UK Health Security Agency

The effect of vaccination on transmission of COVID-19

A rapid review

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Main messages

1. The purpose of this review was to identify and examine evidence on the effect of vaccination on transmission of coronavirus (COVID-19) from people who contract COVID-19 post-vaccination. The review includes 43 primary studies (18 preprints, one non-peer reviewed report) (search up to 22 October 2021): 13 studies assessed the effect of COVID-19 vaccination on transmission of COVID-19, and 32 studies assessed the effect of COVID-19 vaccination on COVID-19 viral loads (2 studies assessed both outcomes).
2. There was evidence across 13 transmission studies (all observational, all variants) that fully vaccinated index cases transmitted COVID-19 to their contacts less than unvaccinated index cases, particularly for wild-type and non-Delta variants (moderate certainty on GRADE), and this reduction was substantial (for example, more than 50% reduction in transmission) in many studies.
3. In most studies assessing both partial and full vaccination, partial vaccination was much less effective for reducing transmission from cases than full vaccination.
4. While most of the transmission studies looked at wild-type and non-Delta variants and were consistent, the evidence from the 3 studies that looked at the Delta variant was more mixed (low certainty on GRADE). Although all 3 studies suggested that fully vaccinated cases transmitted COVID-19 less than unvaccinated cases, 2 studies suggested that vaccine effectiveness against transmission of the Delta variant dropped substantially over time. Additionally, one study suggested that vaccination of the index case was less effective against transmission for the Delta compared with the Alpha variant.
5. Evidence from the 32 viral load studies was broadly supportive of the transmission studies: 23 studies that looked at wild-type and non-Delta variants of COVID-19 (moderate certainty on GRADE) typically showed that fully vaccinated cases had higher Ct values than unvaccinated cases (suggesting a lower viral load), however, evidence was again more mixed for the Delta variant (low certainty on GRADE), as while most of the 16 studies suggested only a small (or no) difference in Ct values between fully vaccinated and unvaccinated cases, some studies suggested Ct values were higher in fully vaccinated cases, and one study suggested lower Ct values in fully vaccinated cases.
6. One study looked at viral load over time in cases after contracting Delta variant COVID-19, and suggested that Ct values of fully vaccinated cases were much higher (suggesting lower viral load) than unvaccinated cases soon after the second dose of vaccine, but the difference became smaller over time: for those infected 180 days or more after the second dose, Ct values were very similar between vaccinated and unvaccinated cases. This study was also the only study that looked at booster doses, and suggested people who contracted COVID-19 after a booster dose of Pfizer had higher Ct values than unvaccinated cases.
7. Three studies examined the infectivity of samples from fully vaccinated and unvaccinated cases with the Delta variant, and suggested infectivity was very similar.
8. In almost all included studies (transmission and viral load) there is a high risk that factors other than vaccination may have affected the results, which may have biased the results in either direction. Most studies were also highly heterogeneous, so caution must be used

when comparing results between different studies. No included studies assessed the Omicron variant.

Background

Randomised controlled trials have shown high levels of efficacy of a range of COVID-19 (SARS-CoV-2) vaccinations in terms of reducing the risks of symptomatic infection, severe disease and mortality from COVID-19 (1 to 5). A living evidence synthesis, incorporating evidence from randomised controlled trials (RCTs) and observational studies and looking at specific vaccines, has suggested that for the Alpha variant of COVID-19, vaccine effectiveness is between 62% and 100% against infection, whereas for the Delta variant of COVID-19, vaccine effectiveness is 42% to 91% effective against any infection and 59% to 92% against symptomatic infection (excluding the Janssen vaccine) (6). A systematic review of 17 studies looking at the Delta variant (currently the dominant variant in the UK), estimated a vaccine effectiveness of 63.1% (95% confidence intervals: [CI]: 40.9% to 76.9%) against asymptomatic infection, 75.7% (95% CI: 69.3% to 80.8%) against symptomatic infection and 90.9% (95% CI: 84.5% to 94.7%) against hospitalisation (7). This review also suggested that vaccine effectiveness against mild outcomes was reduced by 10% to 20% for the Delta variant compared to other variants, while no reduction in effectiveness was seen for more severe outcomes. Although vaccination appears to remain effective at reducing severe outcomes for the Delta variant, the effectiveness against any infection may be reduced, and the extent to which vaccination reduces the infectiousness of breakthrough infections (infections in people who are vaccinated) is unclear.

There is a need to understand the potential for transmission of COVID-19 from vaccinated individuals. Early reviews on this topic found little direct evidence on examining the effectiveness of vaccination against transmission (8), but new studies comparing transmission of COVID-19 from fully or partially vaccinated and unvaccinated cases to their household and other contacts are now emerging (9). The number of studies is still relatively small, and few studies examine the most recent Delta variant.

Therefore, it is also important to understand the extent to which vaccination impacts on earlier indicators of transmission, as viral loads, Ct values and infectiousness of samples are all correlated with transmission of COVID-19 (10, 11).

Objective

The purpose of this rapid review was to identify and examine evidence on whether vaccination against COVID-19 affects transmission of COVID-19 (SARS-CoV-2). We included studies that assessed transmission directly, and, as a secondary outcome, studies that assessed viral load. We were also interested in the effects of vaccination on transmission according to vaccine type, individual vaccine brands, duration of protection after vaccination (time from vaccination), completion of the vaccination course (full or partial vaccination), SARS-CoV-2 variants in index cases, and background COVID-19 infection rate.

Definitions

Within the review we refer to vaccines by the names of their manufacturers: for their generic names, trade names and vaccine types see Table A.1.

SARS-CoV-2 variants are referred to by their World Health Organization designated name and classification (12): for the full list of variants and classifications, see Table A.2.

Cycle threshold (Ct) value

Ct values represent the number of cycles of polymerase chain reaction (PCR) required to cross the threshold value for detection. Ct values are inversely proportional to the concentration of viral genetic material in a sample tested for SARS-CoV-2, in that a higher Ct value represents a lower viral load as more viral genetic material is needed to pass the threshold for detection (13).

Index case

The term ‘index case’ is often used interchangeably with ‘primary case’; in this review we define it as the first confirmed case of COVID-19 in a specific group or household.

Secondary attack rate (SAR)

The probability that an infection occurs after exposure to a disease amongst susceptible contacts within a specific group (14).

Secondary case

Household or close contacts who develop COVID-19 from an index case.

Vaccine efficacy and effectiveness against transmission

A measurement of the proportional reduction in the transmission of a disease from vaccinated cases in a controlled clinical trial (efficacy), or vaccinated cases in the general population (effectiveness), compared to unvaccinated cases, equivalent to the relative risk reduction (1 minus the relative risk) (15, 16).

Viable virus (or culturable virus)

A virus that can infect other cells in a viral culture. Viral culture is performed to determine whether the virus from a sample collected from the body or the environment is infectious. A viral culture is a laboratory test in which samples of a virus are placed with host cells. The virus is detected by the changes in the host cells (cytopathic effects) (15).

Viral load (also known as viral burden or viral titre)

The quantity of virus in a specimen (nasopharyngeal swab) which is determined by the cycle threshold from real-time polymerase chain reaction (RT-PCR).

Methods

A rapid review was conducted, following streamlined systematic methodologies to accelerate the review process (17). A literature search was undertaken to look for primary studies related to the COVID-19 pandemic, published (or available as preprint, that is, available prior to peer review) between 1 January 2020 and 22 October 2021.

Title and abstract screening was completed in duplicate for 10% of the studies, and full text screening, data extraction and risk of bias assessment were conducted by one reviewer and checked by a second. Characteristics of included studies were tabulated, and data combined by narrative review. Meta-analysis was considered for studies that could be combined, but was not performed as the studies were too heterogeneous in design or reporting for any outcome.

Risk of bias was assessed using the quality criteria checklist (QCC) tool which assesses the methodological quality of a study (18). Studies were given a quality rating of high, medium or low (methodological quality). The certainty of the evidence was assessed using a variation of the GRADE framework for systematic reviews without meta-analysis (19 to 21).

Full details on the methodology are provided in Annexe A. A protocol was produced a priori and registered on PROSPERO (CRD42021257125).

Note that throughout this report, the term ‘partial vaccination’ and ‘partially vaccinated’ refer to having received one dose of a 2 dose vaccine, ‘full vaccination’ and ‘fully vaccinated’ refer to having received 2 doses of a 2 dose vaccine or one dose of a one dose vaccine, and ‘booster doses’ refers to a further vaccine dose after full vaccination, all unless otherwise specified.

Evidence

Search results

The database search returned 10,503 records. After removal of duplicates, 6,369 records were screened by title and abstract. Of these, 248 full-text articles were assessed for eligibility. A further 173 studies were identified by searching reference lists of relevant reviews and consultation with topic experts and assessed in full text. Of the 421 full-text papers assessed, 43 were included in the review. We are aware of 3 ongoing studies from trial registries that await formal publication (either journal or preprint) and meet the criteria for inclusion (Supplementary Table 3). A PRISMA diagram is provided in Figure A.1 (22).

This review includes 2 RCTs and 41 observational studies, 2 of which assessed both outcomes (18 preprints and one non-peer-reviewed report).

Transmission

There were 13 observational studies that directly assessed the effectiveness of vaccines in reducing the risk of transmission of COVID-19 from people who had COVID-19 (index cases) to household members, close contacts, or both (secondary cases). Of these, 12 were cohort studies and one was a case-control study (23). Four studies provided UK data (23 to 27).

Viral load

There were 32 studies (2 RCTs and 30 observational studies) that reported on viral load. The 2 RCTs, conducted in the UK and US, randomised participants to be vaccinated with a COVID-19 vaccine or placebo. Although the randomisation in these studies ensured the people in the intervention and control groups were similar, if the vaccines being tested preferentially protected some people, the people who contracted COVID-19 in each group may not have been comparable. As such, the RCTs were treated as observational studies in this report (3, 28). The observational studies compared viral load between vaccinated and unvaccinated people who contracted COVID-19, of which 6 were from the UK (27, 29 to 33).

Full characteristics of included studies can be found in Supplementary Table 1 and Supplementary Table 2.

Evidence on transmission of COVID-19 after COVID-19 vaccination

Studies that directly assessed transmission of COVID-19 from index cases to close contacts form the main evidence for this review.

Thirteen observational studies (1 non-peer reviewed report (23), 8 preprints (27, 34 to 40), one study rated as low (39), 8 studies as medium (34 to 38, 40 to 42), and 4 studies as high quality (23 to 27)) directly assessed the effectiveness of vaccines in reducing the risk of transmission of COVID-19 from people who had COVID-19 (index cases) to household members or close contacts (secondary cases). Of these, 12 were cohort studies and one was a case-control study (23). Four studies provided data from the UK (23 to 27), 4 from Europe (34 to 36, 42), 3 from Israel (37 to 39), and one from China (40). All studies were conducted between Winter 2020 to Summer 2021.

Seven studies were conducted when Alpha was the dominant variant (23 to 25, 35, 38, 41, 42), 4 studies did not report the dominant variant, though were likely pre- Delta as they were conducted before April 2021 (26, 36, 37, 39), and 3 studies were conducted when Delta was the dominant variant (27, 34, 40). All studies included participants who received the Pfizer vaccine (except possibly (40), where the vaccine was not specified), 7 studies the AstraZeneca vaccine (23 to 27, 34, 41, 42), 3 studies the Moderna vaccine (34, 36, 41), and 3 studies the Janssen vaccine (34, 41, 42). Some studies may report on the same populations, either at the same time or at different stages of the pandemic. For instance, 3 studies report on the UK population for January and February (24, 25), March to May (23), and January to July 2021 (27).

While studies reporting different time periods are likely distinct enough that caution does not need to be used when interpreting the results, studies covering the same time period and location may include the same participants and therefore caution must be used to avoid double counting the same data. Where necessary, this has been noted in the summaries below.

Table 1 shows a summary of all transmission studies and their results, and Supplementary Table 1 shows all characteristics of all transmission studies. For all studies detailed below, we have reported the results as given in the individual studies, as many studies used different terms and definitions for fully and partially vaccinated, and different outcome assessments.

UK studies

A matched case-control study by Allen and others (non-peer reviewed report, rated as high quality, n=11,295 index cases) assessed the transmission of COVID-19 from index cases identified from Pillar 2 testing (RT-PCR, 94.9% Alpha, 5.1% Delta) to household members (vaccination status not stated) between March and May 2021 (23). Index cases with household transmission (household members receiving a positive test within 14 days of the index case's

positive test) were matched with cases without household transmission for comparison. The COVID-19 status of secondary cases was confirmed in a laboratory or by lateral flow devices. Fully vaccinated index cases (n=70, 0.6%) had 2 doses of the AstraZeneca or Pfizer vaccine at least 14 days prior to testing positive, and partially vaccinated index cases (n=1,499, 13.2%) had one dose of either vaccine at least 21 days prior to testing positive. The results suggested that:

- there was less transmission to household members from fully vaccinated compared to unvaccinated index cases, but the difference was not statistically significant (SAR not estimable, OR = 0.76, 95% CI: 0.44 to 1.31)
- there was a smaller reduction in transmission from partially vaccinated compared to unvaccinated index cases, which was also non-significant (OR = 0.94, 95% CI: 0.81 to 1.08)

A retrospective cohort study by Eyre and others (rated as high quality, n=108,498 adult index cases, n=146,243 contacts) assessed the transmission of COVID-19 from index cases to their household (66%) and non-household (34%) contacts, both identified from a national testing programme in England (NHS Test and Trace) from January to July 2021 (27). The study includes separate analyses of the Alpha (41% of contacts) and Delta (59% of contacts) variants. COVID-19 status of contacts was confirmed with RT-PCR test taken 1 to 10 days after the index case's positive test. Contacts who did not get a test are not included leading to a possible overestimation of the secondary attack rate (SAR).

Fully vaccinated index cases (18%) and contacts (44%) were defined as having 2 doses of the AstraZeneca or Pfizer vaccine at least 14 days prior to testing positive, and partially vaccinated index cases (27%) and contacts (31%) were defined as having a single dose of either vaccine, or less than 14 days after a second dose prior to testing positive. The results for the Alpha variant may include the same participants in the same time period as Allen (23) and Harris (24, 25).

For the Alpha variant, there was a reduction in the rate of COVID-19 transmission to contacts from index cases fully vaccinated with the AstraZeneca (SAR = 28% vs 46%, rate ratio = 0.48, 95% CI: 0.30 to 0.78) and Pfizer (SAR = 21% vs 46%, rate ratio = 0.32, 95% CI: 0.21 to 0.48) vaccines, compared with unvaccinated index cases. The reduction in the rate of transmission was much smaller for the Delta variant for both vaccines.

(AstraZeneca: rate ratio = 0.76, 95% CI: 0.70 to 0.82; Pfizer: rate ratio = 0.50, 95% CI: 0.39 to 0.65, both comparing fully vaccinated to unvaccinated index cases).

When looking at the vaccination status of contacts rather than index cases, for the Alpha variant, there was a reduction in the rate of COVID-19 transmission from index cases to contacts that were fully vaccinated with the AstraZeneca (SAR = 22% vs 52%, rate ratio = 0.40, 95% CI: 0.27 to 0.59) and Pfizer (SAR = 17% vs 52%, rate ratio = 0.15, 95% CI:

0.11 to 0.21) vaccines, compared with unvaccinated contacts. The reduction in the rate of transmission was similar for the Delta variant (AstraZeneca: rate ratio = 0.42, 95% CI: 0.38 to 0.45; Pfizer: rate ratio = 0.19, 95% CI: 0.16 to 0.23, both comparing fully vaccinated to unvaccinated index cases). The reduction in the rate of transmission was much smaller for partially vaccinated compared with fully vaccinated index cases and contacts (see Table 1).

For both Alpha and Delta variants and both vaccines, the rate of transmission increased as the time from the second dose increased, indicating the vaccine effectiveness against transmission reduced over time (change in rate of transmission for each doubling of weeks after 2 weeks after second dose: AstraZeneca: 1.08, 95% CI: 1.05 to 1.11; Pfizer: 1.13, 95% CI: 1.13 to 1.21).

For Delta, the reduction in transmission (compared to unvaccinated index cases) from full vaccination with Pfizer decreased from 50% (95% CI: 35% to 61%) 2 weeks after the second dose to 24% (95% CI: 20% to 28%) 12 weeks after the second dose, and with AstraZeneca decreased from 24% (95% CI: 20% to 28%) 2 weeks after the second dose to 2% (95% CI: -2% to 6%) 12 weeks after the second dose.

A retrospective cohort study by Harris and others (rated as high quality, n=365,447 households with a COVID-19 index case, n=1,018,842 household contacts) assessed the transmission of COVID-19 from index cases, identified from national testing, to their unvaccinated household members in England in January and February 2021, when the Alpha variant was rising in dominance (24,25). COVID-19 status was confirmed with RT- PCR. Vaccinated index cases were defined as receiving the AstraZeneca or Pfizer vaccine 21 days or more before testing positive (93% received a single dose).

The results suggested that the odds of COVID-19 transmission to unvaccinated household members were around half as large as from index cases vaccinated with the AstraZeneca (SAR = 5.7% vs 10.1%, odds ratio [OR] = 0.53, 95% CI: 0.43 to 0.65) and Pfizer (SAR = 6.2% vs 10.1%, OR = 0.51, 95% CI: 0.44 to 0.59)
vaccines, compared with unvaccinated index cases.

A retrospective cohort study by Shah and others (rated as high quality, n=114,257 healthcare workers, n=194,362 household members) assessed transmission of COVID- 19 from working age healthcare workers employed by NHS Scotland identified from national databases (index cases) to their unvaccinated household members between December 2020 to March 2021 (dominant COVID-19 variant not stated) (26). COVID-19 status was determined by RT-PCR. ‘Post-second dose’ was defined as at least 14 days after vaccination with the second dose of the AstraZeneca or Pfizer vaccine (27.2% of healthcare workers) and ‘post-first dose’ was defined as at least 14 days after vaccination with the first dose (79.1% of healthcare workers, includes post-second dose healthcare workers). As this study looked at all healthcare workers, not just those with a confirmed COVID-19 infection, these results include the effect of vaccines on preventing COVID-19 infection as well as on reducing transmission from index cases, and so

will overestimate the vaccine effectiveness against transmission from index cases. The results suggested that:

- there was a reduction in transmission over time to unvaccinated household members from post-second dose healthcare workers (SAR per 100 person years = 2.98 vs 9.40, hazard ratio [HR] = 0.46, 95% CI: 0.30 to 0.70), and a smaller reduction from post-first dose healthcare workers (SAR per 100 person years =5.93 vs 9.40, HR = 0.70, 95% CI: 0.63 to 0.78), compared with unvaccinated healthcare workers
- there was a non-significant reduction in the rate of COVID-19 associated hospitalisation of unvaccinated household members in households with post- second dose healthcare workers (HR = 0.68, 95% CI: 0.17 to 2.83), and in households with post-first dose healthcare workers (hospitalisation rate per 100 person years = 0.35 vs 0.51, HR = 0.77, 95% CI: 0.53 to 1.10), compared with households with unvaccinated healthcare workers

European studies

A retrospective cohort study by Braeye and others (rated as medium quality, n=131,283 index cases and n=301,741 contacts) assessed the transmission of COVID-19 from index cases identified from national testing to their high risk contacts (93.3% unvaccinated) in Belgium from January to June 2021, when the Alpha variant was becoming dominant (33% to 88% of sequenced cases during the study) (41). 'High risk contact' was defined as more than 15 minutes at less than 1.5m without face coverings or direct physical contact with an infected person and the COVID-19 status of index cases and contacts was confirmed by RT-PCR. Fully vaccinated index cases (n=990, 0.8%) had 2 doses of the Pfizer, AstraZeneca, Moderna vaccines or one dose of Janssen vaccine at least 14 days before last contact, and partially vaccinated index cases (n=3,513, 2.7%) had one dose of a 2 dose vaccine at least 14 days before last contact.

There was a 62% reduction in transmission to high risk contacts from index cases fully vaccinated with the Pfizer vaccine (n=908, 0.7%) compared with unvaccinated index cases (relative risk [RR] reduction = 62%, 95% credible interval [CrI]: 57% to 67%), and a much smaller reduction (16%) in transmission from index cases partially vaccinated with the Pfizer vaccine (n=1,264, 1.0%) (RR reduction = 16%, 95% CrI: 8% to 22%). Few index cases were fully or partially vaccinated with other vaccines (Moderna, AstraZeneca, Janssen), except for partial vaccination with AstraZeneca (n=2,121, 1.6%), which had little evidence for an effect on transmission (RR reduction = -3%, 95% CrI: -10% to 2%).

When looking at the vaccination status of contacts rather than index cases, there was a reduction in transmission from unvaccinated index cases to high risk contacts who were fully vaccinated with the Moderna (n=652, 0.2%) and Pfizer (n=7,275, 2.4%) vaccines compared with unvaccinated high risk contacts (Moderna: RR reduction = 85%, 95% CrI: 79% to 90%; Pfizer: RR reduction = 74%, 95% CrI: 72% to 76%; few participants were fully vaccinated with Janssen

or AstraZeneca), and a smaller reduction in transmission from high risk contacts partially vaccinated with the Moderna (n=507, 0.2%), Pfizer (n=4,444, 1.5%) and AstraZeneca vaccines (Moderna: RR reduction = 65%, 95% CrI: 57% to 81%; Pfizer: RR reduction = 41%, 95% CrI: 37% to 45%; AstraZeneca: RR reduction = 31%, 95% CrI: 27% to 35%).

A retrospective cohort study by De Gier and others (rated as medium quality, n=113,582 index cases, n=253,168 contacts) assessed the transmission of COVID-19 from adult index cases identified from national testing to their household members (n=142,540) and close contacts (n=110,628) (96% unvaccinated) in The Netherlands from February to May 2021, when the Alpha variant was dominant (42). Fully vaccinated was defined as at least 7 days after the second dose of the Pfizer, AstraZeneca or Moderna vaccine or at least 14 days after a single dose of Janssen vaccine (n=622, 0.5% of index cases), and partially vaccinated was defined as having received the first dose of a 2 dose vaccine (n=2,088, 1.8% of index cases).

There was a 71% reduction in COVID-19 transmission to household members from index cases fully vaccinated with any vaccine compared with unvaccinated index cases (SAR = 11% vs 31%, RR reduction = 71%, 95% CI: 63% to 77%), and a smaller and 22% reduction (non-significant) to close contacts (SAR = 11% vs 9%, RR reduction = 22%, 95% CI: -5% to 43%). The results were similar when restricting to unvaccinated household members (RR reduction = 73%, 95% CI: 65% to 79%) and close contacts (RR reduction = 24%, 95% CI: -5% to 45%).

When looking at the vaccination status of contacts, there was a 75% reduction in COVID-19 transmission from index cases to fully vaccinated (any vaccine) household members (RR reduction = 75%, 95% CI: 72% to 78%) and a 79% reduction to other close contacts (RR reduction = 79%, 95% CI: 74% to 83%) compared with unvaccinated household members and other close contacts. There was little evidence of differences in the effectiveness of specific vaccines when fully vaccinated (either for index cases or contacts), though the precision of the results was low.

Finally, partial vaccination of index cases, household contacts and other close contacts were much less effective than full vaccination at reducing transmission (see Table 1).

A further retrospective cohort study by De Gier and others conducted later in the pandemic (preprint, rated as medium quali ty, n=4,912 index cases, n=7,771 contacts) assessed the transmission of COVID-19 from adult index cases identified from national testing to their household members (37.8% unvaccinated) in The Netherlands from August to September 2021, when the Delta variant was dominant (more than 85% sequenced isolates in July) (34). Fully vaccinated (n=1,740, 35.4% of index cases) and partially vaccinated (n=540, 11.0% of index cases) were defined as above, though results were not given for specific vaccines. The results suggested that:

- there was a 63% reduction in COVID-19 transmission to fully vaccinated household members from index cases fully vaccinated with any vaccine compared with unvaccinated index cases (SAR = 12% vs 11%, RR reduction = 63%, 95% CI: 46% to

75%), and a 40% reduction in transmission to unvaccinated household members (SAR = 13% vs 22%, RR reduction = 40%, 95% CI: 20% to 54%)
- there was a 38% reduction (non-significant) in COVID-19 transmission to fully vaccinated household members for index cases partially vaccinated with any vaccine compared with unvaccinated index cases (RR reduction = 38%, 95% CI: - 2% to 62%), and a 46% reduction in transmission to unvaccinated household members (RR reduction = 46%, 95% CI: 20% to 63%)

A retrospective cohort study by Meyer and others (preprint, rated as medium quality, n=14 index cases, n=27 household contacts) assessed the transmission of COVID-19 from staff working in a single care home (index cases) during a COVID-19 outbreak (Alpha variant in 96% of samples tested) to their household members (66.7% unvaccinated) in Germany from January to March 2021 (35). COVID-19 status was confirmed by RT-PCR, and 35.7% of staff had been vaccinated with the Pfizer vaccine (it was not stated if all vaccinated staff had 2 doses). The results suggested that there was a reduction in COVID-19 transmission to household members from vaccinated compared with unvaccinated staff members (SAR = 22% vs 67%, p for difference: 0.046).

A retrospective cohort study by Salo and others (preprint, rated as medium quality, n=288,138 healthcare workers, n=163,766 spouses) assessed the transmission of COVID-19 from healthcare workers (index cases) identified from a national registry to their unvaccinated spouses living in the same household in Finland from December 2020 to March 2021 (dominant COVID-19 variant not stated) (36). COVID-19 status was determined by RT-PCR, and vaccinated was defined as having at least one dose of the Pfizer or Moderna vaccines (33.0% of healthcare workers were vaccinated, more than 40% received their second dose 4 weeks after their first). As this study looked at all healthcare workers, not just those with a confirmed COVID-19 infection, these results include the effect of vaccines on preventing COVID-19 infection as well as on reducing transmission from index cases with COVID-19, and so will overestimate the vaccine effectiveness against transmission from index cases.

The results suggested that there was a 8.7% reduction (non-significant) in COVID-19 transmission to spouses for vaccinated (either vaccine, 2 weeks after the first vaccine dose) compared with unvaccinated healthcare workers (SAR not reported, RR reduction = 8.7%, 95% CI: -28.9% to 35.4%), but a much larger reduction of 42.9% 10 weeks after the first vaccine dose (SAR not reported, RR reduction = 42.9%, 95% CI: 22.3% to 58.1%).

Israel studies

A retrospective cohort study by Gazit (preprint, rated as medium quality, n=4,024 households with an index case identified by national testing, 2 adults and no children in a household and no prior infections) assessed transmission of COVID-19 from index cases (7.5% unvaccinated) to the other household members (13.5% unvaccinated) from December 2020 to March 2021 (dominant COVID-19 variant not stated) (37). The COVID-19 status of index cases and other

household members was confirmed by RT- PCR. Only household contacts with a positive test within 10 days of the diagnosis of the index case were considered. Fully vaccinated was defined as at least 7 days after the second dose of the Pfizer vaccine (n=2,827, 70.3% of other household members).

The results suggested that when looking at the vaccination status of contacts rather than index cases, there was an 80.0% reduction in COVID-19 transmission from index cases (of any vaccination status) to fully vaccinated compared with unvaccinated other household members (SAR = 7.5% vs 37.5%, RR reduction = 80.0%, 95% CI: 73.0% to 85.1%), and an 82.0% reduction in transmission to fully vaccinated compared with recently vaccinated household members (SAR = 7.5% vs 41.7%, RR reduction = 82.0%, 95% CI: 75.5% to 86.7%).

A prospective cohort study by Layan (preprint, rated as medium quality, n=215 index cases, n=687 household contacts) assessed transmission of COVID-19 from index cases (more than 12 years old) to their household contacts from December 2020 to April 2021, when the Alpha variant was dominant (~90% transmission). Participants were recruited from a total of 12,518 healthcare workers and their household contacts, and COVID-19 status was confirmed by RT-qPCR. 'Vaccinated' was defined as at least 7 days after the second dose of the Pfizer vaccine (n=15, 7.0% of index cases, and n=124, 18.0% of household contacts). The results suggested that:

- there was a 78% reduction in COVID-19 transmission to household contacts from vaccinated compared with unvaccinated index cases (SAR = 18.6% vs 40.7%, RR reduction = 78%, 95% CrI: 30% to 94%) when looking at the vaccination status of contacts rather than index cases, there was a 93% reduction in COVID-19 transmission from index cases to vaccinated adult and teenage household contacts who isolated (SAR = 10.8% vs 75.0%, RR reduction = 93%, 95% CrI: 83% to 97%) and an 81% reduction to vaccinated adult and teenage household contacts who did not isolate (SAR = 25.6% vs 75.0%, RR reduction = 81%, 95% CrI: 60% to 93%) compared with unvaccinated adult and teenage household contacts who did not isolate
- the authors estimated that the probability of COVID-19 transmission in a 4 person household was 59.2% if both the index case and household contact were unvaccinated (95% CrI: 46.4% to 70.2%), and 3.6% if both the index case and household contact were vaccinated (95% CrI: 0.7% to 12.8%)

A retrospective cohort study by Prunas (preprint, rated as low quality, n=253,564 individuals in n=65,624 households with at least one COVID-19 case and at least 2 household members) assessed the effect of vaccination on transmission of COVID-19 from index cases identified by national testing to their household contacts (vaccination status not reported) from June 2020 to March 2021 (dominant COVID-19 variant not stated) (39). COVID-19 status was determined by RT-PCR. 'Vaccinated' was defined as at least 10 days from receiving the second dose of the Pfizer vaccine. The study authors developed 2 discreet time-to-event data models of household transmission to estimate vaccine effectiveness against susceptibility to infection and against

infectiousness given infection; we present the results for the primary transmission model only. The results suggested that:

- there was a 41.3% reduction in COVID-19 infectiousness (chance of COVID-19 transmission to household members) in vaccinated compared with unvaccinated index cases (SAR not reported, RR reduction = 41.3%, 95% CrI: 9.5% to 73.0%)

China studies

A retrospective cohort study by Kang (preprint, rated as medium quality, n=73 index cases, n=5,153 close contacts) assessed the effect of vaccination on transmission of COVID-19 from index cases with the Delta variant identified from laboratory testing to the close contacts (55.2% unvaccinated) in Guangdong Province, China, from May to June 2021 (40). COVID-19 status confirmed by RT-PCR for both index cases and close contacts, and close contacts were defined as individuals (household and extended family, social, community and healthcare contacts that were within one metre of an index case during an infective period without proper personal protective equipment) exposed to symptomatic index cases from 2 days before the index case's illness onset or exposed to asymptomatic index cases at close proximity from 2 days before the index case's first positive test. Fully vaccinated (specific vaccine not specified) was defined as at least 14 days after the second dose (n=16, 9.6% of index cases), and partially vaccinated was defined at least 10 days after the first dose (n=30, 18.0% of index cases).

