UK Health Security Agency

The effect of vaccination on transmission of COVID-19

A rapid evidence briefing

Update 1: Search to 12 January 2022

Contents

Main messages

1. This review (search up to 12 January 2022) is an update our previous review (search up to 22 October 2021), and assessing the effect of coronavirus (COVID-19) vaccination on transmission of COVID-19 (SARS-CoV-2, 1 study for the Omicron variant, 10 studies for the Delta variant, and 14 studies for pre-Delta variants and Wild-type COVID-19), and on COVID-19 viral loads (2 studies for the Omicron variant, 25 studies for the Delta variant, and 20 studies for pre-Delta variants and Wild-type COVID-19).
2. All studies were observational, comparing transmission to household and other contacts and viral loads between people infected with COVID-19 who were or were not previously vaccinated against COVID-19 (any number of vaccination doses). Note that transmission cannot occur from people not infected with COVID-19.
3. Evidence from one study suggests that booster vaccinated index cases transmit Omicron and Delta variant COVID-19 less than fully vaccinated (2 doses) index cases, who transmit less than unvaccinated index cases (GRADE assessment: very low certainty).
4. Evidence from 10 studies suggested fully vaccinated (2 doses) cases transmitted Delta variant COVID-19 less than unvaccinated cases (GRADE assessment: low certainty). Two studies from the previous review suggested that vaccine effectiveness against transmission of the Delta variant dropped substantially over time.
5. Evidence from 2 studies suggested there is little difference between the Ct values (an indication of viral load) and genome copy numbers of Omicron and Delta variant COVID-19 cases, though infectious viral loads may be smaller in Omicron cases (indicating lower infectivity).
6. Evidence from 25 studies suggested mixed evidence for a difference in viral load between fully vaccinated (2 doses) and unvaccinated Delta variant cases, with 16 studies suggesting no difference and 8 studies suggesting higher Ct values (lower viral load) in fully vaccinated (2 doses) cases (GRADE assessment: very low certainty).
7. Evidence from 2 studies suggested that although Ct values are higher in fully (2 doses) and booster (3 doses) vaccinated Delta variant cases compared with unvaccinated cases (lower viral load) soon after vaccination, this difference drops quickly, with Ct values becoming similar 61 to 120 days after vaccination. This may help explain the mixed results for differences in Delta variant viral load.
8. Evidence from 6 studies suggested similar levels of infective virus between fully vaccinated (2 doses) and unvaccinated Delta variant cases.
9. 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. Only two included studies included evidence for the Omicron variant.

Purpose

To update our previous review (1), which identified and examined evidence on whether vaccination against coronavirus (COVID-19) affects transmission of SARS-CoV-2, the virus causing COVID-19.

Methods

An update to our previous rapid review (1) was conducted, following streamlined systematic methodologies to accelerate the review process (2). 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 22 October 2021 (end date of last search) and 12 January 2022. Full details on the methodology, including assessment of the quality of individual studies (using the quality criteria checklist (QCC) and certainty of the evidence (using GRADE), are provided in Annexe A.

Note that throughout the report, 'partially' vaccinated indicates 1 dose of a 2 dose vaccine, 'fully vaccinated' indicates 1 dose of a single dose vaccine or 2 doses of a 2 dose vaccine, and 'booster vaccinated' indicates at least 1 additional dose of vaccine beyond full vaccination.

New evidence on transmission of COVID-19 after COVID-19 vaccination (Table 1)

In this update, there were 10 observational studies (3 preprints (3 to 5), 9 studies rated as medium (3 to 11), and one study as high quality (12) on assessment with the QCC tool) 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 or close contacts (secondary cases). Of these, 8 were cohort studies (3 to 6,8 to 11) and 2 were case-control studies (7,12). Three studies provided data from the UK (3,10,12), 4 from Europe (4,5,7,8), and 3 from Asia (6,9,11). All studies were conducted between June 2020 and December 2021.

One study included data from when Omicron was the dominant variant (4), 8 studies from when Delta was the dominant variant (3,5,7 to 12), 5 studies from when Alpha was the dominant variant (3,7,8,10,12), and one study did not report the dominant variant, but was likely pre-Delta as the study only included participants up to April 2021 in India (6) (some studies included data from when different variants were dominant). Table 1 shows a summary of all transmission studies, including studies from both this update (indicated with [U]) and from the previous review (indicated with [P] in grey rows), and Supplementary Table 1 shows full information for all transmission studies.

Evidence for the Omicron variant

No studies in the previous review reported on transmission of Omicron variant COVID-19. One study included in this update reported on transmission of the Omicron variant (4).

A retrospective cohort study by Lyngse and others (preprint, rated as medium quality on QCC assessment, n=11,937 index cases) assessed the transmission of COVID-19 from index cases identified from the Danish Microbiology Database (RT-PCR, 81% Delta, 19% Omicron) to household members in December 2021 (4). Household transmission was determined by household members receiving a positive test within one to 7 days of the index case's positive test. The COVID-19 status of secondary cases was confirmed by RT-PCR or an antigen test. Booster vaccinated cases (3 doses, n=105 [4.7%] Omicron index cases, n=286 [2.9%] Delta index cases) had received a booster dose at least 7 days before a positive test, fully vaccinated index cases (n=1,752 [78.7%] Omicron index cases, n=4,797 [49.4%] Delta index cases) had 2 doses of the Pfizer, Moderna, Janssen or AstraZeneca vaccines at least 7 to 15 days prior to testing positive (depending on vaccine) or had a previous COVID-19 infection at least 14 days before testing positive, and unvaccinated index cases (n=368 [16.5%] Omicron index cases, n=4,629 [47.7%] Delta index cases) had no doses of any vaccine, or one dose of a 2 dose vaccine.

For both variants, there was more transmission to household members from unvaccinated compared to fully vaccinated index cases (secondary attack rate (SAR) not presented, odds ratio (OR) for transmission = 1.41, 95% confidence interval (CI): 1.27 to 1.57), and there was less transmission to household members from booster vaccinated compared to fully vaccinated index cases (OR for transmission = 0.72, 95% CI: 0.56 to 0.92). There was no difference in transmission from index cases with different vaccine statuses between the Omicron and Delta variants.

