavirus* or corona virus*) adj5 (immun* or inoculat* or vaccin*)).ti,ab,kw. (5595)
178 ((2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2) adj5 (immun* or inoculat* or vaccin*)).ti,ab,kw. (13896)
179 (((BNT162 or BNT162-01 or BNT162a1 or BNT162b1 or BNT162b2 or BNT162c2) and vaccin*) or N38TVC63NU).ti,ab,kw. (1123)
180 (((AZD1222 or ChAdOx1) and vaccin*) or Covishield$2 or B5S3K2V0G8).ti,ab,kw. (741)
181 ((Moderna and vaccin*) or EPK39PL4R4).ti,ab,kw. (392)
182 ((mRNA adj3 vaccin*) and (COVID-19 or COVID19 or coronavirus* or corona virus* or 2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2)).ti,ab,kw. (1813)
183 ((messenger RNA adj3 vaccin*) and (COVID-19 or COVID19 or coronavirus* or corona virus* or 2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2)).ti,ab,kw. (161)
184 (LV-SMENP-DC and vaccin*).ti,ab,kw. (1)
185 ((Ad5-nCoV and vaccin*) or hAdOx1 nCoV-19).ti,ab,kw. (26)
186 (("Ad26.COV2.S" or Ad26COVS1 or JNJ 78436735 or JNJ-78436735 or JT2NS6183B) and vaccin*).ti,ab,kw. (145)
187 Viral Vaccines/ and (Coronavirus/ or Betacoronavirus/ or Coronavirus Infections/) (1906)
188 or/175-187 [COVID-19 VACCINES] (35531)
189 COVID-19/pc [prevention & control] (8859)
190 Coronavirus Infections/pc [prevention & control] (10743)
191 Pandemics/pc [prevention & control] (14512)
192 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 (COVID-19 or COVID19)).ti,ab,kw. (27702)
193 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 (coronavirus* or corona virus*)).ti,ab,kw. (5416)
194 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 (2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2)).ti,ab,kw. (7180)
195 ((control* or decreas* or halt* or prevent* or reduc* or stop*) adj5 spread*).ti,ab,kw. (52807)
196 COVID-19/ep [Epidemiology] (17717)
197 COVID-19/tm [Transmission] (3563)
198 COVID-19/vi [Virology] (6344)
199 Coronavirus Infections/ep [Epidemiology] (23509)
200 Coronavirus Infections/tm [Transmission] (4703)
201 Coronavirus Infections/vi [Virology] (7690)
202 exp Disease Transmission, Infectious/ (352747)
203 (transmit* or transmissi* or infectiousness* or infectivit*).ti,ab,kw. (1241265)

204 ((COVID-19 or COVID19) adj5 (caus* or pass or passed or passes or passing or spread*)).ti,ab,kw. (32798)
205 ((coronavirus* or corona virus*) adj5 (caus* or pass or passed or passes or passing or spread*)).ti,ab,kw. (17833)
206 ((virus* or infection*) adj5 (caus* or pass or passed or passes or passing or spread*)).ti,ab,kw. (386369)
207 ((2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2) adj5 spread*).ti,ab,kw. (5298)
208 (unvaccinat* or nonvaccinat* or non-vaccinat* or "not vaccinat*").ti,ab,kw. (42646)
209 or/189-208 [TRANSMISSION] (1929116)
210 188 and 209 [COVID-19 VACCINES - DISEASE TRANSMISSION] (17254)
211 (202105* or 202106* or 202107* or 202108*).up. (1733210)
212 210 and 211 [UPDATE PERIOD] (4802)
213 212 use cctr [CENTRAL RECORDS] (233)
214 86 or 174 or 213 [ALL DATABASES] (2369)
215 remove duplicates from 214 (1983) [TOTAL UNIQUE RECORDS]
216 215 use ppez [MEDLINE UNIQUE RECORDS] (569)
217 215 use oemezd [EMBASE UNIQUE RECORDS] (1206)
218 215 use cctr [CENTRAL UNIQUE RECORDS] (208)
219 202104*.up. (277685)
220 210 and 219 [APRIL UPDATE] (917)
221 220 use cctr [CENTRAL APRIL UPDATE] (25)
222 214 or 221 [ALL UPDATE PERIODS - ALL DATABASES] (2394)
223 remove duplicates from 222 (2007)
224 223 use ppez [MEDLINE UNIQUE RECORDS] (569)
225 223 use oemezd [EMBASE UNIQUE RECORDS] (1206)
226 223 use cctr [CENTRAL UNIQUE RECORDS] (232)
227 226 and 219 [CENTRAL UNIQUE RECORDS - APRIL ONLY] (24)

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PICO - Prevention>SARS-CoV-2 Vaccines-Primary Studies
3819 records