The results suggested that there was a reduction in COVID-19 transmission to close contacts from fully vaccinated compared with unvaccinated index cases (SAR = 0.4% vs 1.3%, OR = 0.35, 95% CI: 0.12 to 0.84), and from fully vaccinated compared with partially vaccinated index cases (SAR = 0.4% vs 2.8%, OR = 0.17, 95% CI: 0.06 to 0.41).

Risk of bias

All transmission studies were observational, comparing people who were vaccinated, either fully or partially, against those that were not. There is a high risk in all these studies that factors other than vaccination affected the results, as people who are vaccinated are likely to be different in many ways than people who are unvaccinated. For example, people who are vaccinated may engage more or less with other behaviours intended to reduce transmission of COVID-19, such as face covering use, hand washing, social distancing and isolation after contact with someone with COVID-19, or after receiving a positive COVID-19 test result. Some people who are vaccinated may be more likely to adhere to guidance designed to reduce transmission of COVID-19, while others may be less likely to adhere to guidance as they feel protected by the vaccine. People who are vaccinated may also be different in terms of age, sex, socioeconomic status and chronic health conditions and may also have different testing behaviour from those who are unvaccinated. Some studies accounted for this reasonably well, so have a lower risk of bias (23 to 26), though a risk of bias remains for any factors (particularly behavioural) not fully

accounted for in these studies. Other studies did not account for this at all so have a much larger risk of bias (35, 37). This bias may affect the results in either direction.

No study established without doubt that transmission occurred from the index case to a contact, rather than the reverse or from transmission from another person. Bias may have occurred in either direction in any study that incorrectly assumed that transmission was from the index case to secondary case, particularly if this more commonly occurred in either the vaccinated or unvaccinated groups. Transmission from other people besides the index case may have reduced the estimates of vaccine effectiveness in any study.

Many studies did not test all contacts for COVID-19 and relied on individuals reporting their own test results, which were taken for a number of reasons, including symptoms and contact with those with positive COVID-19 tests. This means asymptomatic secondary cases may have been missed, which may have spuriously increased the vaccine effectiveness against transmission, particularly if vaccination of index cases reduced symptoms in secondary cases. Additionally, the results may be biased in either direction if the likelihood of being tested was different between vaccinated and unvaccinated secondary cases for any reason.

Finally, many of studies were heterogeneous in terms of their location, prevalence of COVID-19 in the community, prevalence of past infections, dominant variant, background mitigations in place to limit transmission (including both local restrictions and personal protective measures), vaccination status of contacts, and availability of the vaccine to different groups, as well as the demographics of the index cases, household members and other close contacts. This makes direct comparison between studies and specific vaccines difficult.

Main findings

There was evidence across 13 observational transmission studies, conducted between Winter 2020 and Summer 2021, that fully vaccinated index cases transmitted COVID-19 less to their household and other contacts than unvaccinated index cases, particularly for pre-Delta variants. This reduction in transmission to contacts from fully vaccinated index cases was substantial in many studies (for example, a relative risk reduction in transmission of more than 50%, or an OR, RR, HR or rate ratio for transmission of less than 0.5) (24 to 27, 34, 37, 38, 40 to 42), though the reductions were smaller for some studies and different vaccines (27, 34, 39, 41, 42), or inconclusive due to a small number of secondary cases (23). In most studies assessing both partial and full vaccination of index cases, partial vaccination was markedly less effective for reducing transmission than full vaccination (23, 27, 34, 41, 42), though there was less of a difference in other studies (34, 41). In one study, the transmission of COVID-19 to household contacts was reduced if the contacts were isolated from the index case, even when the contacts were fully vaccinated.

The evidence was more mixed for the Delta variant. All 3 Delta studies suggested that fully vaccinated cases transmitted COVID-19 less than unvaccinated cases, but there was evidence

that this reduction in transmission decreased as time since the second dose of vaccine increased. A large study in England suggested that vaccine effectiveness against transmission of the Delta variant drops substantially in the 12 weeks after the index case is fully vaccinated. This study also suggested that vaccination of the index case was less effective against transmission for the Delta variant compared with the Alpha variant, and the reduction in effectiveness over time was larger for Delta then for Alpha.

A study from the Netherlands suggested similar results for the Delta variant, as the effectiveness against transmission of the Delta variant dropped 60 days after the index case is fully vaccinated (when looking at fully vaccinated household contacts).

All transmission studies were observational, comparing people who were vaccinated, either fully or partially, against those that were not, and so there is likely bias in either direction as differences between people who are vaccinated and unvaccinated were unlikely to be fully accounted for in any study. Additionally, many of studies were heterogeneous, which makes direct comparison between studies and specific vaccines difficult.

Table 1. Summary of findings from transmission studies

There are 6 tables.

[A] indicates studies which looked at all healthcare workers, not just those with a confirmed COVID-19 infection, so these results include the effect of vaccines on preventing COVID-19 as well as on reducing transmission from index cases with COVID-19.

The following acronyms are used: CI = confidence interval or credible interval, HR = hazard ratio, NA = not applicable, NR = not reported, OR = odds ratio, RR = relative risk, SAR = secondary attack rate.

1a. Vaccination of index cases on COVID-19 transmission to household contacts (effect estimates by index case vaccination status)

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome	Effect estimate (95% CI)		
					Unvaccinated	Partially vaccinated	Fully vaccinated
Allen (23)	UK, March to May 2021, Alpha	Household members, not stated	AstraZeneca or Pfizer	OR for transmission	Reference	0.94 (0.81 to 1.08)	0.76 (0.44 to 1.31)
De Gier (42)	The Netherlands, February to May 2021, Alpha	Household contacts, 96% unvaccinated	Any	SAR	31%	29%	11%
				RR reduction for transmission	Reference	21% (9% to 33%)	71% (63% to 77%)
			AstraZeneca		Reference	15% (4% to 26%)	58% (12% to 84%)
			Janssen		Reference	-	77% (6% to 94%)
			Moderna		Reference	51% (8% to 74%)	88% (50% to 97%)
			Pfizer		Reference	26% (12% to 37%)	70% (61% to 77%)
De Gier (34)	The Netherlands, August to September 2021, Delta	Household contacts, 100% unvaccinated	Any	SAR	22%	17%	13%
				RR reduction for transmission	Reference	46% (20% to 63%)	40% (20% to 54%)
				SAR (more than or equal to 60 days after second dose)	22%	-	15%
				RR reduction for transmission (more than or equal to 60 days after second dose	Reference	-	55% (19% to 76%)
		Household contacts, 0% unvaccinated		SAR	11%	6%	12%
				RR reduction for transmission	Reference	38% (-2% to 62%)	63% (46% to 75%)
				SAR (more than or equal to 60 days after second dose)	11%	-	20%
				RR reduction for transmission more than or equal to 60 days after second dose)	Reference	-	28% (-4% to 50%)
Harris (24, 25)	UK, January to February 2021, Alpha	Household members, 100% unvaccinated	AstraZeneca	SAR	10.1%	5.7%	
				OR for transmission	Reference	0.53 (0.43 to 0.63)	
			Pfizer	SAR	10.1%	6.2%	
				OR for transmission	Reference	0.51 (0.44 to 0.59)	
Layan (38)	Israel, December 2020 to April 2021, Alpha	Household members, 82% unvaccinated	Pfizer	SAR	40.7%	-	18.6%
				RR reduction for transmission	Reference	-	78% (30% to 94%)

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome		Effect estimate (95% CI)		
						Unvaccinated	Partially vaccinated	Fully vaccinated
Meyer (35)	Germany, January to March 2021, Alpha	Household members, 67% unvaccinated	Pfizer	SAR		67%	22%	
Prunas (39)	Israel, June 2020 to March 2021, NR	Household members, NR	Pfizer	RR reduction for infectiousness		Reference	-	41% (10% to 73%)
Salo (36) [A]	Finland, December 2020 to March 2021, NR	Household members (spouses), 100% unvaccinated	Pfizer, Moderna	RR reduction for transmission weeks after first dose	2 weeks	Reference	9% (-29% to 35%)	-
					10 weeks	Reference	43% (22% to 58%)	-
Shah (26) [A]	UK, December 2020 to March 2021, NR	Household members, 100% unvaccinated	AstraZeneca or Pfizer	SAR per 100 person years (partially vaccinated = partially or fully vaccinated)		9.40	5.93	2.98
				HR for transmission (partially vaccinated = partially or fully vaccinated)		Reference	0.70 (0.63 to 0.78)	0.46 (0.30 to 0.70)

1b. Vaccination of index cases on COVID-19 transmission to close contacts (effect estimates by index case vaccination status)

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome	Effect estimate (95% CI)		
					Unvaccinated	Partially vaccinated	Fully vaccinated
Braeye (41)	Belgium, January to June 2021, Alpha	High risk contacts, 93% unvaccinated	AstraZeneca	RR reduction for transmission	Reference	-3% (-10% to 2%)	8% (-79% to 63%)
			Janssen		Reference	NA	27% (-23% to 62%)
			Moderna		Reference	41% (23% to 57%)	52% (22% to 69%)
			Pfizer		Reference	8% (-79% to 63%)	16% (8% to 22%)
De Gier (42)	The Netherlands, February to May 2021, Alpha	Other close contacts, 96% unvaccinated	Any	SAR	11%	10%	9%
				RR reduction for transmission	Reference	22% (9% to 33%)	22% (5% to 43%)
Kang (40)	China, May to June 2021, Delta	Close contacts, 55% unvaccinated	NR	SAR	1.3%	2.5%	0.4%
				OR for transmission	Reference	-	0.35 (0.12 to 0.84)

1c. Vaccination of index cases on COVID-19 transmission to household and other contacts (effect estimates by index case vaccination status)

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome		Effect estimate (95% CI)		
						Unvaccinated	Partially vaccinated	Fully vaccinated
Eyre (27)	England, January to July 2021, Alpha or Delta	All contacts, 45% unvaccinated	AstraZeneca	SAR		46%	35%	28%
			Pfizer			46%	26%	21%
	England, January to July 2021, Alpha		AstraZeneca	Rate ratio for transmission		Reference	0.90 (0.86 to 0.94)	0.48 (0.30 to 0.78)
			Pfizer			Reference	0.88 (0.85 to 0.91)	0.32 (0.21 to 0.48)
			AstraZeneca	Reduction in transmission, weeks after second dose	2 weeks	-	-	52% (22% to 70%)
					12 weeks	-	-	38% (-1% to 62%)
			Pfizer		2 weeks	-	-	68% (52% to 79%)
					12 weeks	-	-	52% (29% to 67%)
	England, January to July 2021, Delta		AstraZeneca	Rate ratio for transmission		Reference	0.95 (0.91 to 0.99)	0.76 (0.70 to 0.82)
			Pfizer			Reference	0.83 (0.81 to 0.86)	0.50 (0.39 to 0.65)
			AstraZeneca	Reduction in transmission, weeks after second dose	2 weeks	-	-	24% (18% to 30%)
					12 weeks	-	-	2% (-2% to 6%)
			Pfizer		2 weeks	-	-	50% (35% to 61%)
					12 weeks	-	-	24% (20% to 28%)

1d. Vaccination of contacts on COVID-19 transmission to household contacts (effect estimates by contact vaccination status)

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome	Effect estimate (95% CI)		
					Unvaccinated	Partially vaccinated	Fully vaccinated
De Gier (42)	The Netherlands, February to May 2021, Alpha	Household contacts, 98% unvaccinated index cases	Any	RR reduction for transmission	Reference	23% (14% to 50%)	75% (72% to 78%)
			AstraZeneca		Reference	2% (-11% to 14%)	87% (77% to 93%)
			Janssen		Reference	NA	12% (-71% to 54%)
			Moderna		Reference	33% (-27% to 64%)	91% (79% to 97%)
			Pfizer		Reference	-18% (-43% to 2%)	65% (60% to 70%)
Gazit (37)	Israel, December to March 2021, NR	Household members, 8% unvaccinated index cases	Pfizer	SAR	37.5%	41.7%	7.5%
				RR reduction for transmission	Reference	-	80% (73% to 87%)
Layan (38)	Israel, December 2020 to April 2021, Alpha	Household members, 92% unvaccinated	Pfizer	SAR (fully vaccinated contacts who isolated vs unvaccinated contacts who did not isolate)	75.0%	-	10.8%
				RR reduction for transmission (fully vaccinated contacts who isolated vs unvaccinated contacts who did not isolate)	Reference	-	93% (83% to 97%)

1e. Vaccination of contacts on COVID-19 transmission to other contacts (effect estimates by contact vaccination status)

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome	Effect estimate (95% CI)		
					Unvaccinated	Partially vaccinated	Fully vaccinated
Braeye (41)	Belgium, January to June 2021, Alpha	High risk contacts, 100% unvaccinated index cases	AstraZeneca	RR reduction for transmission	Reference	31% (27% to 35%)	55% (11% to 82%)
			Janssen		Reference	NA	57% (21% to 81%)
			Moderna		Reference	65% (57% to 81%)	85% (79% to 90%)
			Pfizer		Reference	41% (37% to 45%)	74% (72% to 76%)
De Gier (42)	The Netherlands, February to May 2021, Alpha	Other close contacts, 98% unvaccinated index cases	Any	RR reduction for transmission	Reference	28% (17% to 38%)	79% (74% to 84%)

1f. Vaccination of contacts on COVID-19 transmission to household and other contacts (effect estimates by contact vaccination status)

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome	Effect estimate (95% CI)		
					Unvaccinated	Partially vaccinated	Fully vaccinated
Eyre (27)	England, January to July 2021, Alpha or Delta	All contacts, 55% unvaccinated index cases	AstraZeneca	SAR	52%	32%	22%
			Pfizer		52%	32%	17%
	England, January to July 2021, Alpha		AstraZeneca	Rate ratio for transmission	Reference	0.94 (0.91 to 0.98)	0.40 (0.27 to 0.59)
			Pfizer		Reference	0.85 (0.82 to 0.88)	0.15 (0.11 to 0.21)
	England, January to July 2021, Delta		AstraZeneca		Reference	0.69 (0.66 to 0.72)	0.42 (0.38 to 0.45)
			Pfizer		Reference	0.67 (0.65 to 0.69)	0.19 (0.16 to 0.23)

Evidence on viral load in those who develop COVID-19 infection after being fully vaccinated

Two RCTs and 30 observational studies (12 preprints, 2 rated as low (29, 43), 29 as medium, and one as high quality (27)) provided evidence on viral load, usually through measuring cycle threshold (Ct) values in vaccinated and unvaccinated people with COVID-19. The Ct value represents the number of cycles of RT-PCR needed to reach the threshold for virus detection, so a higher Ct value is indicative of a lower viral load (every unit increase in Ct value represents a halving of viral load on average) (44).

However, Ct values are unlikely to be directly comparable across studies, as Ct values differ by laboratory and assay type. Ct values also do not indicate that the virus is infectious, meaning lower Ct values do not necessarily indicate higher infectivity, and vice versa. Ct values are also sensitive to how long after being infected the RT-PCR is performed, as viral load rise to a peak, before gradually clearing as the infection is resolved.

The 32 viral load studies assessed difference in viral load between vaccinated and unvaccinated people who developed COVID-19, usually by measurement of Ct values. Of these 32 studies, 2 were secondary analyses of RCTs (3, 28), 27 were cohort studies (27, 29 to 33, 40, 43, 45 to 63) and 3 were case-control or case-case studies (64 to 66).

Seven studies provided data from the UK (3, 27, 29 to 33), 13 from the US (28, 43, 48, 49, 51, 52, 55 to 57, 60 to 63), 4 from Europe (45, 46, 50, 65), 4 from Israel (53, 54, 58, 59), one from Qatar (64), and 3 from Asia (40, 47, 66), all between summer 2020 and summer 2021. Twenty-three studies produced results for the wild-type, Alpha and other non-Delta variants or did not report the variant (3, 27, 28, 30 to 33, 43, 45, 50, 51, 54 to 59, 62 to 65) and 16 studies produced results for the Delta variant (27, 29, 32, 40, 43, 46 to 49, 52, 53, 55, 60, 61, 65, 66). As above, while studies reporting different time periods may be distinct enough that caution does not have to be used when interpreting the results, studies covering the same time period and location may include the same participants and therefore caution must be used to avoid double counting the same data.

Table 2 shows a summary of all viral load studies and their results, and Supplementary Table 2 shows all characteristics of all viral load studies.

Viral load (Ct values)

There were 23 studies that looked at wild-type (the original strain of COVID-19) and non- Delta variants of COVID-19, comparing Ct values or viral load between vaccinated and unvaccinated cases. Twenty of these studies compared fully vaccinated and unvaccinated cases, and 3

studies only compared partially vaccinated and unvaccinated cases. Twenty studies looked at the Pfizer vaccine, 9 studies the Moderna vaccine, 5 studies the AstraZeneca vaccine and 3 studies the Janssen vaccine, though in many studies cases had a mixture of vaccines and results were not split by the vaccine type. Twenty-two studies looked at the difference between mean or median Ct values, and 2 studies looked at the difference in viral load (one study looked at both).

Most studies suggested that fully vaccinated cases (symptomatic, asymptomatic or both) had higher Ct values (by between one and 7 across all studies, suggesting 50% to 99% lower viral loads) or lower viral loads (the one study measuring viral load directly suggested 40% lower viral loads) than unvaccinated cases (3, 27, 28, 31, 32, 43, 45, 46, 51, 56, 58, 59, 62 to 65), though 4 studies suggested no meaningful difference in Ct values (50, 55, 57, 61). Results were mixed for symptomatic infections, as Ct values were higher (by about 5 across studies, suggesting 97% lower viral loads) in fully vaccinated compared with unvaccinated cases in 4 studies (3, 27, 28, 64), but similar in 3 studies (46, 61, 64). In one study (64), cases vaccinated with the Moderna vaccine had higher Ct values than unvaccinated cases, but cases vaccinated with the Pfizer vaccine did not.

However, in all 4 studies looking at asymptomatic cases, Ct values were higher (by between 1 and 6 across studies, suggesting 50% to 98% lower viral loads) in fully vaccinated compared with unvaccinated cases (46, 61, 62, 64). Studies comparing partially vaccinated and unvaccinated cases with wild-type and non-Delta variants also tended to suggest lower Ct values in the partially vaccinated cases (30, 32, 33, 43, 54, 62, 65), although Ct values tended to be higher in partially vaccinated compared with fully vaccinated cases when studies measured both.

The difference in Ct values between fully vaccinated and unvaccinated cases were much more mixed in the 16 studies that looked at the Delta variant of COVID-19. Of these studies, 10 looked at the Pfizer vaccine, 6 studies the Moderna vaccine, 2 studies the AstraZeneca vaccine, 5 studies the Janssen vaccine, and one study the Sinovac and Sinopharm vaccines, though few studies had results split by vaccine type. Fourteen studies looked at the difference between mean or median Ct values, while no studies looked at the difference in viral load directly.

Eight Delta variant studies suggested that fully vaccinated cases (symptomatic, asymptomatic or both) had similar Ct values to unvaccinated cases (27, 32, 43, 47, 52, 55, 60, 61), 4 studies suggested fully vaccinated cases had higher Ct values (by between 0.2 and 4 across studies, suggesting 13% to 94% lower viral loads) than unvaccinated cases (29, 40, 53, 65), and one study suggested fully vaccinated cases had lower Ct values (by around 1.5, suggesting 2.8 times higher viral load) than unvaccinated cases (48). In all 3 studies looking at symptomatic infections, Ct values were similar in fully vaccinated compared with unvaccinated cases (27, 46, 60). However, for asymptomatic cases, one study suggested Ct values were higher (by 1.4, 95% CI: 0.6 to 2.2, suggesting 34% to 78% lower viral load) in fully vaccinated compared with unvaccinated cases (46), and 1 study suggested similar Ct values (60). Studies comparing partially vaccinated and unvaccinated cases with the Delta variant also tended to suggest

similar Ct values in the partially vaccinated and unvaccinated cases (32, 43, 65), although one study suggested that Ct values were higher in partially vaccinated compared with unvaccinated cases (p=0.04) (29).

Only one study looked at the effect of booster vaccination on Ct values with the Delta variant (53), in Israel between May and June 2021. This study suggested that people who developed COVID-19 after a booster dose of Pfizer had higher Ct values (by 2.4, 95% CI: 2.0 and 2.9, suggesting a 74% to 85% lower viral load) than unvaccinated people who developed COVID-19.

Viral load (Ct values, time since vaccination)

One study, conducted in Israel between May and June 2021, assessed Ct values of Delta variant cases by time since the second dose of Pfizer vaccine, and found that Ct values of fully vaccinated cases were much higher than unvaccinated cases soon after the second dose, but the difference reduced with increasing time, from 4.56 (95% CI: 2.19 to 6.94, suggesting a 78% to 99% lower viral load) after 7 to 30 days, to 2.63 (95% CI: 0.67 to 4.59, suggesting a 37% to 96% lower viral load) after 31 to 60 days, 0.58 (95% CI: 0.05 to 1.12, suggesting a 3% to 54% lower viral load) after 61 to 120 days, and 0.06 (95% CI: -0.16 to 0.29, suggesting a 18% lower to 12% higher viral load) after more than 180 days (53).

Viral load (time to viral clearance)

One study assessed Ct values over time during an infection, comparing sequential Ct values in fully vaccinated and unvaccinated Alpha variant cases (28). The results suggested viral clearance was quicker for fully vaccinated (median of 4 days) compared with unvaccinated cases (median of 7 days). The difference in Ct values was highest on the first day after symptom onset (by around 7, suggesting a 99% lower viral load) but reduced over time (after 7 days, for example, by around 4, suggesting a 94% lower viral load), until the Ct values were very similar 14 days after symptom onset. A similar study compared predicted sequential Ct values in fully vaccinated and unvaccinated Delta variant cases from a generalised additional model (40). The results were not compared statistically, but fully vaccinated cases had slightly higher predicted Ct values on the day of symptom onset, 8 days after symptom onset, and 16 days after symptom onset (by between 1 and 2, suggesting 50% to 75% lower viral loads).

One study conducted weekly RT-qPCR testing, comparing both the mean duration of viral RNA detection between fully vaccinated and unvaccinated Alpha variant cases (63). The results suggested viral RNA detection was shorter by a mean of 6.2 days (95% CI: 4.0 to 8.4 days) for fully vaccinated (mean of 2.7 days, standard deviation [SD]: 3 days) compared with unvaccinated cases (mean of 8.9 days, SD: 10.2 days). A similar study compared the median time interval between symptom onset and last positive test between fully vaccinated and unvaccinated Delta variant cases using serial RT-PCR tests (49). Although the time interval between symptom onset and last positive RT-PCR test was slightly shorter for fully vaccinated

(median of 9 days, interquartile range [IQR]: 8 to 10 days) compared with unvaccinated cases (median of 11 days, IQR: 3 to 15 days), this difference was not statistically significant (p=0.37).

Infectious viral load (cytopathic effects)

One study measured whether Alpha variant viral load was infectious by measuring the cytopathic effect (CPE) of viral samples, assessing whether a viral sample from a COVID-19 case can measurably infect and damage cells in a laboratory (57). This study suggested that far fewer fully vaccinated cases had infective virus samples (18.5%) than unvaccinated cases (64.5%, p<0.00001). Three further studies measured the CPE of Delta variant cases, but suggested the proportion of infectious samples were very similar between fully vaccinated and unvaccinated cases (between 38% to 95% across the studies), although none of the studies tested these differences statistically (49, 55, 60).

Risk of bias

As with the transmission studies, all viral load studies were observational, comparing people who were either fully or partially vaccinated against those that were not, and as such have a similar risk of bias as people who are vaccinated are likely to be different in many ways than people that are not vaccinated. One study accounted for some differences between vaccinated and unvaccinated people reasonably well (27), though some risk of bias remains. All other studies did not account for this bias well, and the results may therefore be affected in either direction. Vaccinated people may also have different test seeking behaviour from unvaccinated people, which is particularly problematic for viral load as it changes over time, increasing after infection then decreasing with recovery. As almost all studies only measured Ct values once after infection, there may be systematic bias in the results if vaccinated and unvaccinated people are more likely to have Ct values taken at different points in their illness.

Vaccination may also affect symptoms of COVID-19, meaning the proportion of vaccinated and unvaccinated people who had COVID-19 but did not receive a test may be different. This may affect the results in either direction, as few studies tested all participants in a population, including only people that requested a test (for any reason), which likely meant that symptomatic cases were found more frequently than asymptomatic cases, and the viral loads of symptomatic and asymptomatic cases tended to be different in the studies that measured both. However, this risk of bias was reduced in studies that included only symptomatic or asymptomatic cases, or studies that split their analyses by symptom status. Studies that screened participants by testing everyone regardless of symptoms status also reduced this risk of bias.

The measurement of Ct values is reasonably heterogeneous, with different laboratories using different methods, assays and cut-offs in their measurements. This may bias any of the studies where more than one laboratory was used, and it also means Ct values, or the difference in Ct values between vaccinated and unvaccinated cases, may not be comparable across studies.

Additionally, some studies had participants collect their own virus samples, whereas in others a professional may have collected the sample, although this was not recorded for most studies. As the method of sample collection may affect Ct values, this may also be a source of bias in these studies.

As with the transmission studies, many viral load studies were heterogeneous, which makes direct comparison between studies and specific vaccines difficult.

Main findings

Evidence from across the 32 viral load studies was broadly supportive of the transmission studies. The 20 studies that looked at fully vaccinated cases with wild-type and non-Delta variants of COVID-19 typically suggested that fully vaccinated cases had higher Ct values than unvaccinated cases (and so likely a lower viral load). However, the results of studies looking at the Delta variant were more mixed, with 8 studies suggesting similar Ct values between fully vaccinated and unvaccinated cases, 4 studies suggesting fully vaccinated cases had higher Ct values than unvaccinated cases, and one study suggesting fully vaccinated cases had lower Ct values than unvaccinated cases. One study also suggested that people who contracted Delta variant COVID-19 after a booster dose of Pfizer had higher Ct values (indicating lower viral load) than unvaccinated people who contracted COVID-19.

One study found that Ct values of fully vaccinated cases were much higher than unvaccinated cases soon after the second dose, but the difference reduced with increasing time.

Three studies suggested the infectivity of samples were very similar between fully vaccinated and unvaccinated cases with the Delta variant, although none of the studies tested these differences statistically.

Table 2. Summary of findings from studies reporting viral load
There are 5 tables.

The following acronyms are used: CI = confidence interval, CPE = cytopathic effect (that is, infectious virus), IQR = interquartile range, NR = not reported, SD = standard deviation. When a difference is not reported, a p value presented instead (if reported).