For the Delta variant, there was much more COVID-19 transmission from index cases to unvaccinated compared with fully vaccinated household members (SAR = 28% vs 19%, OR for transmission = 2.31, 95% CI: 2.09 to 2.55). There was much less COVID-19 transmission from index cases to booster vaccinated compared with fully vaccinated household members (SAR = 11% vs 19%, OR for transmission = 0.38, 95% CI: 0.32 to 0.46).

However, for the Omicron variant, there was very similar COVID-19 transmission from index cases to unvaccinated compared with fully vaccinated household members (SAR = 32% vs 29% OR = 1.04, 95% CI: 0.87 to 1.24), although there was less COVID-19 transmission from index cases to booster vaccinated compared with fully vaccinated household members (SAR = 25% vs 32%, OR = 0.54, 95% CI: 0.40 to 0.71).

Overall, evidence from one study (4) suggests that booster vaccinated index cases transmit Omicron and Delta variant COVID-19 less than fully vaccinated index cases, who transmit less than unvaccinated index cases (GRADE assessment: very low certainty). This study also

suggested that Omicron variant COVID-19 transmission to fully vaccinated and unvaccinated household contacts was similar, although there was less transmission to booster vaccinated household contacts.

Evidence for the Delta variant

From the previous review, there was evidence from 3 studies suggesting that fully vaccinated cases transmitted Delta variant COVID-19 less than unvaccinated cases (13 to 15). However, 2 of these studies suggested that vaccine effectiveness against transmission of the Delta variant dropped substantially over time (13,15). Additionally, one study suggested that vaccination of the index case was less effective against transmission for the Delta compared with the Alpha variant (15).

In addition to Lyngse and others (4), reported above, 3 studies included in this update looked at the difference in transmission of the Delta variant COVID-19 alone from vaccinated and unvaccinated index cases (3,9,10) and 3 studies reported on transmission of both Alpha and Delta variants combined (7,8,12). Five of these 7 studies suggested that fully vaccinated index cases transmitted COVID-19 to household or other contacts less than unvaccinated index cases (3,7 to 9,12), although one study did not test for statistical differences (8), and only 2 of these studies indicated that the results were statistically significant (3,12).

Allen and others (rated as high quality), conducted a case-control study of n=5,976 index cases who transmitted COVID-19 to a household member matched with n=11,952 index cases who did not transmit COVID-19 to any member of their household in England between March and June 2021 (12). Results suggested fully vaccinated (2 doses of vaccine) index cases transmitted Alpha (40%) and Delta (43%) variant COVID-19 to household members less than unvaccinated index cases:

- OR for transmission: 0.73, 95% CI: 0.58 to 0.90

Clifford and others (preprint, rated as medium quality) conducted a prospective cohort study of n=195 index cases and n=278 household contacts in the UK between February and September 2021 (3). Results suggested fully vaccinated (2 doses of AstraZeneca or Pfizer vaccines) index cases transmitted Delta variant COVID-19 to household members less than unvaccinated index cases:

- AstraZeneca: relative risk (RR) reduction in transmission = 42%, 95% credible interval (CrI): 14% to 69%
- Pfizer: RR reduction in transmission = 31%, 95% CrI: -3% to 61%

Hsu and others (rated as medium quality) conducted a case-control study of n=357 vaccinated index cases matched with n=357 unvaccinated index cases conducted in Germany between December 2020 and August 2021 (7). Results suggested fully vaccinated (2 doses of Pfizer,

AstraZeneca, Moderna, Sputnik or Sinopharm, one dose of Janssen) index cases transmitted Alpha (57%) and Delta (40%) variant COVID-19 to close contacts less than unvaccinated index cases:

- SAR: 37.8% versus 10.1% for unvaccinated and fully vaccinated index cases, respectively
- OR for transmission: 0.21, 95% CI: 0.16 to 1.77

Martinez-Baz and others (rated as medium quality) conducted a retrospective cohort study of n=12,263 index cases and n=30,240 close contacts conducted in Spain between April and August 2021 (8). Results suggested fully vaccinated (2 doses of Pfizer, AstraZeneca, Moderna, one dose of Janssen) index cases transmitted Alpha (52%) and Delta (40%) variant COVID-19 to close contacts less than unvaccinated index cases:

- SAR: 25% versus 18% for unvaccinated and fully vaccinated index cases

Ng and others (rated as medium quality) conducted a retrospective cohort study of n=228 index cases and n=753 household contacts conducted in Singapore between September 2020 and May 2021 (9). Results suggested fully vaccinated (2 doses of Pfizer or Moderna vaccines) index cases transmitted Delta variant COVID-19 to household contacts less than unvaccinated index cases:

- OR for transmission: 0.73, 95% CI: 0.38 to 1.40

Singanayagam and others (rated as medium quality) conducted a prospective cohort study of n=19 symptomatic index cases and n=602 community contacts conducted in the UK between September 2020 and September 2021 (10). Results suggested little difference in the secondary attack rates of Delta variant COVID-19 of fully vaccinated and unvaccinated index cases, although this was not tested statistically:

- SAR: 23% versus 25% for unvaccinated and fully vaccinated index cases

Six studies included in this update looked at the difference in transmission of Delta variant COVID-19 alone to vaccinated and unvaccinated secondary cases (3,5,9 to 11), while 2 studies reported on transmission of both Alpha and Delta variants combined (7,8). All 6 studies looking at household contacts suggested that index cases transmitted COVID-19 to fully vaccinated household contacts less than unvaccinated household contacts, although 3 studies did not test for statistical differences (5,10,11), and only 2 of these studies indicated that the results were statistically significant (4,9). Two of the 3 studies looking at other contacts (8), or both household and other contacts (10), suggested that index cases transmitted COVID-19 to fully vaccinated contacts less than unvaccinated contacts, with one study indicating statistically significant results (8).

Overall, evidence from 10 studies (3 from the previous review (13 to 15), 7 from this update (3,4,7 to 10,12)) suggested fully vaccinated cases transmitted Delta variant COVID-19 less than

unvaccinated cases (GRADE assessment: low certainty). Two studies from the previous review suggested that vaccine effectiveness against transmission of the Delta variant dropped substantially over time, though no studies in the update assessed this. Additionally, evidence from 9 studies (one from the previous review (15), 8 from this update (3 to 5,7 to 11)) suggested that index cases typically transmitted COVID-19 to fully vaccinated contacts less than unvaccinated contacts.