2a. Booster vaccinated, Delta variant dominant

Study	Country, time, dominant variant	Vaccine	Outcome	Effect estimate		
				Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
Levine-Tiefenbrun (53)	Israel, June to September 2021, Delta (93%)	Pfizer	Mean Ct value	27.7 (5.0)	29.1 (4.7)	2.43 (1.97 to 2.89)

2b. Fully vaccinated, Delta variant dominant

Study	Country, time, dominant variant	Vaccine	Outcome	Effect estimate		
				Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
Blanquart (46)	France, June to July 2021, Delta (91%)	NR	Difference in Ct value (symptomatic)	-	-	-0.25 (-0.96 to 0.46)
			Difference in Ct value (asymptomatic)	-	-	1.68 (1.03 to 2.33)
	France, June to July 2021, Delta (100%)		Difference in Ct values (symptomatic)	-	-	-0.14 (-0.99 to 0.72)
			Difference in Ct values (asymptomatic)	-	-	1.42 (0.61 to 2.24)
Chia (47)	Singapore, April to June 2021, Delta (100%)	Pfizer and Moderna	Median Ct value (first positive test)	18.8 (14.9 to 22.7)	19.2 (15.2 to 22.2)	p=0.929
			Median Ct value (symptom onset)	21.9 (18.8 to 31.2)	19.2 (16.6 to 21.5)	p=0.279
Christensen (48)	US, March to August 2021, Delta (77%)	Pfizer, Moderna, Janssen	Median Ct value (Abbott assay)	22.1	20.5	p=0.0018
			Median Ct value (Hologic Panther assay)	23.5	22.2	p=0.0348
Elliott (29)	UK, June to July 2021, Delta (100%)	NR	Median Ct value	23.1 (20.3 to 25.8)	27.6 (25.5 to 29.7)	p=0.01
Eyre (27)	UK, January to July 2021, Delta (100%)	AstraZeneca	Median Ct value (symptomatic)	17.1	17.3	NR
		Pfizer		17.1	18.2	NR
		AstraZeneca	Proportion of reduction in transmission mediated via index case Ct values at diagnosis	-	-	23% (17% to 33%)
		Pfizer		-	-	7% (5% to 10%)
Griffin (43)	US, May to July 2021, Delta (more than 90%)	Janssen, Moderna, Pfizer	Median Ct value (*ORF1ab* gene)	18.8	19.0	p>0.05
			Median Ct value (*N* gene)	19.3	19.5	
			Median Ct value (*SC2N* gene)	19.3	19.4	
Hagan (49)	US, July to Aug 2021, Delta (100%)	Janssen, Moderna, Pfizer	Median time between symptom onset and last positive RT-PCR (days)	11 (3 to 15)	9 (8 to 10)	p=0.37
			Proportion of CPE positive samples	42%	38%	NR
Kang (40)	China, May to June 2021, Delta	NR	Predicted median Ct value, days — Day 0	24.5 (23.6 to 26.7)	25.5 (25.3 to 25.8)	NR

Study	Country, time, dominant variant	Vaccine	Outcome		Effect estimate		
					Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
	(100%)		after symptom onset	Day 8	27.9 (27.3 to 30.5)	29.7 (29.3 to 30.3)	NR
				Day 16	34.6 (34.0 to 36.6)	36.1 (35.9 to 36.5)	NR
			Difference in Ct value		-	-	0.97 (0.19 to 1.76)
Kerwin (52)	US, February to July 2021, Delta (74%)	NR	Median Ct value		21 (17 to 25)	22 (17 to 26)	p=0.83
Kislaya (65)	Portugal, May to July 2021, Delta (100%)	Pfizer, Moderna	Mean Ct value		16.5 (4.9)	17.7 (5.7)	2.24 (0.85 to 3.64)
		Pfizer	Mean Ct value	All	27.7 (5.0)	26.9 (5.0)	0.22 (0.02 to 0.42)

2c. Partially vaccinated, Delta variant dominant

Study	Country, time, dominant variant	Vaccine	Outcome	Effect estimate		
				Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
Elliott (29)	UK, June to July 2021, Delta (100%)	NR	Median Ct value	23.1 (20.3 to 25.8)	27.4 (24.8 to 30.0)	p=0.04
Eyre (27)	UK, January to July 2021, Delta (100%)	Pfizer	Proportion of reduction in transmission mediated via index case Ct values at diagnosis	-	-	12% (7% to 19%)
		AstraZeneca		-	-	14% (11% to 17%)
Griffin (43)	US, May to July 2021, Delta (more than 90%)	Janssen, Moderna, Pfizer	Median Ct value (ORF1ab gene)	18.8	17.8	p>0.05
			Median Ct value (N gene)	19.3	18.6	
			Median Ct value (SC2N gene)	19.3	20.2	
Kislaya (65)	Portugal, May to July 2021, Delta (100%)	Pfizer, Moderna	Mean Ct value	16.5 (4.9)	16.1 (5.0)	-0.15 (-0.99 to 0.96)
Pouwels (32)	UK, May to June 2021, Delta (more than 61%)	Pfizer, AstraZeneca	Median Ct value (seronegative)	21.5 (16.4 to 31.7)	30.1 (26.0 to 34.0)	NR

2d. Fully vaccinated, pre-Delta variant dominant

Study	Country, time, dominant variant	Vaccine	Outcome	Effect estimate		
				Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
Abu-Raddad (64)	Qatar, February 2020 to July 2021, Wild-type, Alpha, Beta	Pfizer	Mean Ct value	24.0 (6.5)	25.0 (6.6)	1.0 (0.7 to 1.2)
			Mean Ct value (symptomatic)	22.5 (6.0)	22.7 (6.0)	0.2 (-0.2 to 0.6)
			Mean Ct value (asymptomatic)	25.5 (6.6)	26.8 (6.5)	1.3 (0.9 to 1.8)
		Moderna	Mean Ct value	26.8 (7.1)	30.3 (5.9)	3.5 (2.4 to 4.6)
			Mean Ct value (symptomatic)	21.7 (5.5)	26.6 (6.7)	4.9 (2.4 to 7.4)
			Mean Ct value (asymptomatic)	28.0 (6.7)	31.2 (5.5)	3.2 (1.8 to 4.5)

Study	Country, time, dominant variant	Vaccine	Outcome	Effect estimate		
				Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
Bailly (45)	France, March 2021, Beta	Pfizer	Mean Ct value	15	21	p<0.05
Blanquart (46)	France, June to July 2021, non-Delta (100%)	NR	Difference in Ct value (symptomatic)	-	-	-1.91 (-5.99 to 2.16)
			Difference in Ct value (asymptomatic)	-	-	4.07 (1.84 to 6.31)
Emary (3)	UK, May 2020 to January 2021, Alpha (100%)	AstraZeneca	Median Ct value	15.2 (13.0 to 19.3)	19.3 (15.4 to 22.0)	p=0.026
	UK, May 2020 to January 2021, Alpha (35%), Wild-type (65%)			20.2 (15.5 to 29.6)	28.8 (20.5 to 33.5)	p<0.0001
			Median Ct value (symptomatic)	17.9 (15.0 to 25.1)	20.6 (15.4 to 24.5)	p=0.07
Eyre (27)	UK, January to July 2021, Alpha (100%)	AstraZeneca	Median Ct value (symptomatic)	18.4 (15.7 to 22.5)	23.9 (18.1 to 32.5)	NR
		Pfizer		18.4 (15.7 to 22.5)	27.4 (19.7 to 32.1)	NR
		AstraZeneca	Proportion of reduction in transmission mediated via index case Ct values at diagnosis	-	-	18% (9% to 64%)
		Pfizer		-	-	16% (1% to 80%)
Griffin (43)	US, May to July 2021, Alpha (more than 50%)	Janssen, Moderna, Pfizer	Median Ct value (ORF1ab gene)	22.8	27.2	p<0.05
			Median Ct value (N gene)	24.0	30.6	
Ioannou (50)	Greece, January to April 2021, Alpha (98%)	Pfizer	Median Ct value	18.5 (13.5 to 24)	18.5 (16 to 26)	p=0.70
Jacobson (51)	US, December to April 2021, L452R (39.5%)	Pfizer, Moderna	Mean Ct value	23.0 (7.4)	28.5 (7.4)	NR
			Mean Ct value (unvaccinated = unvaccinated or early post-vaccination, vaccinated = fully or partially vaccinated)	22.9	27.9	p<0.001
Kislaya (65)	Portugal, May to July 2021, Alpha (100%)	Pfizer, Moderna	Mean Ct value	18.4 (5.2)	21.8 (5.7)	4.49 (2.07 to 6.91)
Lumley (31)	UK, Mar 2020 to February 2021, Alpha (56%)	AstraZeneca, Pfizer	Median Ct value (seronegative)	18.3 (14.0 to 25.5)	19.7 (15.0 to 27.5)	2.7 (-0.5 to 6.8)
			Median Ct value (seropositive)	27.2 (18.8 to 32.2)	-	-
Luo (55)	US, January to July 2021, Alpha (100%)	Pfizer, Moderna, Janssen	Mean Ct value (CPE positive)	18.1	17.8	p>0.05
			Mean Ct value (CPE negative)	24.9	24.1	p>0.05
			Proportion of CPE positive samples	37.9%	17.4%	p=0.02
McEllistream (56)	US, December 2020 to February 2021, NR	Pfizer	Median Ct value	12.8 (12.4 to 14.9)	19.4 (18.9 to 25.5)	p=0.009
			Mean $\log_{10}$ viral load	9.5 (9.3 to 9.8)	7.1 (5.4 to 8.8)	-2.4 (p=0.004)

2e. Partially vaccinated, pre-Delta variant dominant

Study	Country, time, dominant variant	Vaccine	Outcome		Effect estimate		
					Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
Eyre (27)	UK, January to July 2021, Alpha (100%)	Pfizer	Proportion of reduction in transmission mediated via index case Ct values at diagnosis		-	-	33% (23% to 53%)
		AstraZeneca			-	-	39% (30% to 50%)
Griffin (43)	US, May to July 2021, Alpha (more than 50%)	Janssen, Moderna, Pfizer	Median Ct value (ORF1ab)		22.8	36.6	p<0.05
			Median Ct value (N)		24.0	36.0	
Jacobson (51)	US, December to April 2021, L452R (39.5%)	Pfizer, Moderna	Mean Ct value		23.0 (7.4)	27.7 (8.7)	NR
Jones (30)	UK, January 2021, Alpha	Pfizer	Median Ct value		23.4 (13.5 to 33.0)	30.3 (25.5 to 35.1)	p>0.05
Kislaya (65)	Portugal, May to July 2021, Alpha (100%)	Pfizer, Moderna	Mean Ct value		18.4 (5.2)	20.0 (5.6)	1.87 (0.2 to 3.53)
Levine-Tiefenburn (54)	Israel, December 2020 to February 2021, NR	Pfizer	Mean Ct value (RdRp), days post- vaccination	1 to 11 days	-	-	-0.07 (-0.19 to 0.06)
				12 to 21 days	-	-	1.75 (1.60 to 1.91)
				22 to 37 days	-	-	2.15 (1.87 to 2.42)
Pouwels (32)	UK, December 2020 to May 2021, Alpha (dominant)	Pfizer, AstraZeneca	Median Ct value (seronegative)		28.7 (20.4 to 32.9)	31.6 (26.6 to 33.7)	NR
Shrotri (33)	UK, December 2020 to March 2021, Alpha	AstraZeneca (67%), Pfizer (33%)	Mean Ct value		26.6 (6.6)	31.3 (8.7)	p<0.0001
Tande (62)	US, December 2020 to February 2021, NR	Pfizer (94%), Moderna (5.9%)	Mean Ct value (asymptomatic)	Arizona (Alinity instrument)	26.6 (8.3)	30.5 (6.1)	NR
				Arizona (m2000 instrument)	15.1 (7.7)	11.1 (7.1)	NR
				Rochester	30.4 (4.4)	30.9 (-)	NR

GRADE assessment

GRADE assessments were conducted for each of the following outcomes (see Table 3):

- transmission of Delta variant COVID-19 to household and other contacts, comparing fully vaccinated and unvaccinated index cases
- transmission of wild-type and non-Delta variants of COVID-19 to household and other contacts, comparing fully vaccinated and unvaccinated index cases
- viral load (including Ct values) of Delta variant COVID-19 cases, comparing fully vaccinated and unvaccinated cases
- viral load (including Ct values) of wild-type and non-Delta variant COVID-19 cases, comparing fully vaccinated and unvaccinated cases

For all transmission studies, the risks of indirectness and imprecision were judged as not serious. Despite heterogeneity in population, setting, and vaccine type, results provided evidence of direct relevance to the risk of COVID-19 transmission post-vaccination, and when effect estimates were presented, they were typically relatively precise owing to the large number of participants included in each study. However, there were serious methodological limitations across almost all transmission studies, and a high risk that factors other than vaccination affected the results.

The evidence for the Delta variant from 3 transmission studies suggested that although there was less COVID-19 transmission to households and other contacts from fully vaccinated compared with unvaccinated cases, vaccine effectiveness against transmission dropped substantially over time. This evidence was judged as low certainty as, in addition to the methodological limitations in all studies, there was potentially a serious risk of inconsistency in the findings, although this was difficult to judge as there were only 3 studies. For wild-type and non-Delta variants, most transmission studies suggested that fully vaccinated cases were less likely to transmit COVID-19 to household or close contacts compared to unvaccinated cases. Though there were methodological limitations with the evidence, the findings were relatively consistent across studies and the evidence was judged as moderate certainty.

Across both viral load outcomes, there was no serious risk of imprecision, and although Ct values are not a direct measurement of infectivity, they are considered an important marker of potential transmission and are of relevance to the effect of vaccination on transmission. However, there were serious methodological limitations, and a high risk that factors other than vaccination affected the results.

For the Delta variant, most viral load studies suggested that fully vaccinated cases had a small (or no) difference in Ct values compared to unvaccinated cases, although several studies suggested that fully vaccinated cases had higher Ct values, and one study lower Ct values, than unvaccinated cases. As such, there was a serious risk of inconsistency, and this evidence was judged as low certainty evidence. For the viral load of non-Delta or wild-type COVID-19

infections, most studies found that fully vaccinated individuals had higher Ct values (lower viral load) than unvaccinated individuals and so there was no serious risk of inconsistency. As such, this evidence was judged as moderate certainty.

Table 3. GRADE assessment: summary of findings

Outcome	Variant	Effect	Studies	Certainty in the evidence
Transmission of COVID-19 to household and other contacts, comparing vaccinated (any number of doses) and unvaccinated index cases	Delta	All 3 studies suggested that fully vaccinated cases transmitted COVID-19 less than unvaccinated cases, but 2 studies suggested that vaccine effectiveness against transmission of the Delta variant dropped substantially over time.	3	⨁⨁◯◯ Low
	Wild-type and pre-Delta	Most studies suggested that fully vaccinated cases were less likely to transmit COVID-19 to household or close contacts compared to unvaccinated cases.	11	⨁⨁⨁◯ Moderate
Viral load of COVID-19 positive cases, comparing vaccinated (any number of doses) and unvaccinated cases	Delta	Most studies found that during a COVID-19 infection, fully vaccinated cases had only a small (or no) difference in viral load compared to unvaccinated individuals, though some studies suggested fully vaccinated cases had larger Ct values, and one study smaller Ct values, than unvaccinated cases.	17	⨁⨁◯◯ Low
	Wild-type and pre-Delta	Most studies found that during a COVID-19 infection, fully vaccinated cases had a lower viral load (higher Ct values) than unvaccinated cases.	21	⨁⨁⨁◯ Moderate

Inequalities

There was little evidence availably to explore inequalities through variations across populations and subgroups, for example cultural variations or differences between ethnic, social or vulnerable groups. As such, it was not possible to examine inequalities in this report.

Limitations

The source of evidence in this review included peer-reviewed and preprint articles. We did not conduct an extensive search of other sources (such as websites of public health organisations).

All studies were observational in nature, comparing people who were vaccinated with those who were not. Therefore, there is a high risk in all studies that factors other than vaccination affected the results. This includes factors such as behaviour (including test seeking behaviour and behaviours likely to alter the risk of COVID-19 transmission), individual characteristics (such as age, sex and deprivation), and COVID-19 characteristics (such as variant and symptom status). Partly due to this heterogeneity and partly due to a lack of evidence, we were unable to assess how the risk of onward transmission varied with different vaccine types and baseline community transmission levels. Few studies (4 of 43) were rated as high quality using the QCC tool, largely because few studies accounted for these risks well.

Most studies were heterogeneous, in terms of their location, prevalence of COVID-19 in the community, prevalence of past infections, dominant variant, background mitigations in place to limit transmission (including both local restrictions and personal protective measures), vaccination status of contacts, and availability of the vaccine to different groups, as well as the demographics of the index cases, household members and other close contacts. This makes direct comparison between studies and specific vaccines difficult. However, there was one study offering high quality evidence from the UK for the Delta variant (27).

As with all reviews, the evidence identified may be subject to publication bias, whereby null or negative results are less likely to have been published by the authors. Nineteen of the 43 studies identified were preprints or non-peer-reviewed reports and should be treated with caution as they have not been peer reviewed or subject to publishing standards, and may be subject to change. In addition, our rapid review is limited by the fact that we are reviewing evidence from an emerging field that spans less than one year, even less for the currently dominant Delta variant. Studies conducted in the COVID-19 context are conducted at pace with the aim to provide evidence in a timely manner, which sometimes impacts on the quality of the studies, both in term of design (especially limited statistical analyses) and reporting (insufficient detail). There is currently no evidence for the recently identified Omicron variant.

Conclusions

There was evidence across 13 transmission studies (all observational, looking at all variants) that fully vaccinated index cases transmitted COVID-19 to their contacts less than unvaccinated index cases, particularly for Wild type and non-Delta variants, and this reduction was substantial (for example, a great that 50% reduction in transmission) in many studies. Evidence from the 32 viral load studies was supportive of these studies, as they typically showed that, at least for Wild type and non-Delta variants, fully vaccinated cases had higher Ct values than unvaccinated cases (suggesting a lower viral load).

However, the evidence was more mixed for the Delta variant. Although all 3 of the transmission studies suggested that fully vaccinated index cases transmitted COVID-19 less than unvaccinated index cases, 2 of the studies suggested that vaccine effectiveness against transmission of the Delta variant dropped substantially over time. Additionally, one study suggested that vaccination of the index case was less effective against transmission for the Delta variant compared with the Alpha variant. The 16 viral load studies looking at the Delta variant were supportive of these results, with most studies suggesting only a small (or no) difference in Ct values between fully vaccinated and unvaccinated cases, and some studies suggesting Ct values were higher in fully vaccinated cases. One study looked at viral loads in cases who were vaccinated at different times after contracting COVID-19, and suggested that Ct values of fully vaccinated cases were much higher (suggesting lower viral load) than unvaccinated cases soon after the second dose of vaccine, but the difference became smaller over time. Three studies examined the infectivity of samples between fully vaccinated and unvaccinated cases with the Delta variant, and suggested infectivity was very similar.

In almost all included studies (transmission and viral load) there is a high risk that factors other than vaccination may have affected the results, which may have biased the results in either direction. Most studies were also highly heterogeneous, so caution must be used when comparing results between different studies. Partly because of this heterogeneity, there was insufficient evidence to examine whether transmission varies by vaccine type or at different baseline community transmission levels.

Overall, the evidence suggests that although vaccination was likely effective in reducing transmission of COVID-19 to contacts from cases with Wild type and non-Delta variants, the effectiveness of vaccination against transmission has likely been reduced against the Delta variant, and there is evidence from both transmission and viral load studies that there is a reduction in vaccine effectiveness against transmission of the Delta variant in the time after the second dose of vaccine.

Research needed

Randomised controlled trials of vaccination assessing transmission to household members or other close contacts would help us to understand the true vaccine effectiveness against transmission of COVID-19, and we are aware of 2 ongoing RCTs, one in the US (NCT04811664, estimated publication date December 2021) and one in the UK (NCT04750356, estimated publication date December 2024), that could help estimate this, see Supplementary Table 3.

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56. McEllistrem MC and others. ‘Single dose of a mRNA SARS-CoV-2 vaccine is associated with lower nasopharyngeal viral load among nursing home residents with asymptomatic COVID-19’ Clinical Infectious Diseases 2021: volume 26, page 26
57. Mostafa HH and others. ‘SARS-CoV-2 Infections in mRNA Vaccinated Individuals are Biased for Viruses Encoding Spike E484K and Associated with Reduced Infectious Virus Loads that Correlate with Respiratory Antiviral IgG levels’ medRxiv 2021
58. Muhsen K and others. ‘Effectiveness of BNT162b2 mRNA COVID-19 vaccine against acquisitions of SARS-CoV-2 among health care workers in long-term care facilities: a prospective cohort study’ Clinical Infectious Diseases 2021
59. Regev-Yochay G and others. ‘Decreased Infectivity Following BNT162b2 Vaccination’ The Lancet Regional Health, Europe 2021
60. Riemersma KK and others. ‘Shedding of Infectious SARS-CoV-2 Despite Vaccination when the Delta Variant is Prevalent - Wisconsin, July 2021’ medRxiv 2021
61. Servellita V and others. ‘Predominance of antibody-resistant SARS-CoV-2 variants in vaccine breakthrough cases from the San Francisco Bay Area, California’ medRxiv 2021
62. Tande AJ and others. ‘Impact of the COVID-19 Vaccine on Asymptomatic Infection Among Patients Undergoing Pre-Procedural COVID-19 Molecular Screening’

Clinical Infectious Diseases 2021
63. Thompson MG and others. ‘Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines’ New England Journal of Medicine 2021: volume 385, issue 4, pages 320 to 329
64. Abu-Raddad LJ and others. ‘Effect of vaccination and of prior infection on infectiousness of vaccine breakthrough infections and reinfections’ medRxiv 2021
65. Kislaya I and others. ‘Delta variant and mRNA Covid-19 vaccines effectiveness: higher odds of vaccine infection breakthroughs’ medRxiv 2021
66. Li XN and others. ‘Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study’ Emerging Microbes and Infections 2021: volume 10, issue 1, pages 1,751 to 1,759
67. PHE. 'Transmission of COVID-19 within large events and interventions to minimise transmission: A rapid review' 2021
68. Agency for Healthcare Research and Quality (AHRQ). ‘Systems to rate the strength of scientific evidence’ Evidence report/technology assessment (summary) 2002
69. Higgins JPT and others. ‘The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials’ British Medical Journal 2011, issue 343
70. NCT04811664. ‘A Study of SARS CoV-2 Infection and Potential Transmission in University Students Immunized With Moderna COVID-19 Vaccine’ 2021
71. NCT04324606. ‘A Study of a Candidate COVID-19 Vaccine (COV001)’ 2020
72. NCT04750356. ‘SARS-CoV-2 (COVID-19) Longitudinal Study: Understanding Susceptibility, Transmission and Disease Severity (Legacy Study)’ 2021

Annexe A. Methods

This report employed a rapid review approach to address the review question:

“Does vaccination against COVID-19 affect transmission of COVID-19 to others in the subgroup of people who contract COVID-19 post-vaccination?”

We were also interested in the effects of vaccination on transmission according to vaccine type, individual vaccine brands, duration after vaccination, completion of the vaccination course, age and sex of index cases, SARS-CoV-2 variants in index cases, and background COVID-19 infection rate.

Our rapid review approach follows streamlined systematic methodologies (17). In particular, 10% of the screening on title and abstract were screened in duplicate; full text screening, data extraction and risk of bias assessment were performed by one reviewer and checked by another. A protocol was produced a priori following completion of a sister review (67) and registered on PROSPERO (CRD42021257125). The review has been reported according to PRISMA guidelines (22).

Notes: Within the review we refer to vaccines by the names of their manufacturers. For their generic name, trade names and vaccine types, see Table A.1 below.

Table A.1. Vaccine names

Name in this review	Generic names	Company	Trade names	Vaccine type
AstraZeneca	ChAdOx1 nCoV-19, AZD1222	AstraZeneca	Covishield, Vaxzevria	Viral vector
Janssen	Ad26.COV2.S, JNJ-78436735	Janssen, part of Johnson & Johnson	Janssen	Viral vector
Moderna	mRNA-1273, elasomeran	Moderna	Spikevax	mRNA
Pfizer	BNT162b2, tozinameran	Pfizer/BioNTech	Comirnaty	mRNA
Sinovac		Sinovac Biotech	CoronaVac, Sinovac PiCoVacc	Inactivated virus
Sinopharm BIBP	BBIBP-CorV, BIBP vaccine	Sinopharm's Beijing Institute of Biological Products	Vero Cell	Inactivated virus

Name in this review	Generic names	Company	Trade names	Vaccine type
Sinopharm WIBP	WIBP-CorV	Sinopharm; China National Biotec group Co; Wuhan Institute of Biological Products	WIV04	Inactivated virus

Inactivated virus vaccine: A vaccine containing an inactivated virus, in this review referring to the Sinopharm (BIPP and WIBP) vaccines; mRNA vaccine: A ribonucleic acid (RNA) vaccine or messenger RNA (mRNA) vaccine, such as the Moderna and Pfizer COVID-19 vaccines; Viral vector vaccine: A vaccine that uses a viral vector to deliver genetic material coding for a specific antigen, such as the Astrazeneca and Janssen COVID-19 vaccines.

SARS-CoV-2 variants are referred to by their World Health Organization designated name and classification (12), see Table A.2 below.

Table A.2. SARS-CoV-2 variant names

WHO label	Classification	Pango lineage	Earliest documented samples	Date of designation
Alpha	VOC	B.1.1.7	UK, September 2020	18 December 2020
Beta	VOC	B.1.351	South Africa, May 2020	18 December 2020
Gamma	VOC	P.1	Brazil, November 2020	11 January 2021
Delta	VOC	B.1.617.2	India, October 2020	11 May 2021
Iota*	VOI	B.1.526	USA, November 2020	24 March 2021
Lambda	VOI	C.37	Peru, December 2020	14 June 2021
Mu	VOI	B.1.621	Colombia, January 2021	30 August 2021
Omicron	VOC	B.1.1.529	Multiple countries, November 2021	26 November 2021
Alerts for further monitoring		B.1.427 / B.1.429	USA, March 2020	VOI: 5 March 2021 Alert: 6 July 2021

Alert for future monitoring

Variant with genetic changes that are suspected to affect viral characteristics and with some indication that it may pose a future risk.

Variant of concern (VOC)

Variants that are more transmissible, result in more severe disease, are less responsive to treatments or vaccines, show a significant reduction in neutralisation by antibodies from previous infection or vaccination, or show increased diagnostic failures.

Variant of interest (VOI)

If a variant has concerning epidemiological, immunological or pathogenic properties, it will undergo a formal investigation. At this stage it is considered a variant under investigation. After investigation it may or may not become a variant of concern.

As of 29 November 2021, the Iota variant is no longer a variant of interest.

Protocol

A protocol was produced by the project team before the literature search began, specifying the research question and the inclusion and exclusion criteria. The review was registered prospectively on PROSPERO (CRD42021257125).

Review questions

“What is the evidence on COVID-19 transmission from people who have had one or 2 doses of a COVID-19 vaccination?”

“How does risk of onward transmission vary with vaccine type, completion of the vaccination course, duration after vaccination, at different baseline community transmission levels and SARS-CoV-2 variant in the vaccinated person?”

Sources searched

Ovid Medline, Ovid Embase, CENTRAL, medRxiv and SSRN preprints, WHO COVID-19 Research Database.

Search strategy

Searches were conducted for papers published between 1 January 2020 and 22 October 2021.

Search terms covered aspects of the review question. The search strategy for Ovid Medline is presented below. Additionally, we checked reference lists of relevant systematic reviews and evidence summaries and consulted with topic experts. Searches were run initially on 18 May 2021, then updated every 2 to 3 weeks to enable incorporation of additional evidence as it emerged. Preprints that were published in this time were updated. The 18 studies that had been identified as preprints as of 22 October 2021 were last checked and updated (if necessary) on 22 November 2021.

Search strategy Ovid Medline

1. vaccinat*.tw,kw.
2. vaccine*.tw,kw.
3. previously-vaccin*.tw,kw.
4. post-vaccin*.tw,kw.

5. early-vaccin*.tw,kw.
6. late-vaccin*.tw,kw.
7. moderna.tw,kw.
8. mRNA-1273.tw,kw.
9. pfizer.tw,kw.
10. BNT162b2.tw,kw.
11. JNJ-78436735.tw,kw.
12. "Johnson & Johnson*".tw,kw.
13. Astrazeneca.tw,kw.
14. Oxford-Astrazeneca.tw,kw.
15. AZD 1222.tw,kw.
16. AZD1222.tw,kw.
17. BNT 162b2.tw,kw.
18. ChAdOx1.tw,kw.
19. Novavax.tw,kw.
20. NVX-CoV2373.tw,kw.
21. Sputnik V.tw,kw.
22. Ad26.tw,kw.
23. "Ad26.COV2".tw,kw.
24. Ad5.tw,kw.
25. Janssen.tw,kw.
26. Sinovac.tw,kw.
27. sinopharm.tw,kw.
28. covaxin.tw,kw.
29. exp Vaccination/
30. COVID-19 Vaccines/
31. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. (breakthrough or break through).tw,kw.
33. transmiss*.tw,kw.
34. transmit*.tw,kw.
35. viral load*.tw,kw.
36. viral burden.tw,kw.
37. ((severity or severe) adj2 (disease or illness)).tw,kw.
38. Viral Load/
39. exp Disease Transmission, Infectious/
40. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. exp coronavirus/
42. exp Coronavirus Infections/
43. COVID-19/
44. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.
45. (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV*).ti,ab,kw.
46. covid*.nm.

47. (2019-nCoV or 2019nCoV or nCoV2019 or nCoV-2019 or COVID-19 or COVID19 or CORVID-19 or CORVID19 or WN-CoV or WNCoV or HCoV-19 or HCoV19 or 2019 novel* or Ncov or n-cov or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or SARS- CoV2 or SARSCov19 or SARS-Cov19 or SARSCov-19 or SARS-Cov-19 or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or SARS-2 or SARScoronavirus2 or SARS-coronavirus-2 or SARScoronavirus 2 or SARS coronavirus2 or SARScoronovirus2 or SARS- coronovirus-2 or SARScoronovirus 2 or SARS coronovirus2).ti,ab,kw.
48. (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.
49. ((seafood market* or food market* or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.
50. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei or China* or Chinese* or Huanan*)).ti,ab,kw.
51. or/41-50
52. 31 and 40 and 51
53. COVID-19/tm [Transmission]
54. 31 and 53
55. COVID-19 Vaccines/
56. 40 and 55
57. COVID-19/vi [Virology]
58. 31 and 57
59. 52 or 54 or 56 or 58

Inclusion and exclusion criteria

Article eligibility criteria are summarised in Table A.3, below.

In the protocol, we stated we would include disease severity as an outcome. However, as more transmission evidence became available, the need to include disease severity as a secondary outcome became less necessary, and we decided to focus this review on transmission and viral load only. We also stated in the protocol that we would exclude studies where the only index cases were children, as they were not eligible for vaccination when the protocol was written. We have now removed this exclusion criteria. We have also removed the need for contacts to be unvaccinated in transmission studies from the inclusion criteria.

Table A.3. Inclusion and exclusion criteria

	Included	Excluded
Population	Adults who developed laboratory-confirmed symptomatic or asymptomatic COVID-19 (index cases)	
Settings	All community settings, including households	Healthcare settings
Context	COVID-19 pandemic	Other diseases
Intervention or exposure	Partial or full vaccination against COVID-19; any COVID-19 specific vaccination	
Outcomes	**Direct outcomes** • secondary transmission • transmission of laboratory-confirmed COVID-19 to contacts (secondary cases, assessed as transmission by genomic analysis or proximity, such as household members) **Indirect outcomes** • viral load • duration of infection (if presented with a direct outcome or viral load)	
Language	English	
Date of publication	1 January 2020 to 22 October 2021	
Study design	• randomised controlled trials • cohort study • case-control study	• systematic or narrative reviews • other observational studies • guidelines • opinion pieces • outbreak investigations, unless they include an analytical component
Publication type	Published and preprint	

Screening

Title and abstract screening was completed by 2 reviewers: 10% of the eligible studies were screened in duplicate (disagreements were resolved by discussion) and the remainder were screened by one reviewer.

Full text screening was completed by one reviewer and checked by a second. The PRISMA diagram showing the flow of citations is provided in Figure A.1.

Data extraction and risk of bias assessment

Data extraction was completed by one reviewer and checked by a second. Only results directly relevant to the review questions were extracted.

Studies were assessed using the quality criteria checklist (QCC) for primary research (18). This risk of bias tool can be applied to most study designs (observational and interventional) and is therefore suitable for rapid reviews of mixed type of evidence. It is composed of 10 validity questions based on the criteria and domains identified by the Agency for Healthcare Research and Quality to assess the methodological quality of a study (that is, the extent to which a study has minimised selection, measurement and confounding biases) (68). In the QCC tool, 4 questions are considered critical (on selection bias, group comparability, confounding, interventions or exposure, and outcome). A study will be rated as high quality if the answers to the 4 critical questions are ‘yes’ (and at least one additional ‘yes’). The study will be rated as low quality if 2 or more of the critical questions are answered ‘no’ or if at least 50% of the remaining questions are answered ‘no’. Otherwise, the study will be rated as medium quality.

Judgments were made on case by case for questions answered as ‘unclear’. To note that we report these ratings as ‘quality’ ratings for consistency with the name of the tool, although here quality needs to be understood as ‘methodological quality’ as part of a risk of bias assessment.

In the protocol, we stated we would use the Cochrane Risk of Bias Tool (RoB1) to assess the risk of bias of RCTs (69). Both RCTs in this review randomised 2 groups to either receive a COVID-19 vaccine or a control injection, and all participants were followed to see how many contracted COVID-19 to estimate the vaccine effectiveness. Only some participants developed COVID-19, so Ct values were only available for a subset of each group. The randomisation procedure only randomised participants to receive a vaccine or not (it would be impossible to randomise people with COVID-19 to have previously received a vaccine or not), so in both RCTs the subset of participants developing COVID-19 are not necessarily equivalent between those receiving and not receiving a vaccine.

For instance, if vaccinations preferentially protect younger people from contracting COVID-19, the subset of participants who received the vaccine and contracted COVID-19 would be older, on average, than the subset of participants not receiving the vaccine who contracted COVID-19. Therefore, randomisation no longer guarantees equivalence between the groups, and any

analyses of COVID-19 cases should be treated as observational rather experimental. As such, we treat the 2 RCTs in this report as observational studies, and used the QCC instead of RoB1 to assess risk of bias in these studies.

Risk of bias assessment was completed by one reviewer and checked by a second. QCC ratings are reported in the data extraction tables, Supplementary Table 1 and Supplementary Table 2.

The certainty of the evidence was assessed using a variation of the GRADE framework for systematic reviews without meta-analysis (19 to 21). Each of the 5 GRADE domains (methodological limitations of the studies, indirectness, imprecision, inconsistency and the likelihood of publication bias) was assessed and classified as ‘no limitation or not serious’ (not important enough to warrant downgrading), ‘serious’ (downgrading the certainty rating by one level) or ‘very serious’ (downgrading the certainty rating by 2 levels). The body of evidence for a specific outcome was then classified as high certainty, moderate certainty, low certainty or very low certainty. We used this framework to formally assess the quality of the evidence for 4 outcomes: 1) transmission of the Delta variant, 2) transmission of wild-type and non-Delta variants, 3) viral load of cases with the Delta variant, and 4) viral load of cases with wild-type and non-Delta variants.

Variations across populations and subgroups, for example cultural variations or differences between ethnic, social or vulnerable groups were considered, where evidence was available.

Figure A.1. PRISMA diagram

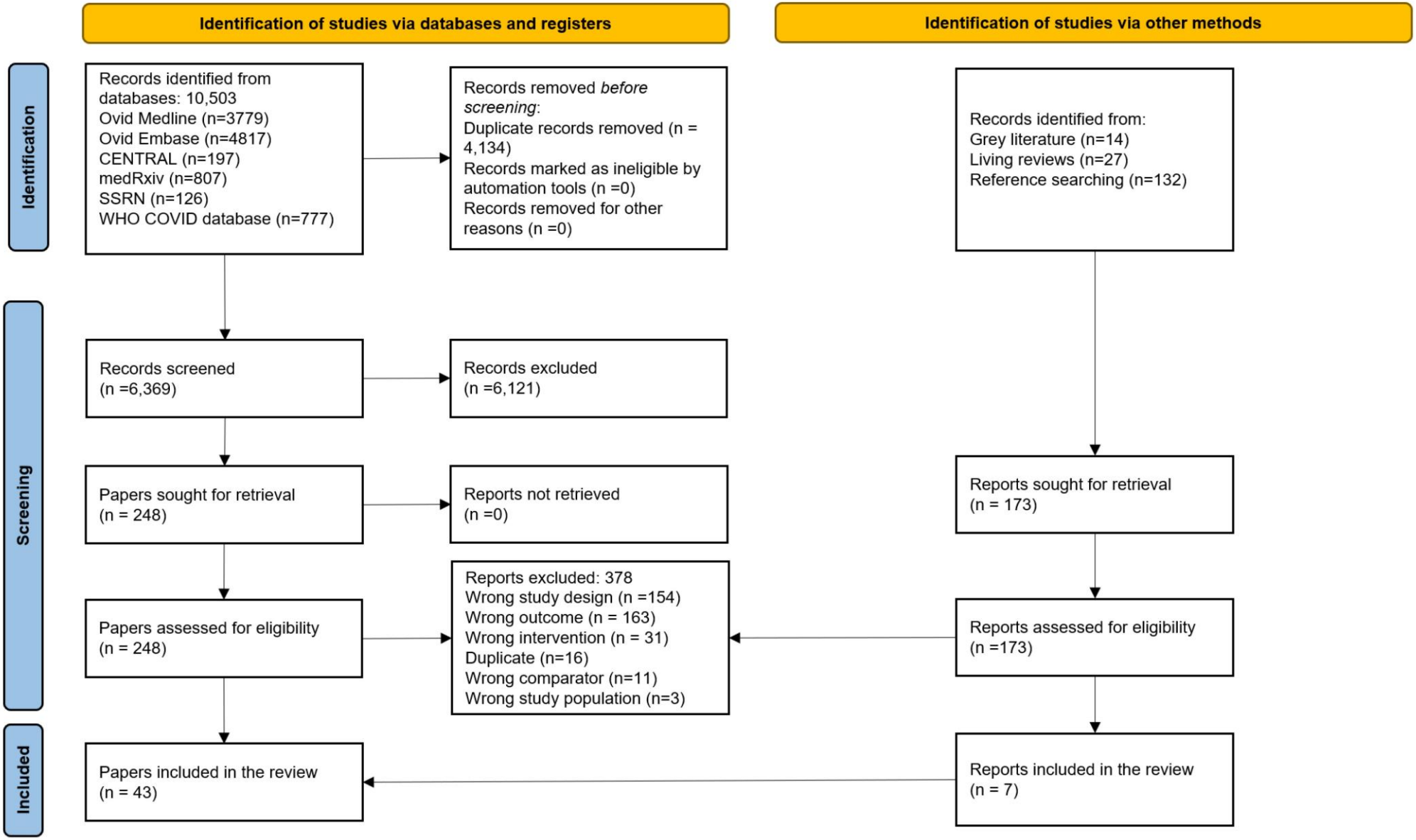

Figure A.1. PRISMA diagram – text alternative

A PRISMA diagram showing the flow of studies through this review.

From identification of studies via databases and registers, n=10,503 records identified from databases:

- Ovid Medline (n=3,779)
- Ovid Embase (n=4,817)
- CENTRAL (n=197)
- medRxiv (n=807)
- SSRN (n=126)
- WHO COVID database (n=777)

From these, records removed before screening:

- duplicate records removed (n=4,134)
- records marked as ineligible by automation tools (n=0)
- records removed for other reasons (n=0)

n=6,369 records screened, of which n=6.121 were excluded, leaving n=248 papers sought for retrieval.

n=173 records identified from identification of studies via other methods, and all sought for retrieval:

- grey literature (n=14)
- living reviews (n=27)
- reference searching (n=132) All identified reports were retrieved.

n=248 papers assessed for eligibility from identification of studies via databases and registers, and n=173 reports from identification of studies via other methods.

Of these, n=378 reports were excluded:

- wrong study design (n = 154)
- wrong outcome (n = 163)
- wrong intervention (n = 31)
- duplicate (n=16)
- wrong comparator (n=11)
- wrong study population (n=3)

n=43 papers included in the review (n=7 reports included from identification by other methods).

Annexe B. Supplementary tables

Supplementary Table 1. Characteristics of included observational studies on transmission

Acronyms: CI = confidence interval, CrI = credible interval, CPE = cytopathic effects, HCW = healthcare worker, HR = hazard ratio, IMD = index of multiple deprivation, IQR = interquartile range, OR = odds ratio, RR = risk ratio, RT-PCR = reverse transcriptase polymerase chain reaction SD = standard deviation, SE = standard error, SIMD = Scottish index of multiple deprivation, VE = vaccine effectiveness

Reference	Study design	Methods	Findings	Risk of bias
Allen and others, 2021 (23) 'Increased household transmission of COVID-19 cases associated with SARS-CoV-2 Variant of Concern B.1.617.2: a national case-control study' NON-PEER REVIEWED PUBLICATION	Study design: Matched case-control Objective: To estimate and compare the odds of household transmission for Delta and Alpha variants Participants: n=11,295 index cases; n=3,765 cases in households with secondary transmission matched with n=7,530 index cases in households without secondary transmission Age: less than 10 years: 6.0%; 10 to 19 years: 23.7%; 20 to 29 years: 19.4%; 30 to 39 years: 21.7%; 40 to 49 years: 15.0%; 50 to 59 years: 9.2%; 60 to 69 years: 3.6%; 70 years and over: 1.5% Sex: 52% Female Ethnicity: 78.1% white, 13.9% Asian, 2.7% Black, 2.1% Mixed, 3.2% Other Vaccination status: fully vaccinated: n=70 (0.6%); partially vaccinated: n=1,499 (13.2%); unvaccinated: n=8,027 (70.6%); less than 21 days post dose 1 (not included in these results): n=779 (6.8%); unknown (not included in these results): n=651 (8.8%) Index cases: First positive test between 18 March to 17 May 2021 with genomic sequencing Secondary cases: Any positive test (including lateral flow) with or without sequencing within 14 days of index case in same household Controls: Index cases with no secondary household	Outcomes: Secondary cases within the household within 14 days of an index case' positive test result. Exposure: Definition of vaccinated: Fully vaccinated: 2 doses of AstraZeneca or Pfizer at least 14 days prior to testing positive Partially vaccinated: one dose of AstraZeneca or Pfizer at least 21 days prior to testing positive Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: Laboratory confirmed pillar 2 cases of COVID-19, secondary cases could be laboratory confirmed or confirmed by lateral flow tests. Asymptomatic screening not conducted. SARS-CoV-2 variant: Delta (n=571, 5.1%) and Alpha (n=10,724, 94.9%) Data collection: Matching was 1:2 (index cases with household transmission to index cases without household transmission) on area of residence (lower tier local authority), fortnight of test date and property type. Datasets used included PHE Second Generation Surveillance System, Laboratory Information Management System, National Immunisation Management System.	Findings OR for household transmission, compared to unvaccinated index cases: • partially vaccinated: 0.94 (95% CI: 0.81 to 1.08) • fully vaccinated: 0.76 (95% CI: 0.44 to 1.31)	Confounding: There is some risk of bias from residual confounding even after adjustment, although the analysis accounted for this well. Other bias: No specific biases to report. QCC rating: High

Reference	Study design	Methods	Findings	Risk of bias
	cases within 14 days Setting: England, March to May 2021	 Statistical analysis: Conditional logistic regression to estimate the effect of vaccination on secondary transmission, adjusted for age, sex, ethnicity, variant and index of multiple deprivation, and matched on area of residence, test date and property type.		
Braeye and others, 2021 (41) 'Vaccine effectiveness against infection and onwards transmission of COVID-19: Analysis of Belgian contact tracing data, January-June 2021'	Study design: Retrospective cohort Objective: To estimate vaccine effectiveness against infection and onwards infection Participants: Mean age: 33 years (SD: 19.4) Sex: 51.5% Female Index cases: (n=131,283) Not vaccinated: n=126,780 (96.5%); partially vaccinated: n=3,513 (2.7%); fully vaccinated: n=990 (0.8%) Previously tested positive: n=290 of 131,283 (0.2%) Contacts: (n=301,741) Not vaccinated: n=281,592 (93.3%); partially vaccinated: n=12,162 (4.0%); fully vaccinated: n=7,987 (2.6%) Previously tested positive: n=697 of 301,741 (0.2%) Setting: Belgium, January to June 2021	Outcomes: Positive COVID-19 test among high risk contacts of index cases. Exposure: Definition of vaccinated: Fully vaccinated: Received all doses of a vaccine more than 14 days before last high risk contact (Moderna, Pfizer, AstraZeneca or Janssen). Partially vaccinated: Received a single dose of a 2 dose vaccine more than 14 days before last high risk contact. Definition of unvaccinated: No vaccine received more than 14 days before positive test result. Prior infections: People with a positive test in the previous 90 days were excluded. Definition of high risk contact: Someone without a positive COVID-19 test (PCR or antigen) in the previous 90 days who had contact with an infected person for more than 15 minutes at less than 1.5m without face coverings, or direct physical contact with an infected person. Testing: Index cases: RT-PCR testing (no asymptomatic screening) High risk contacts: RT-PCR testing at time of exposure and 7 days post-exposure if first test was negative or the contact became symptomatic.	Findings Vaccine effectiveness for transmission from index case to high risk contact: Fully vs unvaccinated index case: • Moderna (n=69): 52% (95% credible interval [CrI]: 33% to 69%) • Pfizer (n=908): 62% (95% CrI: 57% to 67%) • AstraZeneca (n=12): 8% (95% CrI: -79% to 63%) • Janssen (n=22): 27% (95% CrI: -23% to 62%) Partially vs unvaccinated index case: • Moderna (n=106): 41% (95% CrI: 23% to 57%) • Pfizer (n=1,264): 16% (95% CrI: 8% to 22%) • AstraZeneca (n=2,121): -3% (95% CrI: -10% to 2%) Fully vs unvaccinated high risk contact, unvaccinated index case: • Moderna (n=652): 85% (95% CrI: 79% to 90%) • Pfizer (n=7,275): 74% (95% CrI: 72% to 76%) • AstraZeneca (n=55): 55% (95% CrI: 11% to 82%) • Janssen (n=74): 57% (95% CrI: 21% to 81%)	Confounding: There is a high risk of bias from confounding, particularly as age, sex and deprivation were not accounted for. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		SARS-CoV-2 variant: Detection of the Alpha variant via sequencing increased from 33% at the start of the study period to 80% by the end. Data collection: Belgian contact tracing database linked with national identification number of social security. Statistical analysis: Bayesian logistic regression (Bernoulli distribution, non-informative priors for all covariables) with vaccination status of contact, previous COVID-19 infection, household exposure (yes or no) and week of sample collection as covariables.	Partially vs unvaccinated high risk contact, unvaccinated index case: • Moderna (n=507): 65% (95% CrI: 57% to 81%) • Pfizer (n=4,444): 41% (95% CrI: 37% to 45%) • AstraZeneca (n=7,137): 31% (95% CrI: 27% to 35%)	
De Gier and others, 2021 (42) 'Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021'	Study design: Retrospective cohort Objective: To assess vaccine effectiveness in preventing COVID-19 transmission to household members and close contacts of index cases Study participants: Index cases aged at least 18 years. Secondary cases were close contacts of any age and household members of confirmed COVID-19 cases without prior infections. Overall: 113,582 index cases and 253,168 contacts (142,540 household contacts, 110,628 other close contacts) Fully vaccinated index cases (n=622): Age: 0 to 11 years: 0%; 12 to 17 years: 0%; 18 to 29 years: 20%; 30 to 49 years: 29%; 50 to 74 years: 31%; 75 years and over: 20%Sex: 76% female Partially vaccinated index cases (n=2,088):	Outcome: COVID-19 infection in household and close contacts of index cases (within one to 14 days of index case infection). Exposure: Definition of vaccinated: Full vaccination: at least 7 days after second dose (AstraZeneca, Pfizer or Moderna) or at least 14 days after 1 dose of Janssen vaccine. Partial vaccination: having received the first dose of a 2 dose vaccine. Definition of unvaccinated: No vaccine received prior to positive test results. Prior infections: NR Testing: RT-PCR, antigen or loop mediated isothermal amplification test. Index cases: testing after exposure or symptoms (no asymptomatic screening). Contacts: testing encouraged after exposure and 5 days after last exposure.	Findings Secondary attack rate (to household contacts and other close contacts), by index case vaccination status: Household contacts: • unvaccinated: 31% • partially vaccinated: 29% • fully vaccinated: 11% Other close contacts: • unvaccinated: 11% • partially vaccinated: 10% • fully vaccinated: 9% Vaccine effectiveness against transmission, fully vs unvaccinated index cases: Household contacts: • all vaccines: 71% (95% CI: 63% to 77%) • AstraZeneca: 58% (95% CI: -12% to 84%) • Pfizer: 70% (95% CI: 61% to 77%) • Moderna: 88% (95% CI: 50% to 97%) • Janssen: 77% (95% CI: 6% to 94%) Household contacts (unvaccinated):	Confounding: There is a high risk of bias from confounding, particularly as sex and deprivation were not accounted for. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Age: 0 to 11 years: 0%; 12 to 17 years: 0%; 18 to 29 years: 10%; 30 to 49 years: 17%; 50 to 74 years: 55%; 75 years and over: 18% Sex: 63% female Unvaccinated index cases (n=110,872): Age: 0 to 11 years: 0%; 12 to 17 years: 0%; 18 to 29 years: 29%; 30 to 49 years: 38%; 50 to 74 years: 31%; 75 years and over: 2% Sex: 51% female Fully vaccinated contacts (n=5,397): Age: 0 to 11 years: 0%; 12 to 17 years: 0%; 18 to 29 years: 18%; 30 to 49 years: 20%; 50 to 74 years: 42%; 75 years and over: 20%Sex: 77% female Partially vaccinated contacts (n=4,411): Age: 0 to 11 years: 0%; 12 to 17 years: 0%; 18 to 29 years: 10%; 30 to 49 years: 13%; 50 to 74 years: 61%; 75 years and over: 16% Sex: 61% female Unvaccinated contacts (n=243,360) Age: 0 to 11 years: 17%; 12 to 17 years: 8%; 18 to 29 years: 24%; 30 to 49 years: 22%; 50 to 74 years: 24%; 75 years and over: 2%; Unknown: 3% Sex: 50% female Setting: The Netherlands, 1 February to 27 May 2021	SARS-CoV-2 variant: Alpha was dominant throughout the study period. Data collection: symptoms & vaccination status collected via national infectious disease notification registry. Testing data via Municipal Health Services Statistical analysis: Vaccine effectiveness against transmission estimated with a binomial generalised linear model, clustered by contacts, with age of index case and contact, vaccination status of contact and month of notification date of the index case as covariables.	• all vaccines: 73% (95% CI: 65% to 79%) Other close contacts: • all vaccines: 22% (95% CI: -5% to 43%) Close contacts (unvaccinated): • all vaccines: 24% (95% CI: -5% to 45%) Vaccine effectiveness against transmission, partially vs unvaccinated index cases: Household contacts: • all vaccines: 21% (95% CI: 12% to 28%) • AstraZeneca: 15% (95% CI: 4% to 26%) • Pfizer: 26% (95% CI: 12% to 37%) • Moderna: 51% (95% CI: 8% to 74%) Other close contacts: • all vaccines: 22% (95% CI: 9% to 33%) Vaccine effectiveness against transmission, fully vs unvaccinated contacts: Household contacts: • all vaccines: 75% (95% CI: 72% to 78%) • AstraZeneca: 87% (95% CI: 77% to 93%) • Pfizer: 65% (95% CI: 60% to 70%) • Moderna: 91% (95% CI: 79% to 97%) • Janssen: 12% (95% CI: -71% to 54%) Household contacts (unvaccinated index cases): • all vaccines: 76% (95% CI: 73% to 79%) Other close contacts: • All vaccines: 79% (95% CI: 74% to 83%) Other close contacts (unvaccinated index cases): • All vaccines: 80% (95% CI: 74% to 84%) Vaccine effectiveness against transmission, partially vs unvaccinated contacts: Household contacts: • All vaccines: 23% (95% CI: 14% to 30%) • AstraZeneca: 2% (95% CI: -11% to 14%)	

Reference	Study design	Methods	Findings	Risk of bias
			• Pfizer: -18% (95% CI: -43% to 2%) • Moderna: 33% (95% CI: -27% to 64%) Other close contacts: • All vaccines: 28% (95% CI: 17% to 38%)	
De Gier and others, 2021 (34) 'Vaccine effectiveness against SARS-CoV-2 transmission to household contacts during dominance of Delta variant (B.1.617.2), August to September 2021, the Netherlands' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To estimate vaccine effectiveness against transmission of the Delta variant to fully vaccinated and unvaccinated household contacts Study participants: Index cases (n=4,912) aged at least 12 years. Secondary cases (n=7,771) were close contacts and household members of confirmed COVID-19 cases without prior infections, aged at least 12 years. Fully vaccinated index cases (n=1,740, 35.4%): Age: 12 to 17 years: 3%; 18 to 29 years: 32%; 30 to 49 years: 25%; 50 to 74 years: 36%; 75 years and over: 4% Sex: 50% female Partially vaccinated index cases (n=540, 11.0%): Age: 12 to 17 years: 32%; 18 to 29 years: 42%; 30 to 49 years: 19%; 50 to 74 years: 6%; 75 years and over: 1% Sex: 52% female Unvaccinated index cases (n=2,641, 53.7%) Age: 12 to 17 years: 38%; 18 to 29 years: 31%; 30 to 49 years: 23%; 50 to 74 years: 7%; 75 years and over: 1% Sex: 56% female Fully vaccinated contacts (n=4,189, 53.9%): Age: 12 to 17 years: 3%; 18 to 29 years: 16%; 30 to 49 years: 35%; 50 to 74 years: 44%; 75 years and over: 2% Sex: 50% female	Outcomes COVID-19 infections amongst household contacts of index cases (within one to 14 days of index case infection). Exposure: Definition of vaccinated: Full vaccination: at least 14 days after second dose (AstraZeneca, Pfizer, Moderna) or at least 28 days after one dose of Janssen vaccine. Partial vaccination: Having received the first dose of a 2 dose vaccine. Definition of unvaccinated: No vaccine received prior to positive test results. Prior infections: NR Testing: RT-PCR, antigen or loop mediated isothermal amplification test. Index cases: Testing after exposure or symptoms (no formal screening). Contacts: Testing encouraged after exposure and 5 days after last exposure. SARS-CoV-2 variant: Delta was dominant throughout the study period (more than 85% sequenced isolates in July). Data collection: Symptoms and vaccination status data collected via national infectious disease notification registry. Testing, source and contract tracing data collected via Municipal Health Services.	Findings Secondary attack rate (to household contacts), by index case vaccination status: Unvaccinated household contacts: • unvaccinated: 22% • partially vaccinated: 17% • fully vaccinated: 13% • fully vaccinated at least 60 days ago: 15% Fully vaccinated household contacts: • unvaccinated: 11% • partially vaccinated: 6% • fully vaccinated: 12% • fully vaccinated at least 60 days ago: 20% Vaccine effectiveness against transmission, fully vs unvaccinated index cases: • unvaccinated household contacts: 40% (95% CI: 20% to 54%) • fully vaccinated household contacts: 63% (95% CI: 46% to 75%) Vaccine effectiveness against transmission, partially vs unvaccinated index cases: • unvaccinated household contacts: 46% (95% CI: 20% to 63%) • fully vaccinated household contacts: 38% (95% CI: -2% to 62%) Vaccine effectiveness against transmission, fully vaccinated at least 60 days ago vs unvaccinated index cases:	Confounding: There is a high risk of bias from confounding, particularly as sex and deprivation were not accounted for. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Partially vaccinated contacts (n=641, 8.2%) Age: 12 to 17 years: 27%; 18 to 29 years: 34%; 30 to 49 years: 27%; 50 to 74 years: 12%; 75 years and over: 0% Sex: 52% female Unvaccinated contacts (n=2,914, 37.8%) Age: 12 to 17 years: 31%; 18 to 29 years: 24%; 30 to 49 years: 31%; 50 to 74 years: 13%; 75 years and over: 1% Sex: 52% female Setting: The Netherlands, 9 August 2021 to 24 September 2021	Statistical analysis: Vaccine effectiveness against transmission estimated with a binomial generalised linear model, clustered by contacts, with age, vaccination status of contact and week of notification date of the index case as covariables.	• unvaccinated household contacts: 55% (95% CI: 19% to 76%) • fully vaccinated household contacts: 28% (95% CI: -4% to 50%)	
Eyre and others, 2021 (27) The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission PREPRINT (version 2)	Study design: Retrospective cohort Objective: To investigate the impact of vaccination on COVID-19 transmission, and how this varies with Alpha and Delta variants and time since second vaccination Study participants: 108,498 adult index cases (symptomatic and asymptomatic) and 146,243 contacts aged at least 18 years (household contacts: 66%, household visitors: 11%, event or activity contacts: 11%, work or education contacts: 11%) Fully vaccinated index cases (n=19,321, 17.8%) (by vaccine type): AstraZeneca (n=15,086, 13.9%) Median age: 49 years (IQR: 36 to 57 years) Sex: 50% Female Variant: 0.4% Alpha Median time from second dose to positive test (Alpha): 27 days (18.5 to 43 days) Median time from second dose to positive test (Delta): 51 days (35 to 70 days)	Outcomes: COVID-19 in contacts of index cases, confirmed by RT-PCR 1-10 days after index case's positive RT-PCR. Exposure: Definition of vaccinated: Full vaccination: at least 14 days after second Pfizer or AstraZeneca dose. Partial vaccination: First vaccine date to 13 days after second vaccine. Definition of unvaccinated: No vaccine received. Prior infections: NR Definition of contact: Household contacts, or contacts met face-to-face, within 1 metre for at least 1 minute or less than 2 metres for at least 15 minutes, accessing PCR testing 1 to 10 days after the index case's RT-PCR test. Testing: Index cases: RT-PCR performed by three national laboratories were included, symptomatic or asymptomatic.	Findings Secondary attack rate, by index case vaccination status: • unvaccinated: 46% (n=35,459 of 76,401) • partially vaccinated (AstraZeneca): 35% (n=3,878 of 11,236) • partially vaccinated (Pfizer): 26% (n=7,947 of 31,039) • fully vaccinated (AstraZeneca): 28% (n=6,067 of 21,421) • fully vaccinated (Pfizer): 21% (n=1,316 of 6,146) Secondary attack rate, by contact vaccination status: • unvaccinated: 52% (n=34,041 of 65,117) • partially vaccinated (AstraZeneca): 32% (n=3,987 of 12,307) • partially vaccinated (Pfizer): 32% (n=6,756 of 20,999) • fully vaccinated (AstraZeneca): 22% (n=7,241 of 32,363) • fully vaccinated (Pfizer): 17% (n=2,642 of 15,457)	Confounding: There is some risk of bias from residual confounding even after adjustment, although the analysis accounted for this well Other bias: No specific biases to report. QCC rating: High