Evidence for pre-Delta variants

Evidence from 14 studies (8 studies from the previous review (16 to 24) and 6 studies from this update (3,6 to 9,12)) suggested that fully vaccinated index cases transmitted pre-Delta variant and Wild-type COVID-19 to their contacts less than unvaccinated index cases, and this reduction was substantial (e.g. >50% reduction in transmission) in many studies (GRADE assessment: moderate certainty). Results are available in Table 1.

New evidence on viral load in those who develop COVID-19 infection after being vaccinated (Table 2)

In this update, there were 20 observational studies (10 preprints (4, 5 , 25 to 32), all studies rated as medium quality) that compared viral loads (predominantly using Ct values) between vaccinated and unvaccinated COVID-19 cases. Of these, 17 were cohort studies (4, 5, 10, 11, 25 to 27, 29 to 38) and 3 were case-control studies (7, 28, 39). One study provided data from the UK (10), 7 from the US (25, 28 to 31, 34, 38), 7 from Europe (4, 5, 7, 32, 35 to 37), 3 from Asia (11, 26, 33), one from Israel (27), and one from Russia (39). All studies were conducted between April 2020 and December 2021.

Two studies included data from when Omicron was the dominant variant (32), 17 studies from when Delta was the dominant variant (5, 7, 10, 11, 25 to 33, 35 to 38), 8 studies from before the Delta variant became dominant (7, 32 to 38), and 2 studies included data without reporting the variant (31, 39). Table 2 shows a summary of all viral load studies, including studies from both this update (indicated with (U)) and from the previous review (indicated with (P) in grey rows), and Supplementary Table 2 shows full information for all viral load studies.

Evidence for the Omicron variant

No studies in the previous review reported on the viral loads of Omicron variant cases. Two studies included in this update compared the viral loads of Omicron and Delta variant cases (4,32), though neither study reported the difference in Ct value between vaccinated and unvaccinated cases.

A retrospective cohort study by Lyngse and others (preprint) suggested that while the distribution of Ct values for Omicron variant cases (n=2,225, 78% fully vaccinated) were slightly smaller (indicating higher viral load) compared with Delta variant cases (n=8,712, 49% fully vaccinated), the median Ct values were similar (27.2 and 28.3 for Omicron and Delta respectively) (4).

A retrospective cohort study by Puhach and others (preprint) suggested that fully vaccinated Omicron cases (n=18) had similar genome copy numbers to fully vaccinated Delta cases (n=121, p=0.33), but 4.9 fold lower infectious viral loads (p=0.10) (32).

Overall, evidence from 2 studies (4,32) suggests there is little difference between the Ct values and genome copy numbers of Omicron and Delta variant COVID-19 cases, though infectious viral loads may be smaller in Omicron cases (indicating higher infectivity, GRADE assessment: not applicable).

Evidence for the Delta variant

Viral load (Ct values)

Evidence from the previous review was mixed: 8 studies suggested that fully vaccinated cases (symptomatic, asymptomatic or both) had similar Ct values to unvaccinated cases (15, 40 to 46), 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 (14, 47 to 49), 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 (50). One study looked at the effect of booster vaccination (3 doses) on Ct values with the Delta variant, which 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 (49).

Twelve studies in this update looked at differences in Ct values and viral load between fully vaccinated and unvaccinated cases, and had similarly mixed evidence: 8 studies suggested that fully vaccinated cases (symptomatic, asymptomatic or both) had similar peak viral loads (10), or mean or median Ct values to unvaccinated (25 to 27, 29, 30, 32) or partially vaccinated cases (33), and 4 studies suggested fully vaccinated cases had higher Ct values (by between 0.9 and 4.9 across studies, suggesting 46% to 97% lower viral loads) (5, 7, 11) or viral loads (by 2.7 $\log_{10}$ viral copies) (31) than unvaccinated cases.

Overall, evidence from 25 studies (13 studies from the previous review (14, 15, 40 to 50), 12 studies from this update (5, 7, 10, 11, 25 to 27, 29 to 33)) suggests mixed evidence for a difference in viral load between fully vaccinated and unvaccinated cases, with 16 studies suggesting no difference and 8 studies suggesting higher Ct values (lower viral load) in fully vaccinated cases (GRADE assessment: very low certainty). The evidence may be mixed due to the waning effect of vaccination (see ‘time since vaccination’ in the next section), where the Ct values of cases decreases (suggesting viral load increases) as time from vaccination increases, and the differences in time since vaccination between studies.

Viral load (Ct values, time since vaccination)

In the previous review, one study, conducted in Israel between June and September 2021, assessed Ct values of 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 (less viral load), but the difference reduced over time (49).

In this update, Levine-Tiefenbrun and others updated this study to include data from between June and November 2021, assessing Ct values of cases by time since both the second and booster (third) doses of Pfizer vaccine (27). The study suggested that Ct values of fully vaccinated cases were higher than unvaccinated cases soon after vaccination (less viral load), but as before the differences reduced over time: Ct values in cases 7 to 30 days (mean = 30.8,

standard deviation (SD): 4.5) and 31 to 60 days (mean = 28.4, SD: 5.0) after the second dose were higher than unvaccinated cases (mean = 26.8, SD: 5.0), but were similar 61 to 120 days (mean = 27.2, SD: 4.8), 121 to 180 days (mean = 26.9, SD: 5.0) and over 180 days (mean = 26.8, SD: 5.0) after the second dose. The study also suggested a similar reduction in differences in Ct values over time after booster vaccination: compared to unvaccinated cases, Ct values were highest 7 to 30 days after a booster dose (mean difference = 2.7, 95% CI: 2.3 to 3.0), slightly higher 31 to 60 days after a booster dose (mean difference = 1.3, 95% CI: 0.7 to 1.9), and very similar 61 to 120 days after a booster dose (mean difference = 0.8, 95% CI: -0.1 to 1.8).

Overall, evidence from 2 studies (one from the previous review (49), one from this update (27), though the study in this update contains all the data from the study in the previous review) suggested that although Ct values are higher in fully and booster vaccinated cases compared with unvaccinated cases (lower viral load) soon after vaccination, this difference drops quickly, with Ct values becoming similar 61 to 120 days after vaccination.

Viral load (time to viral clearance)

Evidence from one study in the previous review suggested 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 than unvaccinated cases (by between 1 and 2, suggesting 50% to 75% lower viral loads) (14). One further study suggested 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), though this difference was not statistically significant (p=0.37).

In this update, Salvatore and others suggested little difference between fully vaccinated and unvaccinated cases in either the median duration of RT-PCR positivity (13 days for fully vaccinated and 12 days for unvaccinated cases) or viral culture positivity (5 days for both fully vaccinated and unvaccinated cases, p=0.29) (29). Additionally, Singanayagam and others reported on the viral load growth and decline rates per day, suggesting that fully vaccinated cases had higher viral load growth and decline rates per day than unvaccinated cases, but these differences were not tested for statistically (10).

Overall, evidence from 4 studies (2 from the previous review (14, 51), 2 from this update (10, 29)) did not suggest large or statistically significant differences in the time to viral clearance between fully vaccinated and unvaccinated cases.

Cytopathic effect as proxy for infectious viral load

In the previous review, 3 studies measured cytopathic effects (CPE, indicating infective virus) of Delta variant cases, suggesting 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 (43, 45, 51).

In this update, 3 studies also measured the CPE of Delta variant cases, and all suggested the proportion of infectious samples were very similar between fully vaccinated and unvaccinated cases (between 8% to 92% across the studies), although only one of these studies (29) tested for differences statistically (p=0.16) (28, 29, 32). One study also suggested that fewer fully vaccinated cases had CPE positivity 5 days after symptom onset, compared with unvaccinated cases (54% versus 85%), though this difference was not tested for statistically (32).

Additionally, one study assessed the median Ct value in cases with positive and negative viral cultures, suggesting that positive cultures have much smaller mean Ct values (indicating higher viral loads) than negative cultures: mean Ct for positive cultures = 23.2 (SD: 4.8), mean Ct for negative cultures = 28.3 (SD: 4.9), p<0.0001 (35).

Overall, evidence from 6 studies (3 from the previous review (43, 45, 51), 3 from this update (28, 29, 32)) suggested there was little difference in CPE between fully vaccinated and unvaccinated cases.

Evidence for pre-Delta variants

From 20 studies from the previous review (15, 41, 43, 44, 46, 48, 52 to 65) and 8 studies from this update (7, 34 to 39), there was evidence suggesting fully vaccinated cases had higher Ct values than unvaccinated cases (suggesting a lower viral load) (GRADE assessment: low certainty). Results are available in Table 2
.

Inequalities

There was little evidence available to explore inequalities through variations across populations and subgroups, for example cultural variations or differences between ethnic, social or vulnerable groups, either in the previous review or this update. 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, 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 studies in the previous review, one of 25 studies in this update) 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. Nonetheless, there were 2 studies offering high quality evidence from the UK for the Delta variant (12, 15).

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. Ten of the 25 studies identified in this update were preprints and should be treated with caution as they have not been peer reviewed or subject to publishing standards, and may be subject to change. This is in addition to 19 preprints or non-peer reviewed reports of the 43 studies identified in the previous review, although 2 of these have since been published (66, 67). 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, and only 2 months for the currently dominant Omicron 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 little evidence for the recently identified Omicron variant (4, 32).

Conclusion

The main conclusions from the previous review were not changed from the inclusion of 25 additional studies in this update.

There was evidence that fully (2 doses) and booster (3 doses) vaccinated cases transmit COVID-19 less than unvaccinated cases, particularly for pre-Delta and Wild-type variants. There was also evidence that this difference was reduced in the months following a vaccine dose, particularly for the Delta variant. The results from viral load studies are broadly supportive of these results, with most pre-Delta studies showing fully vaccinated cases have larger Ct values or lower viral loads than unvaccinated cases, and most Delta studies showing no clear difference in Ct values between fully vaccinated and unvaccinated cases.

There is limited evidence for the Omicron variant. The one transmission study that reported Omicron data included in this update suggested that fully (2 doses) and booster (3 doses) vaccinated index cases transmit both Omicron and Delta variant COVID-19 less to their household contacts than unvaccinated index cases.

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.

Research needed

Randomised controlled trials (RCTs) 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 from the previous review, 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. The results of these trials have not yet been published.

There was little evidence available to explore inequalities through variations across populations and subgroups, for example cultural variations or differences between ethnic, social or vulnerable groups. To understand inequalities between these groups, research must be conducted that reports on difference between these groups.

Acknowledgment

We would like to thank colleagues within the Public Health Advice, Guidance and Expertise function who either reviewed or input into aspects of the previous or this updated review, especially Helen McAuslane and Mario Aramouni.

Disclaimer

UKHSA's rapid reviews aim to provide the best available evidence to decision makers in a timely and accessible way, based on published peer-reviewed scientific papers, unpublished reports and papers on preprint servers. Please note that the reviews: i) use accelerated methods and may not be representative of the whole body of evidence publicly available; ii) have undergone an internal, but not independent, peer review; and iii) are only valid as of the date stated on the review.

In the event that this review is shared externally, please note additionally, to the greatest extent possible under any applicable law, that UKHSA accepts no liability for any claim, loss or damage arising out of, or connected with the use of, this review by the recipient and/or any third party including that arising or resulting from any reliance placed on, or any conclusions drawn from, the review.