Reference	Study design	Methods	Findings	Risk of bias
	Pfizer (n=4,235, 3.9%): Median age: 48 years (IQR: 32 to 60 years) Sex: 62% Female Variant: 3.0% Alpha Median time from second dose to positive test (Alpha): 42 days (26 to 63 days) Median time from second dose to positive test (Delta): 90 days (69 to 110 days) Partially vaccinated index cases (n=29,221, 26.9%) (by vaccine type): AstraZeneca (n=8.294, 7.6%) Median age: 49 years (IQR: 36 to 57 years) Sex: 50% Female Variant: 0.4% Alpha Pfizer (n=20,927, 19.3%): Median age: 28 years (IQR: 22 to 35.5 years) Sex: 48% Female Variant: 15.6% Alpha Unvaccinated index cases (n=59,956, 55.3%) Median age: 35 years (IQR: 25 to 50 years) Sex: 51% female Variant (in associated index case): 71.9% Alpha Fully vaccinated contacts by vaccine type: (n=47,820, 44.1%) AstraZeneca (n=32,363, 29.8%) Median age: 53 years (IQR: 45 to 58 years) Sex: 58.4% Female Variant (in associated index case): 0.5% Alpha Pfizer (n=15,457, 14.2%) Median age: 51 years (IQR: 38 to 60 years) Sex: 68.8% Female	Contacts: RT-PCR performed by any community or hospital laboratory reporting results to NHS Test and Trace. SARS-CoV-2 Variants: Alpha (n=60,377 contacts, 41.3%) and Delta (n=85,866 contacts, 58.7%). Data collection: COVID-19 status from the English national contact tracing and testing service (NHS Test and Trace). Vaccination status from the National Immunisation Management Service. Statistical analysis: Poisson regression to estimate rate ratios for transmission for vaccination status, adjusting for contact event type; age, sex and symptom status of index cases; age, sex, vaccination status and time since vaccination of contacts; local deprivation; local weekly SARS-CoV-2 incidence from national testing data; and calendar time, and accounting for non-linearity and interactions.	Rate ratio for transmission, compared to unvaccinated index cases, by variant of the index case: Alpha • partially vaccinated (AstraZeneca): 0.90 (95% CI: 0.86 to 0.94) • partially vaccinated (Pfizer): 0.88 (95% CI: 0.85 to 0.91) • fully vaccinated (AstraZeneca): 0.48 (95% CI: 0.30 to 0.78) • fully vaccinated (Pfizer): 0.32 (95% CI: 0.21 to 0.48) Delta • partially vaccinated (AstraZeneca): 0.95 (95% CI: 0.91 to 0.99) • partially vaccinated (Pfizer): 0.83 (95% CI: 0.81 to 0.86) • fully vaccinated (AstraZeneca): 0.76 (95% CI: 0.70 to 0.82) • fully vaccinated (Pfizer): 0.50 (95% CI: 0.39 to 0.65) Rate ratio for transmission, compared to unvaccinated contacts, by variant of the index case: Alpha • partially vaccinated (AstraZeneca): 0.94 (95% CI: 0.91 to 0.98) • partially vaccinated (Pfizer): 0.85 (95% CI: 0.82 to 0.88) • fully vaccinated (AstraZeneca): 0.40 (95% CI: 0.27 to 0.59) • fully vaccinated (Pfizer): 0.15 (95% CI: 0.11 to 0.21) Delta • partially vaccinated (AstraZeneca): 0.69 (95% CI: 0.66 to 0.72) • partially vaccinated (Pfizer): 0.67 (95% CI: 0.65 to 0.69)	

Reference	Study design	Methods	Findings	Risk of bias
	Variant (in associated index case): 2.2% Alpha Partially vaccinated contacts by vaccine type: (n=33,306, 30.7%) AstraZeneca (n=12,307, 11.3%) Median age: 47 years (IQR: 41 to 54 years) Sex: 57.1% Female Variant (in associated index case): 30.4% Alpha Pfizer (n=20,999, 19.4%) Median age: 30 years (IQR: 24 to 37 years) Sex: 57.2% Female Variant (in associated index case): 18.2% Alpha Unvaccinated contacts (n=65,117, 44.5%) Median age: 37 years (IQR: 26 to 51 years) Sex: 53% Female Variant (in associated index case): 80.3% Alpha Setting: England, 1 January 2021 to 31 July 2021		• fully vaccinated (AstraZeneca): 0.42 (95% CI: 0.38 to 0.45) • fully vaccinated (Pfizer): 0.19 (95% CI: 0.16 to 0.23) Reduction in transmission, compared to unvaccinated index cases, by variant of the index case and time since second dose: Alpha • AstraZeneca (2 weeks): 52% (95% CI: 22% to 70%) • AstraZeneca (12 weeks): 38% (95% CI: -1% to 62%) • Pfizer (2 weeks): 68% (95% CI: 52% to 79%) • Pfizer (12 weeks): 52% (95% CI: 29% to 67%) Delta • AstraZeneca (2 weeks): 24% (95% CI: 18% to 30%) • AstraZeneca (12 weeks): 2% (95% CI: -2% to 6%) • Pfizer (2 weeks): 50% (95% CI: 35% to 61%) • Pfizer (12 weeks): 24% (95% CI: 20% to 28%) Change in rate of transmission (compared to vaccinated index cases) for each doubling of weeks after 2 weeks after second dose (higher rates mean reduced vaccine effectiveness against transmission over time): • AstraZeneca: 1.08 (95% CI: 1.05 to 1.11) • Pfizer: 1.13 (95% CI: 1.05 to 1.21)	
Gazit and others, 2021 (37)	Study design: Retrospective cohort Objective: Assessing vaccine effectiveness in preventing COVID-19 transmission within	Outcome: COVID-19 infection in adult household member less than or equal to 10 days after index case diagnosis.	Findings Secondary attack rate, by vaccination status of household member:	Confounding: There is a very high risk of bias from confounding as the analysis was

Reference	Study design	Methods	Findings	Risk of bias
'BNT162b2 mRNA Vaccine Effectiveness Given Confirmed Exposure; Analysis of Household members of COVID-19 patients' PREPRINT (version 1)	households of confirmed cases Study participants: 4,024 households of 2 adults, no children and no prior infections, from a total of 1,312,372 households with active COVID-19 cases Overall: Mean age: 57.6 years (SD: 13.9 years) Sex: 50% female Household members (non-index cases): Fully Vaccinated (n=2,827, 70.3%): Mean age: 63 years (SD: 10 years) Sex: 44% female Partially Vaccinated (n=652, 16.2%): Mean age: 61 years (SD: 11 years) Sex: 47% female Unvaccinated (n=545, 13.5%): Mean age: 56 years (SD: 15 years) Sex: 53% female Index cases (from n=3,627 households where the 2 adults shared the same vaccination status): Fully Vaccinated (n=2,975, 82.0%): Mean age: 56 years (SD: 15 years) Sex: 51% female Partially Vaccinated (n=381, 10.5%): Mean age: 63 years (SD: 12 years) Sex: 50% female Unvaccinated (n=271, 7.5%): Mean age: 68 years (SD: 9 years) Sex: 50% female Setting: Israel, 20 December 2020 to 8 March 2021	Exposure: Definition of vaccinated: Fully vaccinated: at least 7 days after second dose of Pfizer vaccine. Recently vaccinated: 0 to 7 days after first dose of Pfizer vaccine. Definition of unvaccinated: No vaccine received prior to positive test results. Prior infections: Only households with no confirmed previous infections prior to study period were included. Testing: RT-PCR testing for index cases and household contacts. Asymptomatic testing not conducted. SARS-CoV-2 variant: NR Data collection: Nationally centralized database of Maccabi Healthcare Services. Statistical analysis: Unadjusted vaccine effectiveness against transmission. An additional analysis assumed all untested participants were as likely to be infected as tested participants, accounting for differing testing behaviours between people of different vaccine statuses. A final analysis restricted to households where the 2 adults shared the same vaccination status (n=3,627 households).	• unvaccinated: 37.5% (95% CI: 35.7% to 39.3%) • recently vaccinated: 41.7% (95% CI: 38.0% to 45.5%) • fully vaccinated: 7.5% (95% CI: 5.6% to 10.0%) Vaccine effectiveness against transmission, by vaccination status of household member: • fully vaccinated vs unvaccinated: 80.0% (95% CI: 73.0% to 85.1%) • fully vaccinated vs recently vaccinated: 82.0% (95% CI: 75.5% to 86.7%) Vaccine effectiveness against transmission, assuming untested participants were as likely to be infected as tested participants, by vaccination status of household member: • fully vaccinated vs unvaccinated: 72.0% (95% CI: 65.2% to 77.5%) • fully vaccinated vs recently vaccinated: 73.0% (95% CI: 66.0% to 78.5%) Vaccine effectiveness in households where the 2 adults shared the same vaccination status (n=3,627 households), by vaccination status of both household members: • fully vaccinated vs unvaccinated: 74.8% (95% CI: 65.4% to 81.6%) • fully vaccinated vs recently vaccinated: 77.7% (95% CI: 69.0% to 83.9%)	unadjusted. Other bias: Households were defined as two adults only, limiting generalisability. Vaccinated persons did not have to self-isolate after exposure to a positive case, whereas unvaccinated persons did. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
Harris and others, 2021 (24, 25) 'Impact of vaccination on household transmission of SARS-COV-2 in England'	Study design: Retrospective cohort Objective: To determine whether vaccinated individuals are less likely than unvaccinated cases to transmit COVID-19 to their unvaccinated household contacts Participants: Adult (16 years and over) index cases, excluding those tested under pillar 1 (usually health workers & hospitalised patients). Households with any person vaccinated before 4 January were excluded. Household members vaccinated before the index case tested positive were excluded. Overall: n=365,447 residential households of 2 to 10 people with at least 1 index case, with n=1,018,842 household contacts and n=102,662 secondary cases Vaccinated index cases: (n=4107, 1.1%) Age: 16 to 29 years: 18.7%; 30 to 39 years: 24.2%; 40 to 49 years: 23.7%; 50 to 59 years: 22.2%; 60 to 69 years: 7.9%; 70 to 79 years: 1.9%; 80 years and over: 1.4% Sex: 38.3% female IMD quintile: 1: 26.6%; 2: 22.1%; 3: 20.6%; 4: 16.6%; 5: 14.2% Unvaccinated index cases: (n=341,230, 93.4%) Age: 16 to 29 years: 31.5%; 30 to 39 years: 27.0%; 40 to 49 years: 20.5%; 50 to 59 years: 14.4%; 60 to 69 years: 5.3%; 70 to 79 years: 1.0%; 80 years and over: 0.3% Sex: 47.6% female IMD quintile: 1: 27.6%; 2: 24.9%; 3: 19.2%; 4: 15.5%; 5: 12.8% Setting: England, 4 Jan to 28 Feb 2021	Outcomes: Secondary cases of laboratory confirmed COVID-19 within 2 to 14 days of the index case and living in the same household. Exposure: Definition of vaccinated: Vaccinated with AstraZeneca or Pfizer at least 21 days prior to testing positive (93% had received a single dose of vaccine). Definition of unvaccinated: No vaccine received prior to positive test results. Prior infections: NR Testing: Pillar 1 RT-PCR testing for index cases and household contacts. Asymptomatic screening not conducted. SARS-CoV-2 variant: Alpha reported as rising during the study period. Data collection: HOSTED dataset linked to National Immunisation Management System. Statistical analysis: Logistic regression to estimate the effect of vaccination of the index case on transmission to a household member, with age and sex of index cases and contacts, government office region, week of index case, index of multiple deprivation (IMD) and household type as covariables. Also, conditional logistic regression in a matched case control study, with COVID-19 positive household members as cases and COVID-19 negative household members as controls, matched on age and sex of index cases and contacts, region, week, IMD and household type.	Findings Secondary attack rate, by vaccination status of index case: • unvaccinated: 10.1% (n=96,898 of 960,765) • vaccinated with AstraZeneca: 5.7% (n=196 of 3,424) • vaccinated with Pfizer: 6.2% (n=371 of 5,939) OR for being a secondary case, vaccinated vs unvaccinated index case: • AstraZeneca: 0.53 (95% CI: 0.43 to 0.63) • Pfizer: 0.51 (95% CI: 0.44 to 0.59) Matched case-control study: • AstraZeneca: n=1,513 contacts of index cases (64%) matched to contacts of unvaccinated index cases, OR of infection = 0.62 (95% CI: 0.48 to 0.79) • Pfizer: n=2,694 contacts of index cases (67%) were matched to contacts of unvaccinated index cases, OR of infection = 0.51 (95% CI: 0.42 to 0.62)	Confounding: There is some risk of bias from residual confounding even after adjustment, although the analysis accounted for this well. Other bias: No specific biases to report. QCC rating: High

Reference	Study design	Methods	Findings	Risk of bias
Kang and others, 2021 (40) 'Transmission dynamics and epidemiological characteristics of Delta variant infections in China' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To compare epidemiological parameters, temporal trend of viral loads and secondary attack rates in close contacts between the Delta variant and wild-type SARS-CoV-2, and the effect of vaccination on viral load and transmission Participants: Index cases: (n=73 of 167 total) Sex: 41.3% male Median age: 47.0 years (IQR: 31.0 to 66.5); 13.2% aged under 15 years Unvaccinated: n=121 (72.4%); partially vaccinated: n=30 (18.0%); fully vaccinated: n=16 (9.6%) Close contacts: (n=5,153) Sex: 49.5% male Median age: 47.0 years (IQR: 31.0 to 66.5); 8.2% aged under 15 years Unvaccinated: n=2,844 (55.2%); partially vaccinated: n=1,459 (28.3%); fully vaccinated: n=850 (16.5%) Setting: Guangdong, China, May to June 2021	Outcomes: secondary case of COVID-19 in close contacts, confirmed by RT-PCR. Exposure: Definition of vaccinated: Fully vaccinated: at least 14 days after the second dose (inactivated COVID-19 vaccine). Partially vaccinated: at least 10 days after the first dose. Definition of unvaccinated: NR Prior infections: NR Definition of close contact: individuals exposed to symptomatic index cases from 2 days before the index case's illness onset, or exposed to asymptomatic cases at close proximity (less than one meter) without wearing proper personal protection equipment from 2 days before the index case's first positive test. Testing: RT-PCR testing. Asymptomatic screening conducted for index cases and close contacts. Whole genome sequencing to confirm variants for all samples. SARS-CoV-2 variant: Delta (100%) Data collection: Information was collected, though not specified how, for all laboratory-confirmed symptomatic and asymptomatic cases with Delta variant in Guangdong province in May and June 2021. Statistical analysis: Logistic regression to estimate the effect of vaccination of index cases on COVID-19 transmission, with age, sex, disease severity of index case, COVID-19 vaccination of close contacts, type	Findings Secondary attack rate, by index case vaccination status: • unvaccinated: n=37 of 2,892 (1.3%) • partially vaccinated: n=31 of 1,110 (2.8%) • full vaccinated: n=5 of 1,151 (0.4%) OR for transmission of COVID-19, compared with fully vaccinated index case: • partially vaccinated index cases: OR = 6.02 (95% CI: 2.45 to 18.16) • unvaccinated index cases: OR = 2.84 (95% CI: 1.19 to 8.45) Note that the ORs for transmission of COVID-19 were inverted for the report, to give the OR for transmission for fully vaccinated compared with partially vaccinated and unvaccinated index cases.	Confounding: There is a high risk of bias from residual confounding even after adjustment, particularly as deprivation was not accounted for. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		of contact, exposure on the day of symptom onset of the index case, and duration of exposure as covariables.		
Layan and others, 2021 (38) 'Impact of BNT162b2 vaccination and isolation on SARS-CoV-2 transmission in Israeli households: an observational study' PREPRINT (version 1)	Study design: Prospective cohort Objective: To estimate the effect of vaccination and isolation on COVID-19 transmission within household settings Participants: n=210 households, with n=215 index cases and 687 household contacts, of 12,518 healthcare workers (HCWs) and their adult, teenage and child household members eligible for inclusion. Index cases (all): (n=215) Mean age: 32 years (SD: 16 years) Sex: 42% male Symptom status: 85% symptomatic Vaccinated: n=15 (7.0%) Median time from second dose to detection: 44 days (IQR: 13 to 59 days) Index cases (more than 12 years only): (n=191) Mean age: 36 years (SD: 14 years) Sex: 40% male Symptom status: 90% symptomatic Vaccinated: n=15 (7.9%) Median time from second dose to detection: 44 days (IQR: 13 to 59 days) Household contacts (all): (n=687) Mean age: 27 years (SD: 20 years) Sex: 51% male Vaccinated: n=124 (18.0%) Median time from second dose to detection: 23 days (IQR: 14 to 36 days)	Outcomes: Secondary cases of laboratory confirmed COVID-19 within 10 days of the index case's positive test. Exposure: Definition of vaccinated: Vaccinated with 2 doses of Pfizer vaccine, with COVID-19 exposure occurring at least 7 days after the second dose. Definition of unvaccinated: No vaccine received prior to positive test results or exposure. Definition of index case: Household member with the first positive RT-qPCR test. Prior infections: Data collected but not reported. Testing: Healthcare workers: RT-qPCR testing. If a household contact or HCW reported symptoms, HCWs were RT-qPCR tested daily for 10 days. Self-reported symptoms collected via an electronic survey daily. Household contacts: Self-reported results of tests conducted by their respective healthcare providers. For 10 days following detection of an index case, vaccinated contacts instructed to complete 2 tests, and unvaccinated contacts instructed to test on day one and 10. SARS-CoV-2 variant: Alpha (~90% of transmission during study) Data collection: Participant and household characteristic and symptom surveillance data were collected during telephone interviews	Findings Secondary attack rate (SAR) of household contacts (all), by index case (all) vaccination status: • not vaccinated: n=261 of 641 (40.7%) • vaccinated: n=8 of 43 (18.6%) Relative risk of transmission, vaccinated compared with unvaccinated index cases • 0.22 (95% CrI: 0.06 to 0.70) Secondary attack rate, by household contact (more than 12 years) vaccination status • not vaccinated or isolated: n=81 of 108 (75.0%) • not vaccinated and Isolated: n=71 of 259 (27.4%) • vaccinated and not isolated: n=10 of 39 (25.6%) • vaccinated and isolated: n=9 of 83 (10.8%) Relative risk of transmission, compared with household contacts who were not vaccinated and did not isolate (more than 12 years) • not vaccinated, isolated: 0.11 (95% CrI: 0.05 to 0.19) • vaccinated, not isolated: 0.19 (95% CrI: 0.07 to 0.40) • vaccinated and isolated: 0.07 (95% CrI: 0.03 to 0.17) Estimated probability of transmission in a 4 person household between: • unvaccinated index case and household contact (both more than 12 years): 59.2% (95% CrI: 46.4% to 70.2%)	Confounding: There is a high risk of bias from residual confounding even after adjustment, particularly as deprivation was not accounted for. Other bias: The COVID-19 status of healthcare workers who confirmed through RT-qPCR, while the status of household members was self-reported. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Household contacts (more than 12 years only): (n=494) Mean age: 36 years (SD: 17 years) Sex: 49% male Vaccinated: n=124 (25.1%) Median time from second dose to detection: 23 days (IQR: 14 to 36 days) Setting: Israel, 31 December 2020 to 26 April 2021	Statistical analysis: Transmission risk: Bayesian model developed to estimate the effect of age, isolation (after contact), vaccination and household characteristics on person to person risk of transmission in household settings, adjusted for community risk of infection and household contacts infected by a non-index case household member.	• vaccinated index case and household contact (both more than 12 years): 3.6% (95% CrI: 0.7% to 12.8%) Relative risks were converted to relative risk reduction in report (RR reduction = 1 – RR)	
Meyer and others, 2021 (35) 'Two doses of the mRNA BNT162b2 vaccine reduce severe outcomes, viral load and secondary attack rate: evidence from a SARS-CoV-2 Alpha outbreak in a nursing home in Germany, January-March 2021' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To describe the epidemiology of an outbreak of COVID-19 in a German nursing home, including the effect of vaccines on secondary transmission Participants: (n=128 staff members) Sex: 12% male Median age: 49 years (IQR: 32 to 58 years) Index cases: (n=14 COVID-19 positive staff members) Vaccinated: n=5 (35.7%) Contacts: (n=27 household members of index cases, in 14 households) Vaccinated: n=9 (33.3%) Setting: Germany, January to March 2021	Outcome: Secondary cases of COVID-19 in household members of staff index cases one to 14 days after diagnosis of the corresponding index case. Exposure: Vaccination status of nursing staff index cases; staff were vaccinated with the Pfizer vaccine in early and late January 2021, with an inter-dose interval of 3 weeks. Definition of contact: Household members of staff index cases. Prior infections: Data collected and reported: 0 prior infections in household members of vaccinated index cases, 2 prior infections (9.1%) in household members of unvaccinated index cases. Testing: Staff: Screened daily with lateral flow tests, infections confirmed with RT-PCR tests. Household contacts: RT-PCR tested twice within 14 days of exposure. SARS-CoV-2 variant: Alpha (n=27 of 28 samples tested, 96%).	Findings Secondary attack rate, by index case vaccination status: • unvaccinated: n=12 of 18 (67%) • vaccinated: n=2 of 9 (22%) • p value for difference = 0.046	Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		Data collection: Household members were tested twice during quarantine, no further details. Statistical analysis: Fisher's exact test, excluding household members infected within 6 months prior to the infection of the index case and household members who isolated separately from the index case.		
Prunas and others, 2021 (39) 'Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To assess the effectiveness of vaccination in relation to susceptibility to infection and infectiousness (transmission) following vaccination Participants: n=253,564 individuals in n=65,624 households with at least one COVID-19 case and at least 2 household members. Setting: Israel, 15 June 2020 to 24 March 2021	Outcomes: Secondary cases of laboratory confirmed COVID-19, living in the same household Exposure: Definition of vaccinated: At least 10 days after receiving the second dose of Pfizer vaccine. Definition of unvaccinated: Individuals who have received no vaccine doses. Prior infections: NR Testing: Positive RT-PCR test for SARS-CoV-2. SARS-CoV-2 variant: NR Data collection: Data from the Maccabi Healthcare Services centralised database (representing a representative quarter of the Israeli population). Statistical analysis: Two discreet time-to-event data models of household transmission were developed to estimate vaccine effectiveness against susceptibility to infection and against infectiousness given infection: a primary transmission model and an infection-hazard model (results not reported here). The date when a person with a positive RT-PCR test was infected and for how long they were infectious were imputed based on prior knowledge. The primary transmission models accounts for demographics, community risk,	Findings Primary transmission model Vaccine effectiveness against infectiousness given infection, fully vaccinated compared with unvaccinated index cases: 41.3% (95% CI: 9.5% to 73.0%)	Confounding: There is a high risk of bias from residual confounding even after adjustment, particularly as deprivation was not accounted for. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		vaccination status and characteristics of household transmission.		
Salo and others, 2021 (36) 'The indirect effect of mRNA-based Covid-19 vaccination on unvaccinated household members' PREPRINT (version 2)	Study design: Retrospective cohort Objective: To assess the direct and indirect effectiveness of the Pfizer and Moderna vaccines Participants: Healthcare workers (HCWs) aged 15 to 74 years in Finland and their spouses living in the same household Vaccinated HCWs: (n=95,138) Mean age: 47.1 years (SD: 13.1 years) Sex: 86.5% female Unvaccinated spouses of vaccinated HCWs: (n=52,766) Mean age: 48.9 years (SD: 12.4 years) Sex: 10.7% female Unvaccinated HCWs: (n= 193,000) Mean age: 43.8 years (SD: 14.5 years) Sex: 86.4% female Unvaccinated spouses of unvaccinated HCWs: (n=111,000) Mean age: 47.0 years (SD: 13.8 years) Sex: 11.7% female Setting: Finland, 27 December 2020 to 24 March 2021	Outcomes: COVID-19 incidence amongst the unvaccinated spouses of vaccinated and unvaccinated HCWs living in the same household. Exposure: Definition of vaccinated: at least 10 days after vaccination with first dose of Pfizer or Moderna vaccine (more than 40% had received their second dose 4 weeks after their first). Definition of unvaccinated: No vaccine received prior to positive test results. Prior infections: NR Definition of HCW: Physicians, senior nurses, ward sisters, nurses, midwifes, dentists, audiologists, speech therapists. Testing: RT-PCR testing of HCWs and contacts. Asymptomatic screening not conducted. SARS-CoV-2 variant: NR Data collection: Database linkages including the national database for all RT-PCR confirmed infections (Finnish National Infectious Diseases Register), The Finnish National Vaccination Register and The Finnish Incomes Register. Databases were merged with population datasets (Statistics Finland FOLK module 2019) which included identifiers for persons occupying the same household. Statistical analysis: Log-binomial model used to estimate the effect of vaccination on COVID-19 transmission as a relative	Findings This study looked at all healthcare workers, not just those with a confirmed COVID-19 infection, so these results include the effect of vaccines on preventing COVID-19 as well as on reducing transmission from index cases with COVID-19. Relative risk reduction in transmission, compared to unvaccinated index cases • 2 weeks after first dose: 8.7% (95% CI: -28.9 to 35.4) • 10 weeks after first dose: 42.9% (95% CI: 22.3 to 58.1)	Confounding: There is a high risk of bias from residual confounding even after adjustment, particularly as deprivation was not accounted for. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		risk reduction, adjusting for week of infection, age, age-squared and sex.		
Shah and others, 2021 (26) 'Effect of vaccination on transmission of COVID-19: an observational study in healthcare workers and their households'	Study design: Retrospective cohort Objective: To estimate the effect of vaccination transmission of COVID-19 Participants: 144,525 healthcare workers (aged 18 to 65 years) employed by NHS Scotland and 194,362 household members from households with no more than 1 healthcare worker Vaccinated healthcare workers (n=114,257, 79.1%) Mean age: 45.3 years (SD: 11.2 years) Sex: 21.5% male Ethnicity: 96.8% White Fully vaccinated: n=39,368 (34.5%) Partially vaccinated: n=77,889 (68.2%) SIMD: 1 (most deprived): 14.5%; 2: 18.4%; 3: 19.8%; 4: 22.9%; 5: 24.4% Unvaccinated healthcare workers: (n=30,268, 20.9%) Mean age: 41 years (SD: 11 years) Sex: 20.4% male Ethnicity: 96.4% white SIMD: 1 (most deprived): 17.1%; 2: 20.1%; 3: 19.4%; 4: 21.3%; 5: 22.1% Vaccinated household members (n=153,683, 79.1%) Mean age: 31 years (SD: 21 years) Sex: 62.2% male Ethnicity: 96.1% White Fully vaccinated: n=74,889 (65.5%) Partially vaccinated: n=105,476 (68.6%) SIMD: 1 (most deprived): 12.9%; 2: 17.5%; 3:	Outcomes: Transmission of COVID-19 to unvaccinated household members. Exposure: Definition of vaccinated Post-second dose: at least 14 days after vaccination with the second dose of the AstraZeneca or Pfizer vaccine. Post-first dose: at least 14 days after vaccination with the first dose of the AstraZeneca or Pfizer vaccine. Definition of unvaccinated: No vaccine received prior to positive test results. Prior infections: HCWs with a confirmed prior infection before the initiation of the vaccination programme were excluded. Prior infection data for household contacts not reported and inclusion criteria is unclear. Testing: RT-PCR testing for HCWs and household contacts. Asymptomatic screening unclear for HCWs and not conducted for household contacts. SARS-CoV-2 variant: NR Data collection: National database linkages including Community Health Index, Scottish Workforce Information Standard System, and General Practitioner Contractor Database. Statistical analysis: Extended cox regression models used to estimate hazard ratios (HRs) for the effect of vaccination on both transmission and hospitalisation, adjusted for	Findings This study looked at all healthcare workers, not just those with a confirmed COVID-19 infection, so these results include the effect of vaccines on preventing COVID-19 as well as on reducing transmission from index cases with COVID-19. Secondary attack rate of unvaccinated household members, by index case vaccination status: • unvaccinated period: n=2,037 of 194,362 over a mean of 41 person days (9.40 cases per 100 person years) • post-first dose period: n=1,086 of 148,366 over a mean of 45 person days (5.93 cases per 100 person years) • post-second dose period: 2.98 cases per 100 person years HR for transmission to unvaccinated household members, compared with the unvaccinated period: • post-first dose period: 0.70 (95% CI: 0.63 to 0.78) • post-second dose period: 0.46 (95% CI: 0.30 to 0.70) COVID-19 associated hospitalisation rate of unvaccinated household members, by index case vaccination status: • unvaccinated period: n=111 of 194,362 over a mean of 41 person days (0.51 hospitalisations per 100 person years) • post-first dose period: n=64 of 149,689 over a mean of 45 person days (0.35 cases per 100 person years)	Confounding: There is some risk of bias from residual confounding even after adjustment, although the analysis accounted for this well. Other bias: No specific biases to report. QCC rating: High

Reference	Study design	Methods	Findings	Risk of bias
	19.5%; 4: 23.9%; 5: 26.1% Unvaccinated household members: (n=40,679, 20.9%) Mean age: 29.7 years (SD: 20.9 years) Sex: 61.1% male Ethnicity: 95.2% white SIMD: 1 (most deprived): 15.6%; 2: 19.7%; 3: 19.2%; 4: 21.5%; 5: 24.0% Settings: Scotland, 8 Dec 2020 to 3 March 2021	age, sex, Scottish index of multiple deprivation (SIMD), ethnicity, comorbidities, healthcare worker role, occupation and part-time status., clustering on households and stratifying on health board area. Household members were censored from the time of any vaccination.	HR for COVID-19 association hospitalisation of unvaccinated household members, compared with the unvaccinated period: • post-first dose period: 0.77 (95% CI: 0.53 to 1.10) • post-second dose period: 0.68 (95% CI: 0.17 to 2.83)	

Supplementary Table 2. Characteristics of included studies on viral load

Acronyms: CI = confidence interval, CrI = credible interval, CPE = cytopathic effects, HCW = healthcare worker, HR = hazard ratio, IMD = index of multiple deprivation, IQR = interquartile range, OR = odds ratio, RR = risk ratio, RT-PCR = reverse transcriptase polymerase chain reaction SD = standard deviation, SE = standard error, SIMD = Scottish index of multiple deprivation, VE = vaccine effectiveness

Reference	Study design	Methods	Findings	Risk of bias
Abu-Raddad and others, 2021 (64) 'Effect of vaccination and of prior infection on infectiousness of vaccine breakthrough infections and reinfections' PREPRINT (version 1)	Study design: Nested case-control Objective: To assess the effect of vaccination and reinfection on viral load and infectiousness Participants: 307,664 COVID-19 positive cases, from which pairs of vaccinated (Pfizer and Moderna separately) and unvaccinated participants were matched Study 1 (Pfizer) Vaccinated cases (n=4,035) Median age: 42 years (IQR: 34 to 53 years) Sex: 37.4% female Ethnicity: 31% Qatari, 21% Indian Unvaccinated cases (n=4,035) Median age: 41 years (IQR: 34 to 52 years) Sex: 37.4% female Ethnicity: 10% Qatari, 29% Indian Study 2 (Moderna) Vaccinated cases (n=265) Median age: 35 years (IQR: 30 to 42 years) Sex: 21.1% female Ethnicity: 9% Qatari, 42% Indian Unvaccinated cases (n=265) Median age: 35 years (IQR: 30 to 41 years) Sex: 21.1% female Ethnicity: 6% Qatari, 34% Indian Setting: Qatar, 28 February 2020 to 11 July 2021	Outcomes: Mean cycle threshold (Ct) values for COVID-19 positive symptomatic and asymptomatic cases. Exposure: Definition of fully vaccinated: more than 14 days after the second dose of Pfizer or Moderna. Definition of unvaccinated: No vaccine received prior to positive test results. Prior infections: NR Testing: RT-qPCR testing, national laboratory: all positive results, testing due to symptoms and random testing campaigns (asymptomatic screening). TaqPath Combo Kits used for Ct counts (mean of N, ORF1ab and S genes). SARS-CoV-2 variant: First wave peaked late May 2020 (no VOCs), second wave early March 2021 (Alpha), third wave early April 2021 (Beta), low levels of Delta to July 2021. Data collection: Data collected from Qatari Hamad Medical Corporation database (main public healthcare provider and the nationally designated provider for all COVID-19 healthcare needs). Statistical analysis: Mean CT differences between vaccinated and unvaccinated participants, with independent T-tests, matching participants on sex, age, reason for testing, and testing calendar week, for the following comparisons:	Findings Study 1 (Pfizer), mean Ct values All infections • unvaccinated: 24.0 (SD: 6.5, 95% CI: 23.8 to 24.2) • vaccinated: 25.0 (SD: 6.6, 95% CI: 24.8 to 25.2) • mean difference: 1.0 (95% CI: 0.7 to 1.2), p<0.001 Symptomatic infections • unvaccinated: 22.5 (SD: 6.0, 95% CI: 22.2 to 22.8) • vaccinated: 22.7 (SD: 6.0, 95% CI: 22.4 to 23.0), • mean difference: 0.2 (95% CI: -0.2 to 0.6), p=0.34 Asymptomatic infections • unvaccinated: 25.5 (SD: 6.6, 95% CI: 25.2 to 25.8) • vaccinated: 26.8 (SD: 6.5, 95% CI: 26.5 to 27.2) • mean difference: 1.3 (95% CI: 0.9 to 1.8), p<0.001 Study 2 (Moderna), mean Ct values All infections • unvaccinated: 26.8 (SD: 7.1, 95% CI: 25.9 to 27.6) • vaccinated: 30.3 (SD: 5.9, 95% CI: 29.6 to 31.0) • mean difference: 3.5 (95% CI: 2.4 to 4.6), p<0.001 Symptomatic infections • unvaccinated: 21.7 (SD: 5.5, 95% CI: 20.0 to 23.3) • vaccinated: 26.6 (SD: 6.7, 95% CI: 24.6 to 28.6) • mean difference: 4.9 (95% CI: 2.4 to 7.4), p<0.001 Asymptomatic infections • unvaccinated: 28.0 (SD: 6.7, 95% CI: 27.0 to 29.1) • vaccinated: 31.2 (SD: 5.5, 95% CI: 30.4 to 32.1)	Risk of bias Confounding: There is a high risk of bias from residual confounding even after adjustment, particularly as deprivation was not accounted for. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		• all infections • symptomatic infections (tested because of clinical suspicion) • asymptomatic infections (random testing, routine care testing, or through travel)	• Mean difference: 3.2 (95% CI: 1.8 to 4.5), p<0.001	
Bailly and others, 2021 (45) 'BNT162b2 mRNA vaccination did not prevent an outbreak of SARS COV-2 variant 501Y.V2 in an elderly nursing home but reduced transmission and disease severity'	Study design: Prospective cohort (outbreak investigation) Objective: To assess the attack rate amongst nursing home residents during a COVID-19 outbreak, and the symptom status and viral load of positive cases Participants: 31 residents and 59 staff members in a nursing home Residents Fully vaccinated (n=26) Mean age: 87.0 years (SD: 8.2) Sex: 64.5% female Unvaccinated (n=5) No data Setting: France, 8 March to 29 March 2021	Outcome: confirmed COVID-19 infections and associated Ct values. Exposure: Definition of fully vaccinated: 2 doses of Pfizer vaccine administered at least 10 days before the first positive test. Definition of unvaccinated: No vaccine received prior to positive test. Time since vaccination: 96% of vaccinated residents received their second dose more than one month before the outbreak. Prior infections: NR Testing: RT-qPCR testing of all participants at baseline followed by serial asymptomatic screening until no cases were detected. SARS-CoV-2 variant: Whole genome sequencing completed for 10 out of 17 cases, all of which were positive for the 501Y.V2 variant (Beta). Data collection: All data collected by nursing home medial staff during routine care. Testing and variant data collected from an external laboratory. Statistical Analysis: Student t test used for the Ct value comparative analysis.	Findings Mean Ct values • unvaccinated: 15 (Median = 16, IQR: 12.5 to 17) • fully vaccinated: 21 (Median = 19, IQR: 16 to 29) • P for difference: <0.05 Medians and IQRs extracted from a figure.	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other Bias: No specific biases to report. QCC rating: Medium
Blanquart and others, 2021 (46)	Study design: Retrospective cohort Objective: To assess and compare the viral load (Ct values) of COVID-19 positive individuals	Outcom.es: COVID-19 infections and associated Ct values. Exposure:	Findings Comparison of Ct values (all variants), fully vaccinated compared to unvaccinated:	Risk of bias Confounding: There is a high risk of bias from

Reference	Study design	Methods	Findings	Risk of bias
'Characterisation of vaccine breakthrough infections of SARS-CoV-2 Delta and Alpha variants and within-host viral load dynamics in the community, France, June to July 2021'	according to their vaccination status, self-reported symptoms and infecting variant Participants: 8,437 COVID-19 positive adults (primary analysis: Ct analysis not controlled for time since symptom onset) Fully vaccinated cases (n=943) Age: less than or equal to 49 years: 64% Sex: 42% female, 35% male, 23% unknown Variant: 92% Delta Unvaccinated cases (n=7,494) Age: less than or equal to 49 years: 88% Sex: 37% female, 36% male, 27% unknown Variant: 91% Delta Setting: France, 14 June to 30 July 2021	Definition of fully vaccinated: Positive test at least 14 days after the second dose (vaccine not specified). Definition of unvaccinated: No vaccine received prior to positive test results. Testing: RT-PCR testing and genomic screening for the L452R mutation (indicative of Delta variant) for all positive tests. Prior infections: NR SARS-CoV-2 variant: Delta (91% of participants) Data collection: RT-PCR results (including L452R status), Ct values, self-reported symptoms and time since symptom onset, and self-reported vaccination status data was collected from a laboratory group conducting community testing across 3 regions of France. Statistical analysis: Tukey multiple comparisons of means from analysis of variance, accounting for presence of symptoms and the Delta variant. An additional analysis used a linear model, accounting for presence of the Delta variant and time since symptom onset.	• symptomatic: -0.25 (95% CI: -0.96 to 0.46), p=0.80 • asymptomatic: 1.68 (95% CI: 1.03 to 2.33), $p < 10^{-6}$ Comparison of Ct values (Delta only), fully vaccinated compared to unvaccinated: • symptomatic: -0.14 (95% CI: -0.99 to 0.72), p>0.99 • asymptomatic: 1.42 (95% CI: 0.61 to 2.24), p=0.000003 Comparison of Ct values (non-Delta only), fully vaccinated compared to unvaccinated: • symptomatic: -1.91 (95% CI: -5.99 to 2.16), p=0.85 • asymptomatic: 4.07 (95% CI: 1.84 to 6.31), $p < 10^{-6}$	residual confounding even after adjustment, particularly as age, sex and deprivation were not accounted for. Other bias: Measurement bias: Vaccination status and time since symptom onset were self-reported. QCC rating: Medium
Chia and others, 2021 (47) 'Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study'	Study design: Retrospective cohort Objective: To compare the risk of severe COVID-19 infection and the rate of reduction in Ct values over time, in vaccinated and unvaccinated positive cases Participants: 218 COVID-19 (Delta variant) positive adults (aged at least 18 years) admitted to hospital (all COVID-19 positive patients are admitted to hospital routinely in Singapore, even if asymptomatic)	Outcomes: COVID-19 infections confirmed by RT-PCR, and consecutive Ct values over time. Exposure: Definition of fully vaccinated: at least 14 days after the second dose of the Pfizer or Moderna vaccine. Definition of unvaccinated: No vaccine received prior to positive test results . Testing: Serial RT-PCR tests and genomic sequencing for all samples with Ct less than 30, Ct	Findings Median Ct value on day of diagnosis: • unvaccinated: 18.8 (IQR: 14.9 to 22.7) • fully vaccinated: 19.2 (IQR: 15.2 to 22.2) • p = 0.929 Median Ct values for symptom onset • unvaccinated: 21.9 (IQR: 18.8 to 31.2) • fully vaccinated: 19.2 (IQR: 16.6 to 21.5) • p = 0.279	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
PREPRINT (version 1)	Fully vaccinated cases (n=71) Median age: 56 years (IQR: 39 to 64 years) Sex: 62% female Baseline health: median Charlson comorbidity index: 0 (IQR: 0 to 0), 7% diabetes, 19.7% hypertension, 25.4% hyperlipidaemia Vaccines: 93% Pfizer, 7% Moderna Unvaccinated cases (n=130) Median age: 39.5 years (IQR: 30 to 58 years) Sex: 48.5% female Baseline health: median Charlson comorbidity index: 0 (IQR 0 to 1), 21.5% diabetes, 21.5% hypertension, 24.6% hyperlipidaemia Setting: Singapore, 1 April to 14 June 2021	values assessed on Elecsys chemiluminescent immunoassays as part of routine care. Prior infections: NR SARS-CoV-2 variant: Delta detected in all samples included in the analyses. Data collection: RT-PCR results and Ct values collected via electronic records. Statistical analysis: t-test for comparison of median Ct values between vaccinated and unvaccinated. Additionally, serial Ct values were plotted with marginal effect of day of illness by vaccination status using a generalised additive mixed model with a random intercept.	Generalised additive mixed model: Fully vaccinated patients had faster rate of Ct increase than unvaccinated, suggesting faster viral load decline, with trajectories separating at around 7 to 8 days and estimates of the interaction terms for vaccination status and day of illness were between 9.12 (SE: 3.75) and 12.06 (SE: 3.03).	
Christensen and others, 2021 (48) ‘Delta variants of SARS-CoV-2 cause significantly increased vaccine breakthrough COVID-19 cases in Houston, Texas’	Study design: Retrospective cohort Objective: To assess the association between specified patient characteristics and vaccine breakthrough cases. Participants: 16,965 sequenced COVID-19 positive cases (from 18,736 total cases). Positive cases (Delta, n=13,043): Fully vaccinated: 3,088 (23.7) Partially vaccinated: 472 (3.6%) Unvaccinated: 9,483 (72.7%) Positive cases (other variants, 62% Alpha, n=3,922): Fully vaccinated: 258 (6.6%) Unvaccinated: 3,509 (89.5%) Vaccines in breakthrough cases (n=3,346) Pfizer: 2,829 (85%) Moderna: 365 (11%)	Outcomes: Confirmed COVID-19 infections and associated Ct values. Exposure: Fully vaccinated: more than 14 days after final dose of Pfizer, Moderna or Janssen. Unvaccinated: No vaccine received prior to positive test results. Testing: RT-PCR testing and genomic sequencing. Unclear if asymptomatic screening was conducted. Prior infections: NR SARS-CoV-2 variant: Delta (76.9%), Alpha (14.3%) Data collection: Specimens were obtained from registered patients at Houston Methodist hospitals. Patient metadata were acquired from the electronic medical records. Statistical analysis: Mann-Whitney tests.	Findings Median Ct values (Abbott Alinity assay): • unvaccinated (n=4,364): 22.1 • fully vaccinated (n=1,244): 20.5 • p=0.002 Median Ct values (Hologic Panther assay): • unvaccinated (n=1,235): 23.5 • fully vaccinated (n=378): 22.2 • p=0.035	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other Bias: Selection bias: Only 46% of cases had data for Ct value. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Janssen: 147 (4%) Setting: US, 15 March to 20 September 2021			
Elliott and others, 2021 (29) 'REACT-1 round 13 final report: exponential growth, high prevalence of SARS-CoV-2 and vaccine effectiveness associated with Delta variant in England during May to July 2021' REACT study PREPRINT (version 1)	Study design: Prospective cohort Objective: To estimate vaccine effectiveness by analysing COVID-19 incidence trends and the viral load and symptom status of confirmed positive cases Participants: n=57,457, aged 18 to 64 years Fully Vaccinated: n=34,503 (60.1%) Partially vaccinated: n=9,467 (16.5%) Unvaccinated: n=2,574 (4.5%) Setting: UK, 24 June to 12 July 2021	Outcomes: COVID-19 confirmed by RT-PCR, prevalence of variants of concern, Ct values and symptoms of positive cases. Exposure: Definition of fully vaccinated: at least 14 days after the second dose of a COVID-19 vaccine (type not specified). Definition of unvaccinated: No vaccine received prior to positive test results. Prior infections: NR Testing: Self-collected RT-PCR tests (asymptomatic screening conducted). SARS-CoV-2 variant: Delta (100%) Data collection: NHS register, online or telephone questionnaire, NHS record linkage. Statistical analysis: Wilcoxon two-sample test (Mann Whitney-U) comparing Ct values of vaccinated and unvaccinated participants.	Findings Median Ct values: • unvaccinated (n=28): 23.1 (95% CI: 20.3 to 25.8) • partially vaccinated (n=76): 27.4 (95% CI: 24.8 to 30.0), p=0.04 • fully vaccinated (n=145): 27.6 (95% CI: 25.5 to 29.7), p=0.01 Median Ct values, N-gene Ct less than 33 only: • unvaccinated (n=26) 22.9 (95% CI: 20.4 to 25.5) • partially vaccinated (n=62): 25.2 (95% CI: 22.6 to 27.8), p=0.15 • fully vaccinated (n=99): 24.3 (95% CI: 22.5 to 26.1), p=0.41	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: Selection bias: Response rates were low amongst 18 to 24 year olds and ethnic minorities. Measurement bias: Vaccination status was self-reported. QCC rating: Low
Emary and others, 2021 (3) 'Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a	Study type: RCT (analysis of viral load only included participants with COVID-19, so broke randomisation) Objective: To estimate the efficacy of the AstraZeneca vaccine against the Alpha variant. Participants: Previously unexposed adults (aged at least 18 to 55 years), not in occupations with potentially high COVID-19 exposure. Vaccinated group (n=4,244)	Outcome: COVID-19 confirmed with Nucleic Acid Amplification testing (NAAT), Ct values and duration of positivity. Intervention: AstraZeneca, standard dose (5×10^{10} viral particles) or half dose plus booster dose after 3 months as intervention, MenACWY (meningococcal conjugate control), single dose as control. Testing method: Symptomatic testing: Clinical assessment and NAAT	Findings Median Ct values (n=406): • unvaccinated: 20.2 (IQR: 15.5 to 29.6) • vaccinated: 28.8 (IQR: 20.5 to 33.5) • p<0.0001 Median Ct values, symptomatic cases only (n=218): • unvaccinated: 17.9 (IQR: 15.0 to 25.1) • vaccinated: 20.6 (IQR: 15.4 to 24.5) • p=0.07	Risk of bias Confounding: Although an RCT, the viral load analysis only included participants who developed COVID-19, which reduced or removed the effect of randomisation. Therefore, there is likely a very high risk of bias from confounding,

Reference	Study design	Methods	Findings	Risk of bias
randomised controlled trial' Clinical trial number: NCT04400838, ISRCTN: 15281137	Age: 18 to 55 years: 77.8%, 56 to 69 years: 11.2%, at least 70 years: 11.0% Sex: 58.6% female Ethnicity: White: 91.8%, Asian: 5.2% Baseline health: cardiovascular disease: 12.1%, respiratory disease: 11.9%, diabetes: 2.3% SARS-CoV-2 exposure: 65.4% in health or social care occupation COVID-19 cases: n=173 (4.1%) COVID-19 symptomatic cases: n=59 (1.4%) Unvaccinated group (n=4,290) Age: 18 to 55 years: 77.8%, 56 to 69 years: 11.2%, at least 70 years: 11.1% Sex: 60.1% female Ethnicity: White: 92.5%, Asian: 4.7% Baseline health: cardiovascular disease: 12.0%, respiratory disease: 12.5%, diabetes: 2.1% SARS-CoV-2 exposure: 66.4% in health or social care occupation COVID-19 cases: n=347 (8.1%) COVID-19 symptomatic cases: n=210 (4.9%) Settings: UK, Recruitment: 31 May to 13 Nov 2020, Doses administered: 3 Aug to 30 Dec 2020, Follow up: 1 Oct to 14 Jan 2021	Asymptomatic testing: Weekly NAAT using home-testing kits. Symptoms: Weekly assessment, including fever, cough, shortness of breath, change or loss of taste or smell. SARS-CoV-2 variant: 35% Alpha, 65% non-Alpha. Statistical analysis: Viral load analysis: Wilcoxon rank sum test (comparison of minimum Ct values across all positive swabs in intervention vs control group). Duration (weeks) of positivity: Wilcoxon rank sum test (number of weeks from first to last positive test was calculated for intervention vs control group)	Median Ct values, Alpha only (n=67): • unvaccinated: 15.2 (IQR: 13.0 to 19.3) • vaccinated: 19.3 (IQR: 15.4 to 22.0) • p=0.026 Median duration of positivity, symptomatic cases only (n=269): • unvaccinated: 2.0 weeks (IQR: 1.0 to 3.0 weeks) • vaccinated: 1.0 week (IQR: 1.0 to 2.0 weeks) • p=0.001	as the analysis was unadjusted. Other bias: Selection bias: only 15% of swabs were included in the analysis, with exclusions for unclear reasons. QCC rating: Medium
Eyre and others, 2021 (27) 'The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission' PREPRINT (version 2)	Study design: Retrospective cohort Objective: To investigate the impact of vaccination on COVID-19 transmission, including on viral load (Ct values) Study participants: 108,498 adult index cases (symptomatic and asymptomatic) aged at least 18 years Fully vaccinated index cases (n=19,321, 17.8%), by vaccine type: AstraZeneca (n=15,086, 13.9%)	Outcomes: COVID-19 in index cases, confirmed by RT-PCR, Ct values and proportion of reduction in transmission to contacts mediated by index case Ct values. Exposure: Definition of vaccinated: Full vaccination: at least 14 days after second Pfizer or AstraZeneca vaccine. Partial vaccination: First vaccine date to 13 days after second vaccine. Definition of unvaccinated: No vaccine received.	Findings Median Ct values, symptomatic index cases, by variant type and vaccination status: Alpha • unvaccinated: 18.4 (IQR: 15.7 to 22.5) • ully vaccinated (AstraZeneca): 23.9 (IQR: 18.1 to 32.5) • Fully vaccinated (Pfizer): 27.4 (IQR: 19.7 to 32.1) Delta (data extracted from figure) • unvaccinated: 17.1 • fully vaccinated (AstraZeneca): 17.3 • fully vaccinated (Pfizer): 18.2	Risk of bias Confounding: There is some risk of bias from residual confounding even after adjustment, although the analysis accounted for this well. Other bias: No specific biases to report. QCC rating: High

Reference	Study design	Methods	Findings	Risk of bias
	Median age: 49 years (IQR: 36 to 57 years) Sex: 50% Female Variant: 0.4% Alpha Median time from second dose to positive test (Alpha): 27 days (18.5 to 43 days) Median time from second dose to positive test (Delta): 51 days (35 to 70 days) Pfizer (n=4,235, 3.9%): Median age: 48 years (IQR: 32 to 60 years) Sex: 62% Female Variant: 3.0% Alpha Median time from second dose to positive test (Alpha): 42 days (26 to 63 days) Median time from second dose to positive test (Delta): 90 days (69 to 110 days) Partially vaccinated index cases (n=29,221, 26.9%), by vaccine type: AstraZeneca (n=8.294, 7.6%) Median age: 49 years (IQR: 36 to 57 years) Sex: 50% Female Variant: 0.4% Alpha Pfizer (n=20,927, 19.3%): Median age: 28 years (IQR: 22 to 35.5 years) Sex: 48% Female Variant: 15.6% Alpha Unvaccinated index cases (n=59,956, 55.3%) Median age: 35 years (IQR: 25 to 50 years) Sex: 51% female Variant (in associated index case): 71.9% Alpha Setting: England, 1 January 2021 to 31 July 2021	Prior infections: NR Testing: RT-PCR performed by three national laboratories were included, symptomatic or asymptomatic. SARS-CoV-2 Variants: Alpha (n=60,377 contacts, 41.3%) and Delta (n=85,866 contacts, 58.7%). Data collection: COVID-19 status from the English national contact tracing and testing service (NHS Test and Trace). Vaccination status from the National Immunisation Management Service. Statistical analysis: Poisson regression to estimate rate ratios for transmission for vaccination status, adjusting for contact event type; age, sex and symptom status of index cases; age, sex, vaccination status and time since vaccination of contacts; local deprivation; local weekly SARS-CoV-2 incidence from national testing data; and calendar time, and accounting for non-linearity and interactions, incorporating a mediation analysis to estimate proportion of reduction in transmission due to vaccination mediated by index case Ct values at diagnosis.	Median Ct values, asymptomatic index cases, by variant type and vaccination status: Alpha (data extracted from figure) • unvaccinated: 25.8 • fully vaccinated (AstraZeneca): 31.7 • fully vaccinated (Pfizer): 32.3 Delta (data extracted from figure) • unvaccinated: 22.0 • fully vaccinated (AstraZeneca): 24.1 • fully vaccinated (Pfizer): 25.7 Proportion of reduction in transmission mediated via index case Ct values at diagnosis, by variant type and vaccination status: Alpha: • partially vaccinated (AstraZeneca): 33% (95% CI: 23% to 53%) • partially vaccinated (Pfizer): 39% (30% to 53%) • fully vaccinated (AstraZeneca): 16% (1% to 80%) • fully vaccinated (Pfizer): 18% (9% to 64%) Delta: • partially vaccinated (AstraZeneca): 12% (95% CI: 7% to 19%) • partially vaccinated (Pfizer): 14% (11% to 17%) • fully vaccinated (AstraZeneca): 7% (5% to 10%) • fully vaccinated (Pfizer): 23% (17% to 33%)	
Griffin and others, 2021 (43)	Study design: Retrospective cohort	Outcomes: Confirmed COVID-19 infections and associated Ct values.	Findings	Risk of bias

Reference	Study design	Methods	Findings	Risk of bias
'SARS-CoV-2 Infections and Hospitalizations Among Persons Aged ≥16 Years, by Vaccination Status — Los Angeles County, California, May 1–July 25, 2021'	Objective: To assess vaccine effectiveness of the Moderna, Janssen and Pfizer vaccines against COVID-19 infection and hospitalisation. Participants: 43,127 COVID-19 positive adults (at least 16 years); a convenience sample within this was used for viral load outcomes. Fully vaccinated cases (n=10,895, 25.3%) Median age: 37 years (IQR: 28 to 52 years) Sex: 50.6% female Ethnicity: 31.7% Hispanic or Latino, 31.2% White, 8.3% Asian, 6.3% Black or African American Partially vaccinated cases (n=1,431, 3.3%) Median age: 35 years (IQR: 27 to 51 years) Sex: 52.9% female Ethnicity: 35.7% Hispanic or Latino, 22.4% White, 7.3% Asian, 9.6% Black or African American Unvaccinated cases (n=30,801, 71.4%) Median age: 32 years (IQR: 26 to 44 years) Sex: 50.2% female Ethnicity: 33.1% Hispanic or Latino, 18.2% White, 15.4% Black or African American, 3.1% Asian Setting: US, 1 May to 25 July 2021	Exposure: Definition of fully vaccinated: at least 14 days after the second dose of the Moderna or Pfizer vaccine, or the first dose of Janssen vaccine. Definition of partially vaccinated: at least 14 days after the first dose and less than 14 days after the second dose of the Moderna or Pfizer vaccine. Definition of unvaccinated: Less than 14 days after any vaccine, or no vaccine received prior to positive test results. Prior infections: NR Testing: RT-PCR or antigen testing of all cases and whole genome sequencing of a subset of cases. SARS-CoV-2 variant: Alpha and Delta (Delta increased from 8.5% to 91.2% amongst vaccinated cases during study). Data collection: COVID-19 surveillance and California Immunization Registry 2 databases. Statistical analysis: Kruskal-Wallis tests for differences in median Ct values by vaccination status (P values not reported).	Median Ct values in Alpha dominant period (May 2021, more than 50%): ORF1ab gene target • unvaccinated: 22.8 • partially vaccinated: 36.6 • fully vaccinated: 27.2 N gene target • unvaccinated: 24.0 • partially vaccinated: 36.0 • fully vaccinated: 30.6 Median Ct values in Delta dominant period (July 2021, more than 90%): ORF1ab gene target • unvaccinated: 18.8 • partially vaccinated: 17.8 • fully vaccinated: 19.0 N gene target • unvaccinated: 19.3 • partially vaccinated: 18.6 • fully vaccinated: 19.5 SC2N gene target • unvaccinated: 19.3 • partially vaccinated: 20.2 • fully vaccinated: 19.4	Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: Measurement bias: Some participants were vaccinated outside of California and may have been misclassified as unvaccinated. The RT-PCR tests used to obtain CT values were qualitative and not approved for quantitative analysis of SARS-CoV-2 viral nucleic acid. Selection bias: Ct values were only available for 16% of cases. QCC rating: Low
Hagan and others, 2021 (49) 'Outbreak of SARS-CoV-2 B.1.617.2 (Delta) Variant Infections Among Incarcerated Persons in a Federal Prison — Texas, July–August 2021'	Study design: Retrospective cohort (outbreak investigation) Objective: To analyse and compare attack rates, symptoms, hospitalisation rates and viral loads of COVID-19 (Delta variant) positive cases according to their vaccination status. Participants: 233 male adults (at least 18 years) incarcerated in 2 housing units within a federal prison, of whom 172 (74%) tested positive for COVID-19.	Outcomes: RT-PCR confirmed infections and associated Ct values and cell culture cytopathic effects. Exposure: Definition of fully vaccinated: at least 14 days after the second dose of Moderna (27%) or Pfizer (66%) vaccines, or first dose of Janssen (7%). Definition of unvaccinated: No vaccine received prior to positive test results.	Findings Median time interval between symptom onset and last positive RT-PCR test (n=70) • unvaccinated: 11 days (IQR: 3 to 15 days) • vaccinated: 9 days (IQR: 8 to 10 days) • p=0.37 Proportion of samples with infectious virus recovered via cell culture • unvaccinated (n=12): 42% • vaccinated (n=37): 38%	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: Selection bias: Neither the participants providing serial swabs for RT-PCR testing, nor those