Table 1. Summary of findings from transmission studies

There are 6 tables.
[U] indicates studies which are from this updated search.
[P] and light grey highlighting indicate studies from a previous search.
[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.
[D] indicated studies have been updated from previous report (preprint was published or updated).
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 (16) [P]	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)
Allen (12) [U]	UK, March to June 2021, Alpha (40%), Delta (43%)	Household members, not stated	Any	OR for transmission	Reference	0.94 (0.84 to 1.05)	0.73 (0.58 to 0.90)
Bobdey (6) [U]	India, February to April 2021, NR	Hospital dormitory residents, not stated	AstraZeneca	SAR	21.4%	4.3%	
Clifford (3) [U]	UK, February to September 2021, Alpha	Household members, 75% unvaccinated or partially vaccinated	AstraZeneca	RR reduction for transmission	Reference	-7% (-60% to 29%)	35% (-26% to 74%)
			Pfizer		Reference	26% (-11% to 54%)	57% (5% to 85%)
	UK, February to September 2021, Delta		AstraZeneca		Reference	14% (-11% to 52%)	42% (14% to 69%)
			Pfizer		Reference	9% (-16% to 49%)	31% (-3% to 61%)
De Gier (17) [P]	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 (13) [P]	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%)

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome		Effect estimate (95% CI)		
						Unvaccinated	Partially vaccinated	Fully vaccinated
		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 (18,19) [P]	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 (20) [P]	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%)
Lyngse (4) [U]	Denmark, December 2021, Delta (81%), Omicron (19%)	Household members, not stated	AstraZeneca, Janssen, Moderna, Pfizer	OR for household transmission (*partially vaccinated = fully vaccinated, fully vaccinated = booster vaccinated, 3 doses*)		1.41 (1.27 to 1.57)	Reference	0.72 (0.56 to 0.92)
Meyer (21) [P]	Germany, January to March 2021, Alpha	Household members, 67% unvaccinated	Pfizer	SAR		67%	22%	
Ng (9) [U]	Singapore, September 2020 to May 2021, Alpha	Household members, 70% unvaccinated	Moderna, Pfizer	SAR		12.9%	-	33.3%
	Singapore, September 2020 to May 2021, Delta					25.8%	-	11.3%
				OR for household transmission		Reference	0.62 (0.22 to 1.69)	0.73 (0.38 to 1.40)
Prunas (22,68) [P]	Israel, June 2020 to March 2021, NR	Household members, NR	Pfizer	RR reduction for infectiousness		Reference	-	41% (10% to 73%)
Salo (69) [A] [P]	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 (23) [A] [P]	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 (24) [P]	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 (17) [P]	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%)
Hsu (7) [U]	Germany, December 2020 to August 2021, Alpha (57%), Delta (40%)	Close contacts, not stated	AstraZeneca, Janssen, Moderna, Pfizer, Sinopharm, Sputnik	SAR	37.8%	-	10.1%
				OR for transmission	Reference	-	0.21 (0.16 to 0.27)
Kang (14) [P]	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)
Martinez-Baz (8) [U]	Spain, April to August 2021, Alpha (52%), Delta (40%)	Close contacts, 47% unvaccinated	AstraZeneca, Moderna, Pfizer, Janssen	SAR	25%	19%	18%

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 (15) [P]	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		2 weeks	-	-	24% (18% to 30%)

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome		Effect estimate (95% CI)		
						Unvaccinated	Partially vaccinated	Fully vaccinated
				Reduction in transmission, weeks after second dose	12 weeks	-	-	2% (-2% to 6%)
			Pfizer		2 weeks	-	-	50% (35% to 61%)
					12 weeks	-	-	24% (20% to 28%)
Singanayagam (10) [U]	UK, September 2020 to September 2021, Delta	All contacts, not stated	AstraZeneca, Pfizer	SAR		23%	37%	25%

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
Clifford (3) [U]	UK, February to September 2021, Alpha	Household members, 23% unvaccinated	AstraZeneca	RR reduction for transmission	Reference	3% (-38% to 39%)	26% (-39% to 73%)
			Pfizer		Reference	53% (7% to 83%)	71% (12% to 95%)
	UK, February to September 2021, Delta		AstraZeneca		Reference	2% (-19% to 31%)	14% (-5% to 46%)
			Pfizer		Reference	4% (-21% to 44%)	24% (-2% to 64%)
De Gier (17) [P]	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 (66,70) [P] [D]	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% (74% to 85%)
Layan (20) [P]	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%)
Lyngse (5) [U]	Denmark, June to November 2021, Delta	Household members, 52% unvaccinated	AstraZeneca, Janssen, Moderna, Pfizer	SAR	28%	-	15%
Lyngse (4) [U]	Denmark, December 2021, Omicron	Household members, not stated	AstraZeneca, Janssen, Moderna, Pfizer	SAR (*partially vaccinated = fully vaccinated, fully vaccinated = booster vaccinated, 3 doses*)	29%	32%	25%

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome	Effect estimate (95% CI)		
					Unvaccinated	Partially vaccinated	Fully vaccinated
				OR for transmission (*partially vaccinated = fully vaccinated, fully vaccinated = booster vaccinated, 3 doses*)	1.04 (0.87 to 1.24)	Reference	0.54 (0.40 to 0.71)
	Denmark, December 2021, Delta			SAR (*partially vaccinated = fully vaccinated, fully vaccinated = booster vaccinated, 3 doses*)	28%	19%	11%
				OR for transmission (*partially vaccinated = fully vaccinated, fully vaccinated = booster vaccinated, 3 doses*)	2.31 (2.09 to 2.55)	Reference	0.38 (0.32 to 0.46)
Ng (9) [U]	Singapore, September 2020 to May 2021, Delta	Household members, 70% unvaccinated	Moderna, Pfizer	SAR	25.8%	-	11.3%
				OR for transmission	Reference	0.61 (0.33 to 1.12)	0.33 (0.17 to 0.63)
Singanayagam (10) [U]	UK, September 2020 to September 2021, Delta	Household members, not stated	AstraZeneca, Pfizer	SAR	38%	18%	25%
Yi (11) [U]	South Korea, August 2021, Delta	Household members, 39% unvaccinated	Pfizer	SAR	27.8%	25%	12.5%

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 (24) [P]	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 (17) [P]	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%)
Martinez-Baz (8) [U]	Spain, April to August 2021, Alpha (52%), Delta (40%)	Close contacts, 47% unvaccinated	All	SAR	34%	18%	14%
			AstraZeneca			19%	18%
			Janssen			-	21%
			Moderna			14%	8%
			Pfizer			17%	13%
			AstraZeneca	RR reduction for transmission	Reference	41% (34% to 48%)	54% (48% to 60%)

Study	Country, time, dominant variant	Contact type, vaccination status	Vaccine	Outcome	Effect estimate (95% CI)		
					Unvaccinated	Partially vaccinated	Fully vaccinated
			Janssen			-	50% (42% to 57%)
			Moderna			66% (56% to 73%)	82% (78% to 86%)
			Pfizer			57% (52% to 61%)	69% (66% to 72%)

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 (15) [P]	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)
Hsu (7) [U]	Germany, December 2020 to August 2021, Alpha (57%), Delta (40%)	Close contacts, 50% unvaccinated	AstraZeneca, Janssen, Moderna, Pfizer, Sinopharm, Sputnik	OR for transmission	Reference	-	1.26 (0.90 to 1.77)
Singanayagam (10) [U]	UK, September 2020 to September 2021, Delta	All contacts, not stated	AstraZeneca, Pfizer	SAR	34%	15%	22%

Table 2. Summary of findings from studies reporting viral load

There are 5 tables.
[U] indicates studies which are from this updated search.
[P] and light grey highlighting indicate studies from a previous search.
[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.
[D] indicated studies have been updated from previous report (preprint was published or updated).
The following acronyms are used: CI = confidence interval, CPE = cytopathic effect (that is, infectious virus), HYT = Healthy Yolo Together (testing centre), IQR = interquartile range, NR = not reported, RR = relative risk, SD = standard deviation, UeS = Unidos en Salud (testing centre).
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 (49) [P]	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)
Levine-Tiefenbrun (27) [U]	Israel, June to November 2021, Delta (more than 93%)	Pfizer	Mean Ct values	7 to 30 days after booster (third) dose	26.8 (5.0)	29.4 (4.7)	2.7 (2.3 to 3.0)
				31 to 60 days after booster (third) dose		28.5 (4.4)	1.3 (0.7 to 1.9)
				61 to 120 days after booster (third) dose		28.9 (4.5)	0.8 (-0.1 to 1.8)

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
Acharya (25) [U]	US, June to August 2021, Delta (more than 95%)	NR	Median Ct value (UeS)	22.7 (19.1 to 27.3)	22.2 (18.9 to 26.9)	p=0.54
			Median Ct (UeS, symptomatic)	21.9 (18.9 to 26.1)	21.2 (18.9 to 25.8)	p=0.62
			Median Ct (UeS, asymptomatic)	23.6 (19.8 to 28.7)	24.0 (20.3 to 29.1)	p=0.89
			Median Ct (HYT, asymptomatic)	25.7 (22.9 to 28.2)	26.1 (22.7 to 28.8)	p=0.80
Blanquart (54) [P]	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 (40,71) [P]		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

Study	Country, time, dominant variant	Vaccine	Outcome		Effect estimate		
					Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
	Singapore, April to June 2021, Delta (100%)		Median Ct value (symptom onset)		21.9 (18.8 to 31.2)	19.2 (16.6 to 21.5)	p=0.279
Christensen (50) [P]	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 (47) [P]	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 (15) [P]	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 (41) [P]	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 (51) [P]	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
Hirotsu (26) [U]	Japan, February to September 2021, Delta (100%)	Moderna, Pfizer	Mean viral load (log_{10} copies/ml)		6.0 (1.6)	6.5 (0.8)	NR
Hsu (7) [U]	Germany, December 2020 to August 2021, Delta (100%)	Pfizer, Janssen, AstraZeneca, Moderna, Sputnik, Sinopharm	Mean Ct values		24.1 (6.4)	25.0 (6.7)	p<0.001
Kale (33) [U]	India, January to May 2021, Delta (70%), Kappa (24%)	AstraZeneca	Median Ct values (*unvaccinated = partially vaccinated*)		21.1 (12.0 to 29.5)	23.2 (0.0 to 33.1)	p=0.82
Kang (14) [P]	China, May to June 2021, Delta (100%)	NR	Predicted median Ct value, days after symptom onset	Day 0	24.5 (23.6 to 26.7)	25.5 (25.3 to 25.8)	NR
				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 (42) [P]	US, February to July 2021, Delta (74%)	NR	Median Ct value		21 (17 to 25)	22 (17 to 26)	p=0.83
Kislaya (48) [P]	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)
Levine-Tiefenbrun (49) [P]	Israel, June to September 2021, Delta (93%)	Pfizer	Mean Ct value	All	27.7 (5.0)	26.9 (5.0)	0.22 (0.02 to 0.42)
				7 to 30 days after second dose		31.2 (4.5)	4.56 (2.19 to 6.94)
				31 to 60 days after second dose		29.3 (5.1)	2.63 (0.67 to 4.59)

Study	Country, time, dominant variant	Vaccine	Outcome		Effect estimate		
					Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
				61 to 120 days after second dose		27.2 (4.8)	0.58 (0.05 to 1.12)
				121 to 180 days after second dose		27.0 (5.0)	0.29 (0.08 to 0.51)
				more than 180 days after second dose		26.7 (5.0)	0.06 (-0.16 to 0.29)
			Mean Ct value (*unvaccinated* = 2 months after the second dose, *vaccinated* = 2 to 6 months after the second dose)		-	-	-3.1 (-4.6 to -1.6)
Levine-Tiefenbrun (27) [U]	Israel, June to November 2021, Delta (more than 93%)	Pfizer	Mean Ct values	7 to 30 days after second dose	26.8 (5.0)	30.8 (4.5)	NR
				31 to 60 days after second dose		28.4 (5.0)	NR
				61 to 120 days after second dose		27.2 (4.8)	NR
				121 to 180 days after second dose		26.9 (5.0)	NR
				more than 180 days after second dose		26.8 (5.0)	NR
Li (72) [P]	China, May to June 2021, Delta (100%)	Sinovac, Sinopharm	Proportion of Ct value less than 24 (*vaccinated* = partially or fully vaccinated)		49.6%	44.7%	p=0.23
			Proportion of Ct value 24 to 40 (*vaccinated* = partially or fully vaccinated)		36.5%	52.6%	
Luo (43,67) [P] [D]	US, January to July 2021, Delta (100%)	Janssen, Moderna, Pfizer	Mean Ct value		21.1	20.2	NR
			Mean Ct less than or equal to 5 days after symptom onset		20.3	20.3	NR
			Mean Ct more than 5 days after symptom onset		24.6	21.1	NR
			Proportion of CPE positive samples		74.4%	76.6%	NR
Lyngse (5) [U]	Denmark, June to November 2021, Delta	AstraZeneca, Janssen, Moderna, Pfizer	Mean Ct values		NR	NR	1.6
Magalis (31) [U]	US, October 2020 to August 2021, Delta (100%)	Janssen, Moderna, Pfizer	Mean viral load (log_{10} copies/ml)		7.36 (3.29 to 10.8)	4.66 (1.2 to 10.6)	p<0.00001
Pena-Hernandez (28) [U]	US, July to August 2021, Delta	Moderna, Pfizer	Proportion of CPE positive samples		40%	21%	RR=0.49 (0.27 to 0.91)
Pouwels (44) [P]	UK, May to June 2021, Delta (more than 61%)	Pfizer or AstraZeneca	Median Ct value (seronegative)		21.5 (16.4 to 31.7)	32.3 (26.0 to 34.0)	NR
	UK, June to August 2021, Delta (more than 92%)				25.7 (19.1 to 30.8)	25.3 (19.1 to 31.3)	p=0.35
Puhach (32) [U]	Switzerland, April 2020 to December 2021, Delta	Pfizer, Moderna, CoviVac, other	Ct value (E gene)		13.8 to 26.3	16.3 to 26.1	NR
			Proportion of CPE positive samples		91.7%	83.8%	NR
			CPE positive samples at 5 days after symptom onset		84.6%	53.8%	NR
			Mean Ct value (N1)		23.3 (5.6)	22.8 (5.9)	p=0.23