Reference	Study design	Methods	Findings	Risk of bias
	Fully vaccinated participants (n=185) Age: 18 to 29 years: 3.2%, 30 to 39 years: 24.9%, 40 to 49 years: 28.6%, 50 to 59 years: 29.7%, at least 60 years: 13.5% Sex: 100% male Ethnicity: 67.0% White (non-Hispanic), 15.7% Black (non-Hispanic), 13.5% Hispanic Unvaccinated participants (n=42) Age: 18 to 29 years: 7.1%, 30 to 39 years: 38.1%, 40 to 49 years: 26.2%, 50 to 59 years: 23.8%, at least 60 years: 4.8% Sex: 100% male Ethnicity: 45.2% White (non-Hispanic), 38.1% Black (non-Hispanic), 16.7% Hispanic Setting: US, 12 July to 14 August 2021	Testing: Any positive rapid antigen or RT-PCR test and genomic sequencing for each positive case. Of fully vaccinated participants, 17% had vaccinations 2 weeks to 2 months before the outbreak, 33% had vaccinations 2 to 4 months before the outbreak, and 50% had vaccinations 4 to 6 months before the outbreak. A subset of 70 participants provided swabs for serial RT-PCR testing. Prior infections: 17% of unvaccinated and 11% of vaccinated participants had documented previous infections. SARS-CoV-2 variant: Delta (100% of sequenced tests). Data collection: Vaccination status, demographic and baseline health data was collected via the prison's electronic health records. Statistical analysis: Chi-square or Fisher's exact test used to compare outcomes by vaccination status.		providing samples for viral cultures, were selected randomly. QCC rating: Medium
Ioannou and others, 2021 (50) 'Transmission of SARS-CoV-2 variant B.1.1.7 among vaccinated health care workers'	Study design: Prospective cohort Objective: To compare the viral load, incidence and exposure type of COVID-19 positive vaccinated and unvaccinated healthcare workers (HCWs). Participants: 2,250 HCWs (80% vaccinated), of whom 55 (2.4%) had COVID-19 Vaccinated cases (n=24) Mean age: 41.3 (SD: 10.1) Sex: 67% female SARS-CoV-2 exposure: 82% likely hospital acquired; 18% likely household contact acquired Fully vaccinated: 87.5% Unvaccinated cases (n=31)	Outcomes: RT-PCR confirmed infections and associated Ct values Exposure: Definition of fully vaccinated: Vaccinated with 2 doses of Pfizer vaccine more than 2 weeks after the second dose Definition of vaccinated: Vaccinated with at least 1 dose of Pfizer vaccine Definition of unvaccinated: No vaccine received prior to positive test results Testing: RT-PCR test. Genomic sequencing for all positive samples. SARS-CoV-2 variant: Alpha (98%)	Findings Median Ct values: • unvaccinated: 18.5 (IQR: 13.5 to 24) • vaccinated: 18.5 (IQR: 16 to 26) • p=0.70	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Mean age: 43.1 (SD: 9.8) Sex: 81% female SARS-CoV-2 exposure: 77% likely hospital acquired; 23% likely household contact acquired Setting: Greece, 4 Jan to 14 April 2021	 Data collection: Data collected by study staff for each HCW infected during the hospital outbreak. Statistical analysis: NR		
Jacobson and others, 2021 (51) 'Post-Vaccination Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infections and Incidence of the Presumptive B.1.427/B.1.429 Variant Among Healthcare Personnel at a Northern California Academic Medical Center'	Study design: Retrospective cohort Objective: To estimate the effect of early, partial and full vaccination on wild-type and B.1.427/B.1.429 COVID-19 infections and associated Ct values. Participants: 22,729 healthcare workers, of which 660 (2.9%) developed COVID-19. SARS-CoV-2 exposure: 68.3% patient- facing, 29.1% non-patient facing Baseline health: 3.7% immunocompromised Fully vaccinated (n=26, 3.9%): Mean age: 39.1 years (SD: 9.5 years) Sex: 69.2% female Partially vaccinated (n=49, 7.4%): Mean age: 44.0 years (SD: 12.6 years) Sex: 65.3% female Early post-vaccination (n=114, 17.3%): Mean age: 39.8 years (SD: 10.8 years) Sex: 65.8% female Unvaccinated (n=471, 71.4%): Mean age: 36.1 years (SD: 10.0 years) Sex: 71.3% female Setting: US, 18 December 2020 to 2 April 2021	Outcomes: RT-qPCR confirmed infections and associated Ct values Exposure: Definition of vaccinated: Fully vaccinated: more than 14 days after second dose of Pfizer (91.5%) or Moderna (7.9%) vaccine Partially vaccinated: more than 14 days after first dose and less than 14 days after second dose. Early post-vaccination: less than or equal to 14 days after first dose. Definition of unvaccinated: No vaccine received prior to positive test results. Testing: Occupational Health RT-qPCR testing for symptomatic, asymptomatic with exposure, weekly optional testing. Dec 2020 to Feb 2021: all samples with Ct less than or equal to 30 sequenced to identify variants. March 2021: samples with Ct less than or equal to 34 sequenced for variants. SARS-CoV-2 variant: • L452R mutation detected in 39.5% of samples (B.1.427/B.1.429 alert for future monitoring) • N501Y mutation detected in 6.1% of samples (Alpha, Beta, P.1) Data collection: Occupational health records Statistical analysis: NR	Findings Mean Ct values (n=283): • unvaccinated: 23.0 (SD: 7.4) • early post-vaccination: 22.6 (SD: 7.0) • partially vaccinated: 27.7 (SD: 8.7) • fully vaccinated: 28.5 (SD: 7.4) • unvaccinated or early post-vaccination: 22.9 • fully or partially vaccinated: 27.9 • p<0.001 for comparison of unvaccinated or early post-vaccination versus fully or partially vaccinated	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: Selection bias: Only 43% of cases had data for Ct value. QCC rating: Medium
Jones and others, 2021 (30)	Study design: Prospective cohort	Outcome: COVID-19 cases confirmed with RT-PCR and associated Ct values	Findings	Risk of bias

Reference	Study design	Methods	Findings	Risk of bias
'Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection'	Objective: To assess the incidence of COVID-19 infections and viral load amongst partially vaccinated and unvaccinated asymptomatic healthcare workers Participants: 8,776 healthcare workers Partially vaccinated at least 12 days after dose 1 (n=1,989, 22.6%) Partially vaccinated less than 12 days after dose 1 (n=3,535, 40.2%) Unvaccinated (n=3,252, 37.1%) Setting: UK, 18 to 31 January 2021	Exposure: Definition of partially vaccinated: less than 12 or at least 12 days after the first dose of Pfizer. Definition of unvaccinated: No vaccine received prior to positive test results. Prior infections: Partially vaccinated (at least 12 days after dose 1): 5.7%; partially vaccinated (less than 12 days after dose 1): 5.6%; unvaccinated: 7.1%. Testing: Weekly RT-PCR asymptomatic testing with self-swabbing kits. Serology testing used to confirm serostatus. SARS-CoV-2 variant: Alpha dominant period. Data collection: Testing, vaccination and serology data collected from the hospital laboratory. Statistical analysis: Fisher's exact test used to compare COVID-19 incidence between study groups. Wilson's method used to calculate 95%CI.	Median Ct values: • unvaccinated: 23.3 (IQR: 13.5 to 33.0) • partially vaccinated at least 12 days after first dose: 30.3 (IQR: 25.5 to 35.1) • p>0.05	Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium
Kang and others, 2021 (40) 'Transmission dynamics and epidemiological characteristics of Delta variant infections in China' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To compare epidemiological parameters, temporal trend of viral loads and secondary attack rates in close contacts between the Delta variant and wild-type SARS-CoV-2, and the effect of vaccination on viral load and transmission Participants: Index cases: (n=73 of 167 total) Sex: 41.3% male Median age: 47.0 years (IQR: 31.0 to 66.5); 13.2% aged under 15 years Unvaccinated: n=121 (72.4%); partially vaccinated: n=30 (18.0%); fully vaccinated: n=16 (9.6%)	Outcomes: Confirmed COVID-19 infections and associated Ct values Exposure: Definition of vaccinated: Fully vaccinated: at least 14 days after the second dose (inactivated COVID-19 vaccine) Partially vaccinated: at least 10 days after the first dose Definition of unvaccinated: NR Prior infections: NR Testing: RT-PCR testing. Asymptomatic screening conducted for index cases and close contacts.	Findings Participants vaccinated with 1 or 2 doses of inactivated vaccine had Ct values on average 0.97 (95% CI: 0.19 to 1.76) higher than unvaccinated participants. Predicted median Ct values, by day of symptom onset and vaccination status (n=159) (data extracted from figure): Day 0 of symptom onset • unvaccinated: 24.5 (IQR: 23.6 to 26.7) • vaccinated: 25.5 (IQR: 25.3 to 25.8) Day 8 of symptom onset • unvaccinated: 27.9 (IQR: 27.3 to 30.5) • vaccinated: 29.7 (IQR: 29.2 to 30.3) Day 16 of symptom onset	Confounding: There is a high risk of bias from residual confounding even after adjustment, particularly as deprivation was not accounted for. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Close contacts: (n=5,153) Sex: 49.5% male Median age: 47.0 years (IQR: 31.0 to 66.5); 8.2% aged under 15 years Unvaccinated: n=2,844 (55.2%); partially vaccinated: n=1,459 (28.3%); fully vaccinated: n=850 (16.5%) Setting: Guangdong, China, May to June 2021	Whole genome sequencing to confirm variants for all samples. SARS-CoV-2 variant: Delta (100%) Data collection: Information was collected, though not specified how, for all laboratory-confirmed symptomatic and asymptomatic cases with Delta variant in Guangdong province in May and June 2021. Statistical analysis: Multivariate generalised additive models used to estimate the effect of vaccination on viral load, adjusting for with days of symptom onset, age, and disease severity.	• unvaccinated: 34.6 (IQR: 34.0 to 36.6) • vaccinated: 36.1 (35.9 to 36.5)	
Kerwin and others, 2021 (52) 'An Analysis of SARS-CoV-2 Vaccine Breakthrough Infections and Associated Clinical Outcomes' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To assess the effect of vaccination on COVID-19 infections, viral load and clinical outcomes. Participants: 6,399 positive cases (any age) Fully vaccinated cases (n=338, 5.5%) Age: 0 to 19 years: 3%, 20 to 39 years: 34.9%, 40 to 59 years: 30.2%, 60 to 79 years: 27.2%, at least 80 years: 4.7% Sex: 58% female Ethnicity: 84.9% White, 6.3% Asian, 3.5% Black Unvaccinated cases (n=6,060, 94.5%) Age: 0 to 19 years: 20.9%, 20 to 39 years: 40.6%, 40 to 59 years: 26.5%, 60 to 79 years: 10.6%, at least 80 years: 1.5% Sex: 49.1% female Ethnicity: 86.3% White, 6.2% Asian, 6.4% Black Setting: US, 12 February 2021 to 29 July 2021	Outcomes: RT-PCR confirmed COVID-19 infections and associated Ct values. Exposure: Definition of vaccine breakthrough case: at least 14 days after second vaccination dose (vaccine not specified). Definition of non-vaccine breakthrough case (unvaccinated): less than 14 days after second vaccination dose. Testing: RT-PCR Prior infections: NR SARS-CoV-2 variant: Delta (74% of vaccinated cases with Ct values). Statistical analysis: Mann-Whitney U tests and Chi-squared or Fisher exact tests used to assess differences in demographics and outcomes by vaccination status.	Findings Median Ct values: • unvaccinated (all variants, n=797): 21 (IQR: 17 to 25) • fully vaccinated (all variants, n=120): 22 (IQR: 17 to 26) • fully vaccinated (Delta variant, n=77): 20 (IQR: 16 to 24) • fully vaccinated (non-Delta variants, n=27): 21 (IQR: 18 to 26) • p value for difference between fully vaccinated and unvaccinated (all variants) = 0.83	Risk of Bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: Selection bias: Inclusion and exclusion criteria were not reported, and only 14% of cases had reported Ct values. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
Kislaya and others, 2021 (65) 'Delta variant and mRNA Covid-19 vaccines effectiveness: higher odds of vaccine infection breakthroughs' PREPRINT (version 1)	Study design: Case-case Objective: To assess and compare mRNA vaccine effectiveness against breakthrough Delta and Alpha COVID-19 infections and associated viral load Participants: 2,097 COVID-19 positive adults (at least 40 years) Alpha variant cases Fully vaccinated: n=38 Partially vaccinated: n= 49 Early post-vaccination: n=73 Unvaccinated: n=517 Delta variant cases Fully vaccinated: n=162 Partially vaccinated: n=198 Early post-vaccination: n=229 Unvaccinated: n=777 Setting: Portugal, 17 May 2021 to 4 July 2021	Outcomes: RT-PCR positive COVID-19 infections and associated Ct values Exposure: Definition of vaccinated: Fully vaccinated: at least 14 days after second dose of Pfizer or Moderna vaccine. Partially vaccinated: at least 14 days after first dose or less than 14 days before second dose. Early post-vaccination: less than 14 days after first dose. Definition of unvaccinated: No vaccine received prior to positive test results. Testing: RT-PCR testing (symptomatic or asymptomatic). 46.1% of variants identified via whole genome sequencing (WGS) and 53.9% via spike gene target failure (SGTF). Prior infections: NR SARS-CoV-2 variant: Alpha (n=384) and Delta (n=873). Data collection: Data linkage of RT-PCR results obtained via the National Epidemiological Surveillance Information System, and vaccination status data collected via the electronic national vaccination register. Statistical analysis: A linear multiple regression model (adjusted for age, sex and week of diagnosis, with an interaction term between vaccination status and variant) was used to assess Ct value differences by variant and vaccination status.	Findings Mean Ct values, by variant and vaccination status: Delta: • unvaccinated: 16.5 (SD: 4.9) • early post-vaccination: 15.7 (SD: 4.9) • partially vaccinated: 16.1 (SD: 5.0) • fully vaccinated: 17.7 (SD: 5.7) • mean difference between partially vaccinated and unvaccinated: -0.15 (95% CI: -0.99 to 0.96) • mean difference between fully vaccinated and unvaccinated: 2.24 (95% CI: 0.85 to 3.64) Alpha: • unvaccinated: 18.4 (SD: 5.2) • early post-vaccination: 19.2 (SD: 5.6) • partially vaccinated: 20.0 (SD: 5.6) • fully vaccinated: 21.8 (SD: 5.7) • mean difference between partially vaccinated and unvaccinated: 1.87 (95% CI: 0.2 to 3.53) • mean difference between fully vaccinated and unvaccinated: 4.49 (95% CI: 2.07 to 6.91)	Risk of bias Confounding: There is a high risk of bias from residual confounding even after adjustment, particularly as deprivation was not accounted for. Other bias: Selection bias: RT-PCR results were not collected from hospitals, reducing the probability of including older and sicker participants, who would more likely be diagnosed in hospital. QCC rating: Medium
Levine-Tiefenburn and others, 2021 (53)	Study design: Retrospective cohort Objective: To compare the viral loads (Ct values) of fully vaccinated, booster vaccinated and unvaccinated COVID-19 (Delta) positive cases	Outcomes: RT-PCR positive COVID-19 infections and associated Ct values. Exposure:	Findings Mean Ct values (*RdRp* gene): • unvaccinated: 27.7 (SD: 5.0)	Risk of bias Confounding: There is a high risk of bias from residual confounding

Reference	Study design	Methods	Findings	Risk of bias
'Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2'	Participants: 16,553 COVID-19 positive adults (at least 20 years). Booster vaccinated (n=519): Mean age: 58.6 years (SD: 14.0 years) Sex: 44% female Fully vaccinated (n=12,934): Mean age: 42.0 years (SD: 14.5 years) Sex: 55% female Unvaccinated group (n=3,100): Mean age: 40.3 years (SD: 14.4 years) Sex: 58% female Setting: Israel, 28 June to 9 September 2021	Definition of vaccinated: Booster vaccinated: at least 7 days after third dose of Pfizer vaccine Fully vaccinated (2 dose): at least 7 days after second dose Definition of unvaccinated: No vaccine received prior to positive test results. Testing: RT-qPCR testing at central laboratory. Ct values for *E, N* and *RdRp* genes determined for each sample. Prior infections: People with previous positive samples excluded. SARS-CoV-2 variant: Delta (93%) Data collection: Testing data collected via the Maccabi Healthcare Services (MHS) central laboratory. Vaccination data collected via the centralised MHS database. Statistical analysis: Linear regression model to estimate the change in Ct between vaccinated and unvaccinated participants over time, adjusting for sex, age, and calendar date.	• fully vaccinated (all): 26.9 (SD: 5.0) • fully vaccinated (7 to 30 days after second dose): 31.2 (SD: 4.5) • fully vaccinated (31 to 60 days after second dose): 29.3 (SD: 5.1) • fully vaccinated (61 to 120 days after second dose): 27.2 (SD: 4.8) • fully vaccinated (121 to 180 days after second dose): 27.0 (SD: 5.0) • fully vaccinated (more than 180 days after second dose): 26.7 (SD: 5.0) • booster vaccinated: 29.1 (SD: 4.7) Difference in Ct values (*RdRp* gene), compared with unvaccinated: • fully vaccinated (all): 0.22 (95% CI: 0.02 to 0.42) • fully vaccinated (7 to 30 days after second dose): 4.56 (95% CI: 2.19 to 6.94) • fully vaccinated (31 to 60 days after second dose): 2.63 (95% CI: 0.67 to 4.59) • fully vaccinated (61 to 120 days after second dose): 0.58 (95% CI: 0.05 to 1.12) • fully vaccinated (121 to 180 days after second dose): 0.29 (95% CI: 0.08 to 0.51) • fully vaccinated (more than 180 days after second dose): 0.06 (95% CI: -0.16 to 0.29) • booster vaccinated: 2.43 (95% CI: 1.97 to 2.89) Difference in Ct values in fully vaccinated participants over time (*RdRp* gene): Ct values decreased by 3.1 (95% CI: -4.6 to -1.6) between the first 2 months after the second vaccination to 2 to 6 months after vaccination. Similar results were found for the *N* and *E* genes	even after adjustment, particularly as deprivation was not accounted for. Other bias: No specific biases to report. QCC rating: Medium
Levine-Tiefenburn and others, 2021 (54)	Study design: Retrospective cohort and matched case-control	Outcomes: RT-PCR positive COVID-19 infections and associated Ct values. Exposure:	Findings Difference in mean Ct values (*RdRp*), compared unvaccinated (data extracted from figure):	Risk of bias Confounding: There is a high risk of bias from

Reference	Study design	Methods	Findings	Risk of bias
'Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine'	Objective: To evaluate effect of the first dose of Pfizer vaccine on Ct values over time. Participants: n=4,938 adult (at least 16 years) cases with one dose of the Pfizer vaccine, matched (on sex, age and calendar date of positive sample) with n=4,938 unvaccinated cases. Sex: 48% female Setting: Israel, 21 December 2020 to 11 February 2021	Definition of vaccinated: Vaccinated with the first dose of the Pfizer vaccine. Definition of unvaccinated: No vaccine received prior to positive test results. Testing: RT-qPCR testing at central laboratory. Ct values for *E, N* and *RdRp* genes determined for each sample. Prior infections: People with previous positive samples excluded. SARS-CoV-2 variant: NR Data collection: Maccabi Healthcare Services, database linkages including Community Health Index, workforce and GP databases. Statistical analysis: Linear regression model to estimate the change in Ct between vaccinated and unvaccinated participants, adjusting for sex and age.	• 1-11 days post-vaccination: -0.07 (95% CI: -0.19 to 0.06) • 12 to 21 days post-vaccination: 1.75 (95% CI: 1.60 to 1.91) • 22 to 37 days post-vaccination: 2.15 (95% CI: 1.87 to 2.42) Similar results were found for the *N* and *E* genes Difference in mean Ct values of 12 to 37 days (n=1,888) compared with less than or equal to 11 days (n=3,050) vaccinated: • *RdRp* gene: 1.7 (SE: 0.2) • *N* Gene: 1.4 (SE: 0.2) • *E* Gene: 1.6 (SE: 0.2)	residual confounding even after adjustment, particularly as deprivation was not accounted for. Other bias: No specific biases to report. QCC rating: Medium
Li and others, 2021 (66) 'Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: A test-negative case-control real-world study'	Study design: Test-negative case-control study Objective: To estimate the vaccine effectiveness of COVID-19 inactivated vaccines against COVID-19 Delta infections and associated symptoms and viral load. Participants: 366 participants aged 18 to 59 years: 74 COVID-19 positive cases and 292 COVID-19 negative close contact controls. Vaccinated (n=38 in Ct analysis) Median age: 45.5 (IQR: 39.5 to 51.7) Sex: 60.5% female Unvaccinated (n=115 in Ct analysis) Median age: 65.0 (IQR: 21.5 to 71.5) Sex: 58.3% female	Outcomes: Confirmed COVID-19 infections and associated Ct values Cases: Patients with a confirmed COVID-19 infection. Cases classified as mild, moderate, severe or critical. Controls: All close contacts with a higher frequency of contact (jointly living, eating, or working). Exposure: Definition of vaccinated: Cases: clinical diagnosis at least 14 days after first dose with inactivated vaccines (Sinovac or Sinopharm). Controls: contact with cases diagnosis at least 14 days after first dose. Definition of unvaccinated: less than 14 days after first dose.	Findings Ct values: Ct value less than 24: • unvaccinated: 49.6% • vaccinated: 44.7% Ct value 24 to 40: • unvaccinated: 36.5% • vaccinated: 52.6% • p value for difference: 0.23	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Setting: China, 18 May to 20 June 2021	Testing: RT-PCR (asymptomatic or symptomatic). SARS-CoV-2 variant: Delta (100%) Data collection: By researchers in Guangzhou and investigations at Center for Disease Control and Prevention. Statistical analysis: Chi-squared or t-tests for differences in Ct values between vaccinated and unvaccinated.		
Lumley and others, 2021 (31) 'An observational cohort study on the incidence of SARS-CoV-2 infection and B.1.1.7 variant infection in healthcare workers by antibody and vaccination status'	Study design: Prospective cohort Objective: To assess the effect of vaccination and seropositivity on the incidence of COVID-19 infection and associated viral loads amongst healthcare workers. Participants: 13,109 healthcare workers from Oxford University Hospitals Median age: 39 years (IQR: 30 to 50 years) Sex: 74% female Seropositivity: n=1273 (9.7%) seropositive Fully vaccinated: n=1,356 (10.3%) Partially vaccinated: n=9,667 (73.7%) Unvaccinated: n=2,086 (15.9%) Setting: UK, 27 March 2020 to 28 February 2021	Outcome: Confirmed COVID-19 infections and associated Ct values and variant. Exposure: Definition of fully vaccinated: more than 14 days after second dose of Pfizer or AstraZeneca vaccine. Definition of partially vaccinated: more than 14 days after first dose. Definition of unvaccinated: No vaccine received prior to positive test results. Prior infections: Serostatus data collected and reported. Seropositive individuals were included in the analysis. Testing: Sequencing conducted for all RT-PCR positive samples. Symptomatic testing: RT-PCR test triggered by onset of COVID-19 symptom. Asymptomatic testing: Bi-weekly voluntary RT-PCR tests and serological testing (IgG, ELISA) every 2 months. SARS-CoV-2 variant: Alpha (56%) Data collection: Testing, vaccination and serostatus data collected by the NHS from Oxford University Hospitals.	Findings Median Ct values: • unvaccinated and seronegative: 18.3 (IQR: 14.0 to 25.5) • unvaccinated and seropositive: 27.2 (IQR: 18.8 to 32.2) • vaccinated and seronegative: 19.7 (IQR: 15.0 to 27.5) Difference in median Ct values, compared to unvaccinated seronegative participants: • unvaccinated and seropositive: 5.7 (95% CI: -0.9 to 13.2) • vaccinated and seronegative: 2.7 (95% CI: -0.5 to 6.8)	Risk of bias Confounding: There is an unclear risk of bias from confounding as it is not clear which, if any, variables were adjusted for, although a high or very high risk of bias from confounding is likely present. Other Bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		Statistical analysis: Quantile (median) regression used to compare Ct values between symptomatic and asymptomatic infections by vaccination and serostatus; it is unclear which, if any, variables were adjusted for in the analysis.		
Luo and others, 2021 (55) 'Infection with the SARS-CoV-2 Delta Variant is Associated with Higher Infectious Virus Loads Compared to the Alpha Variant in both Unvaccinated and Vaccinated Individuals' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To assess the incidence of COVID-19 breakthrough infections and associated disease severity and viral load for the Delta and Alpha VOCs and B.1.2 lineage Participants: 2,785 patients across the Johns Hopkins Medical System Delta Fully vaccinated (n=30): Median age: 40.5 years Sex: 60% female Ethnicity: 60% White, 20% Black, 16.7% Asian Baseline health: 36.7% cancer, 33.3% hypertension, 20% immunosuppression, 16.7% diabetes (additional comorbidities reported) Unvaccinated (n=69): Median age: 37 years Sex: 63.8% female Ethnicity: 50.7% Black, 31.9% White, 5.8% Asian Baseline health: 23.2% hypertension, 18.8% lung disease, 10.1% coronary artery disease, 10.1% cancer, 5.8% diabetes, 5.8% immunosuppression Alpha Fully vaccinated (n=59): Median age: 51 years Sex: 71.2% female Ethnicity: 64.4% White, 22% Black, 1.7% Asian	Outcomes: Confirmed COVID-19 infections and associated Ct values and cell cultures. Exposure: Vaccinated with 1 or 2 doses of the Pfizer, Moderna or Janssen vaccine. Definition of fully vaccinated: at least 14 days after the second dose of Pfizer and Moderna or a single dose of Johnson and Johnson. Definition of unvaccinated: No vaccine received prior to infection episode. Testing: RT-PCR testing (asymptomatic or symptomatic) of nasopharyngeal or lateral mid-turbinate nasal swabs, *N* gene testing for Ct values, cell culturing for virus isolation, genomic sequencing and antibody (ELISA) testing. Prior infections: NR SARS-CoV-2 variant: • January to February: B.1.2 lineage dominant • Late February to June: Alpha dominant • June to July: Delta dominant (88.2%) Data collection: Clinical data retrieved from electronic medical records. Statistical analysis: Comparative analyses of categorical and continuous independent variables conducted with Chi-square or Fisher exact tests and t-test or Kruskal-Wallis ANOVA tests respectively.	Findings Mean Ct values (*N* gene) of samples from which infectious virus was recovered (CPE positive), by variant and vaccination status: Delta • unvaccinated: 17.6 • fully vaccinated: 16.1 • p>0.05 Alpha • unvaccinated: 18.1 • fully vaccinated: 17.8 • p>0.05 Mean Ct values (*N* gene) of samples from which infectious virus was not recovered (CPE negative) by variant and vaccination status: Delta • unvaccinated: 25.3 • fully vaccinated: 24.4 • p>0.05 Alpha • unvaccinated: 24.9 • fully vaccinated: 24.1 • p>0.05 Samples with recoverable infectious virus (CPE positive), by variant and vaccination status: Alpha • unvaccinated (n=95): 37.9% • fully vaccinated (n=46): 17.4% • p=0.02 Delta • unvaccinated (n=63): 66.7%	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Baseline health: 52.5% cancer, 44.1% hypertension, 30.5% coronary heart disease, 25.4% immunosuppression, 23.7% lung disease Unvaccinated (n=1,298): Median age: 34 years Sex: 58% female Ethnicity: 60.6% Black, 25.4% White, 2.3% Asian Baseline health: 28.4% hypertension, 23.9% lung disease, 17.8% cancer, 14.4% smoker, 14.2% diabetes, 13.9% coronary artery disease Setting: US, January to July 2021		• fully vaccinated (n=27): 70.4% • p>0.05	
McEllistrem and others, 2021 (56) 'Single dose of a mRNA SARS-CoV-2 vaccine is associated with lower nasopharyngeal viral load among nursing home residents with asymptomatic COVID-19'	Study design: Retrospective cohort Objective: To assess vaccine effectiveness against high viral loads amongst asymptomatic COVID-19 cases Participants: 150 nursing home residents, of whom 10 developed asymptomatic COVID-19 Vaccinated (n=5): Age: 80% at least 65 years Co-existing conditions: 100% Unvaccinated (n=5): Age: 80% at least 65 years Co-existing conditions: 100% Setting: US, 2 December 2020 to 6 February 2021	Outcomes: Asymptomatic COVID-19 confirmed infections and associated viral load (Ct values and log10 viral load). Exposure: Definition of vaccinated: Vaccinated with first dose of Pfizer 12 to 15 days prior to testing positive for COVID-19. Definition of unvaccinated: No vaccine received prior to testing positive for COVID-19. Testing: Surveillance testing: SARS-CoV-2 antigen tests were conducted every 2 to 5 days to monitor for asymptomatic infections. Diagnostic testing: SARS-CoV-2 RT-PCR testing of nasopharyngeal swabs was conducted to confirm a positive antigen test. Symptom monitoring: All residents screened daily for COVID-19 symptoms, plus surveillance testing with BD Veritor antigen assay every 2 to 5 days (positive results checked with RT-PCR). Prior infections: NR SARS-CoV-2 variant: NR	Findings One dose of Pfizer was associated with a 2.4 mean log10 viral load reduction in nasopharyngeal samples compared to samples collected from unvaccinated participants Median Ct values: • unvaccinated: 12.8 (IQR: 12.4 to 14.9) • vaccinated:19.4 (IQR: 18.9 to 25.5) • p=0.009 Mean log_{10} viral load: • unvaccinated: 9.5 (95% CI: 9.3 to 9.8) • vaccinated: 7.1 (95% CI: 5.4 to 8.8) • mean difference = -2.4, p=0.004	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		Data collection: Testing and vaccination data collected from the nursing home. Statistical analysis: Cycle threshold analysis: compared with two-tailed t-tests. Log10 viral load: calculated with average RNAse P over 10 samples and compared with two-tailed t tests.		
Mostafa and others, 2021 (57) 'SARS-CoV-2 Infections in mRNA Vaccinated Individuals are Biased for Viruses Encoding Spike E484K 2 and Associated with Reduced Infectious Virus Loads that Correlate with Respiratory Antiviral IgG levels' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To assess and compare the viral load and respiratory antiviral IgG levels of CVOID-19 positive cases who were fully vaccinated with Pfizer or Moderna compared to unvaccinated cases Participants: 133 COVID-19 positive cases Cycle threshold analysis: Fully vaccinated: n=49 Unvaccinated: n=90 Cell culture analysis: Fully vaccinated: n=114 Unvaccinated: n=124 Setting: US, January to May 2021	Outcomes: Confirmed COVID-19 infections and associated Ct values and recovery of infectious virus (cell culture CPE). Exposure: Definition of fully vaccinated: Positive samples were collected at a median of 52 days (range: 2 to 99 days) after the second dose of Pfizer or Moderna vaccines. Definition of unvaccinated: No vaccine received prior to positive test results. Testing: RT-qPCR testing and whole genome sequencing for all samples. Cell culture analysis: Vero cell culture and RT-qPCR testing. SARS-CoV-2 variant: Vaccinated and unvaccinated samples were matched for variants. Cell culture analysis: Alpha and other variants predominant before March Cycle threshold analysis: 61% Alpha, 9% B.1.526 (Iota), 4.5% B.1.526.1 (Iota). Data collection: Test and vaccination data collected from the John Hopkins Clinical Microbiology Laboratory and GISAID.	Findings Median Ct (*N* gene) values (data extracted from figure): • unvaccinated: 19.6 (IQR: 16.3 to 22.8) • fully vaccinated: 19.2 (IQR: 16.6 to 22.0) Cell culture CPE positive (predominantly Alpha samples): • unvaccinated: n=80 of 124 (64.5%) • gully vaccinated: n=17 of 92 (18.5%) • p<0.00001 Proportion of CPE positive samples displaying CPE on cell culture after 2 days • fully vaccinated: n=44 of 80 (55%) • unvaccinated: n=0 of 17 (0%)	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted except for variant and date. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		Statistical analysis: Unvaccinated controls and vaccinated cases were matched on variant and sample collection date. Fisher Exact test used for cell culture analysis.		
Muhsen and others (58) 'Effectiveness of BNT162b2 mRNA COVID-19 vaccine against acquisitions of SARS-CoV-2 among health care workers in long-term care facilities: a prospective cohort study'	Study design: Prospective cohort Objective: To assess vaccine effectiveness against confirmed COVID-19 infections and associated viral load Participants: 9,162 healthcare workers (HCWs) (16 to 65 years) who adhered to regular testing (of 46,024 HCWs from 1,078 long term care facilities), of whom 124 developed COVID-19 Fully vaccinated (n=6,960): Mean age: 47.2 years (SD: 11.7) Sex: 78.4% female Ethnicity: 79.6% general Jewish, 18.9% Arab Residential area COVID-19 exposure: 31.9% low risk, 30.4% intermediate risk, 29.1% high risk COVID-19 positive: n=40 Unvaccinated (n=2,202): Mean age: 43.1 years (SD: 11.7) Sex: 83% female Ethnicity: 79.2% general Jewish, 17.8% Arab Residential area COVID-19 exposure: 23.8% low risk, 28.7% intermediate risk, 33.2% high risk COVID-19 positive: n=84 Setting: Israel, 30 January to 11 April 2021	Outcomes: Confirmed COVID-19 infections and associated Ct values. Exposure: Fully vaccinated: more than 14 days after second dose of Pfizer. Definition of unvaccinated: No vaccine received prior to positive test results. Testing: Routine weekly RT-PCR testing of nasopharyngeal swabs (asymptomatic screening). Prior infections: Participants with prior infections excluded. SARS-CoV-2 variant: Alpha variant dominant throughout study period. Data collection: Demographic, vaccination and RT-PCR test data were collected through the Senior Shield program. Statistical analysis: Mann-Whitney U test of medians and IQRs used to calculate statistical significance.	Findings Median Ct values (*ORF1ab* gene) (data extracted from figure): • unvaccinated (n=44): 26.7 (IQR: 22.9 to 31.0) • fully vaccinated (n=20): 32.0 (IQR: 28.7 to 33.5) • p=0.008	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium
Pajon and others, 2021 (28) 'Initial Analysis of Viral Dynamics and Circulating	Study design: RCT (secondary analysis) Objective: To assess the impact of vaccination on the viral kinetics of confirmed COVID-19 infections	Outcomes: Confirmed COVID-19 infections and associated viral load, viral shedding, and time to viral clearance (viral log10 copies per ml). Exposure:	Findings Median viral copies per ml (log10), by vaccination status and day of illness: Day 1 • unvaccinated: 6.7	Risk of bias: Confounding: Although an RCT, the viral load analysis only included participants who