Study	Country, time, dominant variant	Vaccine	Outcome	Effect estimate		
				Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
Riemersma (45) [P]	US, June to July 2021, Delta (69% to 95%)	mRNA or adenovirus vaccines	Mean Ct value (N1, symptomatic)	22.9 (5.5)	22.6 (5.8)	p=0.74
			Mean Ct value (N1, asymptomatic)	27.0 (5.6)	26.1 (7.1)	p=0.05
			Proportion of CPE positive samples	88.2%	94.9%	NR
Salvatore (29) [U]	US, July to August 2021, Delta	Janssen, Moderna, Pfizer	Median Ct value (day 1 of symptom onset or first positive test)	28.5 (24.8 to 31.8)	26.4 (23.5 to 28.4)	p>0.0026
			Median Ct value (day 10 after symptom onset or positive test)	34.5 (29.4 to 35.2)	32.9 (30.5 to 34.6)	p>0.0026
			Proportion of CPE positive samples	12%	8%	p=0.16
			Median duration of RT-PCR positivity	12 days	13 days	NR
			Median duration of viral culture	5 days	5 days	p=0.29
Servellita (46,73) [P]	US, February to June 2021, Delta (100%)	Moderna, Pfizer, Janssen	Mean Ct value (*N* gene)	19.5	21.5	p=0.09
Siddle (30) [U]	US, July to August 2021, Delta (99%)	Janssen, Moderna, Pfizer	Mean Ct values (asymptomatic)	24.1 (2.25)	24.0 (6.0)	NR
			Mean Ct values (symptomatic)	24.3 (6.7)	24.4 (6.1)	NR
Singanayagam (10) [U]	UK, September 2020 to September 2021, Delta (100%)	AstraZeneca, Pfizer	Median viral load growth rate per day (ORF1ab gene) (2.5% and 97.5% centiles reported)	4.16 (2.19 to 11.8)	4.43 (3.01 to 10.2)	NR
			Median viral load decline rate per day (ORF1ab gene) (2.5% and 97.5% centiles reported)	1.81 (1.52 to 2.2)	2.18 (1.88 to 2.57)	NR
			Median peak log_{10} viral load per ml (ORF1ab gene) (2.5% and 97.5% centiles reported)	8.09 (7.74 to 8.42)	8.19 (7.99 to 8.41)	NR
Yi (11) [U]	South Korea, August 2021, Delta (100%)	Moderna, Pfizer	Mean Ct values (asymptomatic)	17.2	18.1	NR
			Mean Ct values (symptomatic)	15.1	20	NR

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 (47) [P]	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 (15) [P]	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 (41) [P]	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	

Study	Country, time, dominant variant	Vaccine	Outcome	Effect estimate		
				Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
			Median Ct value (*SC2N* gene)	19.3	20.2	
Hirotsu (26) [U]	Japan, February to September 2021, Delta (100%)	Moderna, Pfizer	Mean viral load (log_{10} copies/ml)	6.0 (1.6)	5.5 (2.2)	NR
Kislaya (48) [P]	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 (44) [P]	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
	UK, June to August 2021, Delta (more than 92%)			25.7 (19.1 to 30.8)	24.7 (18.8 to 31.3)	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
Adamson (34) [U]	US, December 2020 to March 2021, NR	Janssen, Moderna, Pfizer	Median Ct value		20.1 (16.9 to 25.1)	30.4 (20.8 to 34.1)	NR
Abu-Raddad (52) [P]	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)
Bailly (53) [P]	France, March 2021, Beta	Pfizer	Mean Ct value		15	21	p<0.05
Blanquart (54) [P]	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)
Boschi (35) [U]	France, January to July 2021, Alpha and Delta (proportions NR)	AstraZeneca, Janssen, Moderna, Pfizer	Mean Ct value		21.5 (4.5)	23.4 (5.4)	NR
			Proportion of CPE positive samples		80%	66%	p<0.0001
Brunner-Ziegler (36) [U]	Austria, January to July 2021, Alpha (81%)	AstraZeneca, Pfizer	Mean Ct value		22.6 (7.1)	24.8 (6.4)	NR
Costa (37)	Spain, February to July 2021, Alpha (54%), Delta (46%)	AstraZeneca, Janssen, Pfizer	Mean viral load (log_{10} copies/ml)	All	8.1	7.8	p=0.31
				Asymptomatic	8.4	8.7	p=0.85
				Symptomatic	8.1	7.4	p=0.12