Reference	Study design	Methods	Findings	Risk of bias
Viral Variants During the mRNA-1273 Phase 3 COVE Trial 2021' PREPRINT (version 1)	Participants: 701 COVID-19 positive symptomatic cases (at least 18 years) included in the viral load analysis. All participants were at risk of COVID-19 and/or high risk of severe COVID-19. Vaccinated positive cases (n=48) Mean age: 49.5 years (SD: 14.6 years) Median age: 49 years (IQR: 24 to 74 years) Sex: 47.9% female Ethnicity: 89.6% White, 18.8% Hispanic or Latino, 4.2% Black, 2.1% Asian Baseline health: 14.6% severe obesity, 6.3% diabetes, 6.3% significant cardiac disease, 8.8% chronic lung disease, 2.1% liver disease, 0% HIV Mean BMI: 30.4 kg per m^2 (SD: 7.0 kg per m^2) Unvaccinated positive cases (n=653) Mean age: 48.0 years (SD: 14.4 years) Median age: 48 years (IQR: 18 to 87 years) Sex: 49.7% female Ethnicity: 85.6% White, 22% Hispanic or Latino, 4.6% Black, 4% Asian Baseline health: 9.9% severe obesity, 9.8% diabetes, 4.5% significant cardiac disease, 3.7% chronic lung disease, 0.8% liver disease, 0.3% HIV Mean BMI: 32.3 kg per m^2 (SD: 7.1 kg per m^2) Setting: US, July 2020 to 26 March 2021	Fully vaccinated: at least 14 days after final dose of Moderna vaccine. Unvaccinated: No vaccine received prior to positive test results. Definition of COVID-19 case: at least 2 systemic symptoms or at least one respiratory symptom and positive RT-qPCR test. Testing: RTq-PCR testing triggered by symptoms. For COVID-19 positive cases, serial testing of nasopharyngeal swabs was completed on day 1 and saliva samples on day 3, 5, 7, 9, 14, 21 and 28 of illness. Prior infections: Participants with prior infections were excluded from the analysis. SARS-CoV-2 variant: Wild-type (93% B.1/B.1.2 lineage), Epsilon (5.4%), Alpha (1%). Data collection: Testing, vaccination and demographic data collected from the COVE RCT. Statistical analysis: Mixed model repeated measures analysis compared the change from baseline viral load from day 1 to 28 of illness in the vaccinated and unvaccinated groups. Ct values converted to log10 viral genome copy numbers.	• fully vaccinated: 3.4 • difference: 3.4 Day 3 • unvaccinated: 3.0 • fully vaccinated: 0 • difference: 3.0 Day 5 • unvaccinated: 2.3 • fully vaccinated: 0 • difference: 2.3 Day 7 • unvaccinated: 0 • fully vaccinated: 0 • difference: 0 Estimated viral copies per ml (log10), by vaccination status and day of illness: Day 1 • unvaccinated: 6.20 (95% CI: 6.04 to 6.37) • fully vaccinated: 4.10 (95% CI: 3.44 to 4.76) • difference: -2.10 (95% CI: -2.78 to -1.42) Day 3 • unvaccinated: 2.77 (95% CI: 2.58 to 2.97) • fully vaccinated: 1.02 95% CI: (0.21 to 1.84) • difference: -1.75 (95% CI: -2.59 to -0.91) Day 5 • unvaccinated: 2.09 (95% CI: 1.91 to 2.27) • fully vaccinated: 0.35 (95% CI: 0 to 1.20) • difference: -1.74 (95% CI: -2.51 to -0.96) Day 7 • unvaccinated: 1.74 (95% CI: 1.57 to 1.91) • fully vaccinated: 0.50 (95% CI: 0 to 1.20) • difference: -1.24 (95% CI: -1.96 to -0.52) Day 9 • unvaccinated: 1.09 (95% CI: 0.94 to 1.24) • fully vaccinated: 0.06 (95% CI: 0 to 0.64) • difference: -1.03 (95% CI: -1.63 to -0.43) Day 14	developed COVID-19, which reduced or removed the effect of randomisation. Therefore, there is likely a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
			• unvaccinated: 0.51 (95% CI: 0.40 to 0.62) • fully vaccinated: 0.39 (95% CI: 0 to 0.83) • difference: -0.12 (95% CI: -0.58 to 0.34) <u>Day 21</u> • unvaccinated: 0.25 (95% CI: 0.18 to 0.33) • fully vaccinated: 0.00 (95% CI: 0 to 0.31) • difference: -0.27 (95% CI: -0.59 to 0.06) <u>Day 28</u> • unvaccinated: 0.09 (95% CI: 0.05 to 0.13) • fully vaccinated: 0.00 (95% CI: 0 to 0.18) • difference: -0.09 (95% CI: -0.27 to 0.10) Viral copies per ml were converted to Ct values in the report: Day 1 values were multiplied by -3.3385 and 40.9578 was added (the difference was only multiplied by -3.3385), days 3 to 28 values were multiplied by -3.3346 and 41.0349 was added (the differences were only multiplied by -3.3346). <u>Median time to viral clearance</u> • unvaccinated 7 days • fully vaccinated: 4 days • difference: 3 days	
Pouwels and others, 2021 (32) 'Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK' Office for National Statistics (ONS) COVID-19	<u>Study design</u>: Prospective cohort <u>Objective</u>: To assess the effectiveness of vaccination against COVID-19 infections and associated symptoms and viral load <u>Participant visits</u>: Adults (at least 18 years) Alpha dominant period: 2,580,021 visits with 384,543 adults from 221,909 households Delta dominant period: 811,624 visits with 358,983 adults from 213,825 households Alpha period 1 Dec 2020 to 16 May 2021 Median age: 56 years (IQR: 41 to 68 years) Sex: 53.6% female Ethnicity: 93.7% White	<u>Outcomes:</u> Confirmed COVID-19 infections and associated Ct values. <u>Exposure</u>: <u>Fully vaccinated</u>: at least 14 days after second dose of Pfizer or AstraZeneca vaccine. <u>Partially vaccinated</u>: at least 21 days after first dose Definition of unvaccinated: at least 21 days before first vaccine dose. <u>Testing:</u> Weekly RT-PCR testing of nasopharyngeal and throat swabs for 4 weeks following enrolment, followed by monthly testing for 12 months (regardless of symptoms). A portion of samples with	<u>Findings</u> <u>Median Ct values, by variant and vaccine status</u> Alpha-dominant period (1 Dec 2020 to 16 May) • unvaccinated (n=10,853): 28.7 (IQR: 20.4 to 32.9) • partially Vaccinated (n=577): 31.6 (IQR: 26.6 to 33.7) • fully Vaccinated (n=56): 33.3 (IQR: 31.6 to 34.0) • p for trend<0.0001 (increasing Ct with time from first vaccination and number of doses) • p=0.02, comparing fully vaccinated and unvaccinated Early Delta-dominant period (17 May to 13 June 2021) • unvaccinated (n=75): 21.5 (IQR: 16.4 to 31.7)	<u>Risk of bias</u> <u>Confounding:</u> There is a high risk of bias from residual confounding even after adjustment, particularly as deprivation was not accounted for. <u>Other bias:</u> No specific biases to report. <u>QCC rating:</u> Medium

Reference	Study design	Methods	Findings	Risk of bias
Infection Survey (CIS) ISRCTN21086382	Baseline health: 28% have had a long-term health condition Deprivation centile: 6 (IQR: 3 to 8) Delta period 16 May to 1 August 2021 Median age: 57 years (IQR: 42 to 69 years) Sex: 54.2% female Ethnicity: 93.2% White Baseline health: 28.5% have had a long-term health condition Deprivation centile: 6 (IQR: 3 to 8) Setting: UK, 1 December 2020 to 2 August 2021	Ct values less than 32 was sent for genomic sequencing. Prior infections: Analyses were stratified by serostatus; patients with evidence of prior infection are not reported here. SARS-CoV-2 variant: Alpha dominant period: From 1 Dec 2020 to 16 May 2021 Alpha was dominant. Sequencing data not reported. Early Delta dominant period: From 17 May to 13 June 2021 Delta was dominant (61% of samples from 17 May). Delta dominant period: From 14 June to 2 August 2021 Delta was dominant (more than 92% of samples). Data collection: Data collected monthly from participants identified via NHS Digital, based on an NHS GP patient list. Follow-up via NHS record linkage, including national immunization programme data. Statistical analysis: Ct values compared by vaccination status using quantile (median) regression, adjusted for age and sex.	• Partially Vaccinated (n=110): 30.1 (IQR: 26.0 to 34.0) • Fully Vaccinated (n=104): 32.2 (IQR: 26.0 to 34.0) Late Delta-dominant period (14 June to 2 August 2021) • unvaccinated (n=326): 25.7 (IQR: 19.1 to 30.8) • partially Vaccinated (n=705): 24.7 (IQR: 18.8 to 31.3) • fully Vaccinated (n=1593): 25.3 (IQR: 19.1 to 31.3) • p=0.35, comparing fully vaccinated and unvaccinated	
Regev-Yochay and others, 2021 (59) ‘Decreased infectivity following BNT162b2 vaccination’	Study design: Prospective cohort Objective: To assess the effectiveness of Pfizer vaccine at reducing the risk of COVID-19 infections that are symptomatic or have a high viral load. Participants: 3,578 healthcare workers (from 9,347 HCWs aged at least 18 years) from a single medical centre received 26,651 RT-PCR tests within the study period, of which n=295 (8.2%) were positive. Fully vaccinated (n=31):	Outcomes: RT-qPCR confirmed COVID-19 infections and associated N-gene Ct values. Exposure: Definition of vaccinated: Fully vaccinated: at least 11 days after second dose of Pfizer. Definition of unvaccinated: No vaccine received prior to positive test results. Testing:	Findings Ct values available for 76% of 295 positive cases (224 cases). Mean Ct values (*N* gene): • unvaccinated: 22.2 (SD: 1.0) • fully vaccinated: 27.3 (SD: 1.2) • mean difference: 5.09 (95% CI: 2.8 to 7.4), p<0.001 Median Ct values (*N* gene): • unvaccinated: 23.3	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Age: 65% 18 to 45 years, 35% 46 to 65 years, 0% more than 65 years Sex: 32% male Unvaccinated (n=163) Age: 73% 18 to 45 years, 26% 46 to 65 years, 1% more than 65 years Sex: 21% male Setting: Israel, 19 December 2020 to 14 March 2021	Symptom monitoring: HCWs reported daily health status and symptoms on arrival at work. Rapid antigen testing (Ag-RDT): For HCWs reporting mild symptoms or low-risk exposure. RT-qPCR testing: Of all HCWs with confirmed exposure or symptoms. Prior infections: Participants with a prior confirmed COVID-19 infection were excluded. SARS-CoV-2 variant: NR Data collection: Epidemiological investigations were conducted with electronic surveys to collect demographic data, symptom status and origin or risk of exposures. Statistical analysis: Mean Ct values compared using 2 sample t-tests.	• fully vaccinated: 25.8 • p<0.001	
Riemersma and others, 2021 (60) 'Shedding of Infectious SARS-CoV-2 Despite Vaccination when the Delta Variant is Prevalent - Wisconsin, July 2021' PREPRINT (version 6)	Study design: Retrospective cohort Objective: To compare the viral load of COVID-19 positive cases according to their vaccination status Participants: 699 COVID-19 positive cases Fully Vaccinated positive cases (n=310) Symptomatic: n=228 Asymptomatic: n=12 Unknown symptom status: n=71 Unvaccinated positive cases (n=389) Symptomatic: n=252 Asymptomatic: n=24 Unknown symptom status: n=132 Setting: US, 29 June to 31 July 2021	Outcomes: Confirmed COVID-19 infections and associated Ct values and cell culture cytopathic effect (CPE) detection. Exposure: Definition of vaccinated: Fully vaccinated: final vaccine dose (mRNA or adenovirus vector vaccine, otherwise not specified) at least 14 days prior to testing. Definition of unvaccinated: No vaccine received prior to positive test. Testing: RT-PCR testing (symptomatic or asymptomatic), genome sequencing and cell culture. Prior infection: NR SARS-CoV-2 variants: Delta (increased in study region from 69% to 95% through the study period).	Findings Mean N1 Ct value (data extracted from figure): • unvaccinated (n=389): 23.3 (SD: 5.6) • fully Vaccinated (n=310): 22.8 (SD: 5.9) • p=0.23 Mean N1 Ct value (symptomatic) (data extracted from figure): • unvaccinated (n=232): 22.9 (SD: 5.5) • fully Vaccinated (n=225): 22.6 (SD: 5.8) • p=0.74 Mean N1 Ct value (asymptomatic) (data extracted from figure): • unvaccinated (n=24): 27.0 (SD: 5.6) • fully Vaccinated (n=11): 26.1 (SD: 7.1) • p=0.05 Proportion of samples with Ct values less than 25:	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		Data collection: Provenance of testing unclear. Vaccination status via Wisconsin Immunisation Registry or Wisconsin Electronic Disease Surveillance System (n=292 vaccinated, n=11 unvaccinated) or self-reported (n=18 vaccinated, n=378 unvaccinated). Statistical analysis: Mean Ct values compared using independent two-group Mann Whitney U tests.	• unvaccinated: 63% (n=246 of 389) • gully vaccinated: 68% (n=212 of 310) Proportion of samples with Ct values less than 25 (asymptomatic cases): • unvaccinated: 29% (n=7 of 24) • gully vaccinated: 82% (n=9 of 11) Proportion of samples with Ct values less than 25 (symptomatic cases): • unvaccinated: 68% (n=158 of 232) • fully vaccinated: 69% (n=156 of 225) CPE positive samples (Ct values less than 25) • unvaccinated: 88.2% (n=15 of 17) • fully Vaccinated: 94.9% (n=37 of 39)	
Servellita and others, 2021 (61) 'Predominance of antibody-resistant SARS-CoV-2 variants in vaccine breakthrough cases from the San Francisco Bay Area, California' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To analyse the viral load, infecting variant, and symptom status of COVID-19 positive cases Participants: 1,373 COVID-19 positive cases identified via hospital and community testing. Fully vaccinated (n=125) Median time interval from completion of vaccination course and infection: 73.5 days (range: 15 to 140) Vaccines: 51% Pfizer, 28% Moderna, 10% Janssen Unvaccinated (n=1,169) Setting: US, 1 February to 30 June 2021	Outcome: Confirmed COVID-19 infections and associated variants, and Ct values. Exposure: Definition of vaccinated: Fully vaccinated: at least 14 days after the completion of vaccination course with the Moderna, Pfizer or Janssen vaccine. Definition of unvaccinated: No vaccine received prior to positive test. Testing: Rt-qPCR testing and whole genome sequencing attempted for of all samples. Prior infections: NR SARS-CoV-2 variant: Fully vaccinated: 35% Delta, 25% Alpha, 22% Gamma, 9% Epsilon, 5% Iota, 3% Beta. Unvaccinated: 32% Other, 27% Epsilon, 25% Alpha, 8% Gamma, 5% Delta, 3% Iota.	Findings Mean Ct values (*N* gene): • unvaccinated (n=1,061): 23.1 • fully vaccinated (n=121): 23.1 • p=0.99 Mean Ct values (*N* gene), by vaccination and symptom status: Symptomatic (n=302) • unvaccinated: 21.9 • fully vaccinated: 21.2 • p=0.64 Asymptomatic (n=139) • unvaccinated: 24.6 • fully vaccinated: 30.1 • p=0.023 Mean Ct values (*N* gene), by vaccination status and infecting variant Alpha (n=305) • unvaccinated: 21.5	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other Bias: Selection of participants unclear. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		Data collection: Samples and clinical chart, demographic and vaccination status data collected from hospitals and clinics at the University of California (43.5%) and community testing centres in San Francisco County (56.4%). Statistical Analysis: Significance testing conducted for the Ct value comparative analysis using Welch's t-test.	• fully vaccinated: 22.1 • p=0.70 Beta (n=21) • unvaccinated: 22.8 • fully vaccinated: 26.5 • p=0.27 Gamma (n=55) • unvaccinated: 19.8 • fully vaccinated: 20.2 • p=0.78 Delta (n=85) • unvaccinated: 19.5 • fully vaccinated: 21.5 • p=0.09 Epsilon (n=140) • unvaccinated: 21.0 • fully vaccinated: 24.3 • p=0.15 Iota (n=80) • unvaccinated: 21.8 • fully vaccinated: 20.9 • p=0.64 Other (n=177) • unvaccinated: 22.3 • fully vaccinated: 23.8 • p=0.45	
Shrotri and others, 2021 (33) 'Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities	Study design: Prospective cohort Objective: To estimate the effect of partial vaccination on the incidence and viral load of COVID-19 infections amongst adults in residential care settings. Participants: n=10,412 adults (at least 65 years) in 228 for-profit, 72 not-for-profit and 10 independent long-term care facilities (LTCFs) Partially vaccinated (n=9,160):	Outcomes: Confirmed COVID-19 infections, time to positive RT-PCR tests, and mean Ct values of positive samples (available for 80.1% of positive tests). Exposure: Definition of vaccinated: Vaccinated at least 28 days after the first dose of AstraZeneca or Pfizer vaccine. Definition of unvaccinated: No vaccine received prior to positive test results.	Findings Mean Ct values (mean of *N*, *ORF1ab* and *S* genes, if available): • unvaccinated (n=552): 26.6 (SD: 6.6) • vaccinated (n=107): 31.3 (SD: 8.7) • p<0.0001	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: Measurement bias: 13 laboratories using 6 different assays were

Reference	Study design	Methods	Findings	Risk of bias
in England (VIVALDI): a prospective cohort study' ISRCTN: 14447421	Median age: 86 years (IQR: 80 to 91 years) Sex: 69.9% female Vaccines: AstraZeneca: 6,138 (67%), Pfizer: 3,022 (33%), 9.8% vaccinated with 2 doses Unvaccinated (n=1,252): Median age: 86 years (IQR: 80 to 92 years) Sex: 65% female Setting: England, 8 Dec 2020 to 15 Mar 2021	Testing: Monthly RT-PCR testing and symptoms monitoring. Prior infections: 11.1% of participants had evidence of a prior infection. SARS-CoV-2 variant: Alpha dominant throughout study period. Data collection: Database linkages including the national testing programme, the National Immunisation Management Service and National Health Service (NHS) numbers. Statistical analysis: Two-tailed t-tests were used to estimate the difference in mean Ct values between exposure groups.		used to determine Ct values. QCC rating: Medium
Tande and others, 2021 (62) 'Impact of the Coronavirus Disease 2019 (COVID-19) Vaccine on Asymptomatic Infection Among Patients Undergoing Preprocedural COVID-19 Molecular Screening'	Study design: Retrospective cohort Objective: To assess the effect of vaccination on the risk of RT-PCR confirmed asymptomatic infections and associated viral load. Participants: 39,156 adults (at least 18 years) undergoing COVID-19 screening prior to medical procedures or tests, self-declared free of COVID-19 symptoms. Vaccinated (n=3,006): Mean age: 46.9 years (SD: 14.9 years) Sex: 64.8% female Ethnicity: 80% White, 2% African descent, 6% Asian, 6% Hispanic COVID-19 positive: n=42 Unvaccinated (n=45,327): Mean age: 55.2 years (SD: 18.4 years) Sex: 51.7% female	Outcomes: RT-PCR confirmed asymptomatic COVID-19 infections and associated Ct values. Exposure: Definition of vaccinated: vaccinated with at least one dose of Pfizer (94%) or Moderna (5.9%): • 0 to 10 days after first dose • more than 10 days after first dose • more than 0 days after second dose Definition of unvaccinated: No vaccine received prior to positive test results. Testing: Pre-procedure RT-qPCR testing (asymptomatic screening). Prior infections: NR SARS-CoV-2 variant: NR	Findings Ct values available for 91% of vaccinated and 78% unvaccinated positive tests. Mean Ct values (Arizona, Alinity instrument) • unvaccinated (n=453): 26.6 (8.3) • more than 10 days after first dose, before second dose (n=6): 30.5 (6.1) • more than 0 days after second dose (n=3): 30.0 (6.1) Mean Ct values (Arizona, m2000 instrument): • unvaccinated (n=449): 15.1 (SD: 7.7) • more than 10 days after first dose, before second dose (n=4): 11.1 (SD: 7.1) • more than 0 days after second dose (n=2): 18.6 (SD: 9.3) Mean Ct values (Rochester) • unvaccinated (n=88): 30.4 (SD: 4.4)	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Ethnicity: 86% white, 2%African descent, 2% Asian, 5% Hispanic COVID-19 positive: n=1436 Setting: US, 17 Dec 2020 to 8 Feb 2021	Data collection: Patient data from RT-qPCR screening tests and demographic data recorded in electronic health records. Statistical analysis: Mean Ct values presented, no further analysis.	• more than 10 days after first dose, before second dose (n=1): 30.9	
Thompson and others, 2021 (63) 'Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines' HEROES-RECOVER Network data	Study design: Prospective cohort Objective: To evaluate the effect of partial and full vaccination with mRNA vaccines on confirmed COVID-19, viral load, febrile symptoms, and duration of illness amongst vaccinated and unvaccinated adults. Participants 3,975 healthcare workers (HCWs, at least 18 years), first responders and frontline workers, of whom 204 had COVID-19. Vaccinated (at least 1 dose) (n=3,179): Sex: 64.1% female Race: 87.2% White Baseline health: 33% had at least 1 chronic condition Unvaccinated (n=796): Sex: 53.1% female Race: 82.8% White Baseline health: 27% had at least 1 chronic condition Setting: US, 14 Dec 2020 to 10 April 2021	Outcomes: RT-qPCR confirmed COVID-19 and associated viral load (log_{10} copies per ml), frequency and duration of illness. Exposure: Definition of vaccinated: Fully vaccinated: at least 14 days after second dose of Pfizer (67%) or Moderna (33%) vaccine. Partial vaccination: at least 14 days after first dose to less than 14 days after second dose. Definition of unvaccinated: No vaccine received prior to positive test results or less than 14 days after first dose. Testing: Weekly RT-qPCR testing of nasal swabs (asymptomatic) and additional saliva sample testing when symptomatic. Genomic sequencing for a subset of 71 samples. Prior infections: Participants with a confirmed prior infection excluded. SARS-CoV-2 variant: Unvaccinated: Wild-type (90%) Vaccinated: Wild-type (70%) Data collection: Self-reported symptoms and COVID-19 exposure data were collected via electronic surveys, texts, and emails. Statistical analysis: Viral load: Poisson model, adjusted for days from symptom onset to sample collection, and time in transit to laboratories. Duration of illness: Student's t-tests.	Findings Mean viral RNA log_{10} copies per ml: • not vaccinated (n=155) 3.8 (SD: 1.7) • partial or full vaccination (n=16) 2.3 (SD: 1.7) • relative difference: 40.2% (95% CI: 16.3% to 57.3%) Mean duration of viral RNA detection: • not vaccinated (n=155): 8.9 days (SD: 10.2 days) • partial or full vaccination (n=16): 2.7 days (SD: 3.0 days) • Mean Difference: 6.2 days (95% CI: 4.0 to 8.4 days) Mean duration spent in sick bed: • not vaccinated (n=147): 3.8 days (SD: 5.9 days) • partial or full vaccination (n=15): 1.5 days (SD: 2.1 days) • mean difference: 2.3 days (95% CI: 0.8 to 3.7 days)	Risk of bias Confounding: There is a very high risk of bias from residual confounding even after adjustment, particularly as age, sex and deprivation were not accounted for. Other bias: No specific biases to report. QCC rating: Medium

Supplementary Table 3. Characteristics of ongoing studies

Acronyms: RCT = randomised controlled trial

Reference	Study description	Methodology
NCT04811664 (70) 'A Study of SARS CoV-2 Infection and Potential Transmission in Individuals Immunized With Moderna COVID-19 Vaccine (CoVPN 3006)'	**Design:** Open label Phase III RCT, with crossover assignment. Estimated 37,500 participants. **Aim:** To evaluate the efficacy of the Moderna COVID-19 vaccine against SARS-CoV-2 infection, as well as its effect on peak nasal viral load as a measure of infection and a proxy of infectiousness. **Population:** Adults aged 18 to 29 years **Setting:** US, March 2021 to December 2021	**Intervention or treatment:** Moderna COVID-19 Vaccine **Primary Outcomes:** 1.Vaccine Efficacy against infection during a 4-month follow-up 2. Effect of vaccine on peak nasal viral load during a 4-month follow-up.
NCT04324606 (71) 'A Study of a Candidate COVID-19 Vaccine (COV001)'	**Design:** Phase I/II single-blinded, randomised, multi-centre study. 1,009 participants. **Aim:** To determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) "AstraZeneca" vaccine (ChAdOx1 nCoV-19). **Population:** UK healthy adult volunteers aged 18 to 55 years **Setting:** UK, April 2020 to October 2021	**Intervention or treatment:** Intervention: AstraZeneca Comparator: Placebo **Primary Outcomes:** 1**.** Candidate Vaccine efficacy against COVID-19: number of confirmed symptomatic cases with PCR at 12 months within a 6 month time-frame 2. Candidate Vaccine safety: Occurrence of serious adverse events (SAEs) throughout the study (18 months time-frame) until a cut-off date of 1 July 2021 or 6 months post late vaccination visit, whichever is latest.
NCT04750356 (72) 'SARS-CoV-2 (COVID-19) Longitudinal Study: Understanding Susceptibility, Transmission and Disease Severity (Legacy Study)'	**Design:** Prospective observational cohort study. 6,000 participants. **Aim:** To investigate SARS-CoV-2 susceptibility, transmission and disease severity in healthcare workers and patients. **Population:** Healthcare workers and patients aged 18 years and older. **Setting:** UK, January 2021 to December 2024	**Exposure:** Residual specimens from existing collections of samples in viral inactivating buffer and derivatives and serum and additional biological material collected prospectively Vaccine status to be used to stratify the participants and recruit to the study **Primary Outcomes**: SARS-CoV-2 susceptibility, transmission (assessed by analysis of sample sequencing data) and severity during a 24 month follow-up

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