Study	Country, time, dominant variant	Vaccine	Outcome	Effect estimate		
				Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
Emary (55) [P]	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 (15) [P]	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 (41) [P]	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	
Hsu (7) [U]	Germany, December 2020 to August 2021, Alpha (100%)	Pfizer, Janssen, AstraZeneca, Moderna, Sputnik, Sinopharm	Mean Ct values	26.9 (6.4)	33.1 (6.0)	p<0.001
Ioannou (56) [P]	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 (57) [P]	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 (48) [P]	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)
Kolobukhina (39) [U]	Russia, December 2020 to April 2021, NR	Sputnik V	Mean Ct value	31.5 (27.2 to 33.7)	34.8 (31.4 to 36.5)	p=0.026
Lumley (58) [P]	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 (43,67) [P] [D]	US, January to July 2021, Alpha (100%)	Pfizer, Moderna, Janssen	Mean Ct values	21.7	22.7	NR
			Mean Ct values less than or equal to 5 days after symptom onset	21.3	21.5	NR
			Mean Ct values more than 5 days after symptom onset	24.6	24.2	NR
			Proportion of CPE positive samples	37.9%	17.4%	p=0.02
Magalis (31) [U]	US, October 2020 to August 2021, non-Delta	Janssen, Moderna, Pfizer	Mean viral load (log_{10} copies/ml)	6.15 (3.56 to 10.9)	5.39 (1.41 to 8.36)	p<0.00001
McEllistream (59) [P]	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)

Study	Country, time, dominant variant	Vaccine	Outcome		Effect estimate		
					Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
Mostafa (60) [P]	US, January to May 2021, Alpha (61%), Iota (13.5%)	Pfizer, Moderna	Median Ct value (*N* gene)		19.6 (16.3 to 22.8)	19.2 (16.6 to 22.0)	NR
			Proportion of CPE positive samples		64.5%	18.5%	p<0.00001
Muhsen (61) [P]	Israel, January to April 2021, Alpha (dominant)	Pfizer	Median Ct value (*ORF1ab* gene)		26.7 (28.7 to 33.5)	32.0 (22.9 to 31.0)	p=0.008
Pajon (62) [P]	US, July 2020 to March 2021, Wild-type (B.1/B.1.2) (93%)	Moderna	Median time to viral clearance (days)		7	4	3
			Estimated Ct values (symptomatic), days after symptoms	Day 1	20.26	27.27	7.01 (4.74 to 9.28)
				Day 3	31.80	37.63	5.84 (3.03 to 8.64)
				Day 5	34.07	39.87	5.80 (1.73 to 8.37)
				Day 7	35.23	39.37	4.13 (1.73 to 6.54)
				Day 28	40.73	41.03	0.30 (-0.33 to 0.90)
Pouwels (44) [P]	UK, December 2020 to May 2021, Alpha (dominant)	Pfizer, AstraZeneca	Median Ct value (seronegative)		28.7 (20.4 to 32.9)	33.3 (31.6 to 34.0)	p=0.02
			p value for trend (increasing Ct value with time from first vaccination and number of doses)		-	-	p<0.0001
Regev-Yochay (63) [P]	Israel, December 2020 to March 2021, NR	Pfizer	Mean Ct value		22.2 (1.0)	27.3 (1.2)	5.09 (2.8 to 7.4)
			Median Ct value		23.3	25.8	p<0.001
Servellita (46,73) [P]	US, February to June 2021, All	Moderna, Pfizer, Janssen	Mean Ct value (*N* gene)		23.1	23.1	p=0.99
			Mean Ct value (*N* gene, symptomatic)		21.9	21.2	p=0.64
			Mean Ct value (*N* gene, asymptomatic)		24.6	30.1	p=0.023
	US, February to June 2021, Alpha		Mean Ct value (*N* gene)		21.5	22.1	p=0.70
	US, February to June 2021, Beta				22.8	26.5	p=0.27
	US, February to June 2021, Gamma				19.8	20.2	p=0.78
	US, February to June 2021, Epsilon				21.0	24.3	p=0.15
	US, February to June 2021, Iota				21.8	20.9	p=0.64
	US, February to June 2021, Other				22.3	23.8	p=0.45
Smith (38) [U]	Worldwide, March 2020 to November 2021, Non-Delta (100%)	NR	Mean viral load (log_{10} PFU/ml)		3.2	3.1	NR
Tande (64) [P]	US, December 2020 to February 2021, NR	Pfizer, Moderna	Mean Ct value (asymptomatic)	Arizona (Alinity instrument)	26.6 (8.3)	30.0 (6.1)	NR
				Arizona (m2000 instrument)	15.1 (7.7)	18.6 (9.3)	NR
Thompson (65) [P]	US, December 2020 to April 2021, Wild-type (70% to 90%)	Pfizer (67%), Moderna (33%)	Mean log_{10} viral copies/µL (*vaccinated = partial or full vaccination*) (relative difference reported)		3.8 (1.7)	2.3 (1.7)	40.2% (16.3% to 57.3%)

Study	Country, time, dominant variant	Vaccine	Outcome	Effect estimate		
				Unvaccinated (SD or IQR)	Vaccinated (SD or IQR)	Difference (95% CI) or p value
			Mean days of viral RNA detection (*vaccinated = partial or full vaccination*)	8.9 (10.2)	2.7 (3.0)	6.2 (4.0 to 8.4)
			Mean days spent in sick bed (*vaccinated = partial or full vaccination*)	3.8 (5.9)	1.5 (2.1)	2.3 (0.8 to 3.7)

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
Brunner-Ziegler (36) [U]	Austria, January to July 2021, Alpha (81%)	AstraZeneca, Pfizer	Mean Ct value		22.6 (7.1)	25.5 (7.4)	NR
Eyre (15) [P]	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 (41) [P]	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 (57) [P]	US, December to April 2021, L452R (39.5%)	Pfizer, Moderna	Mean Ct value		23.0 (7.4)	27.7 (8.7)	NR
Jones (74) [P]	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 (48) [P]	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 (75) [P]	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 (44) [P]	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 (76) [P]	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 (64) [P]	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

References

1. UKHSA COVID-19 Rapid Evidence Service. 'The effect of vaccination on transmission of COVID-19: A rapid review' 2022
2. Tricco A and others. 'Rapid reviews to strengthen health policy and systems: a practical guide' World Health Organization (WHO) 2017
3. Clifford S and others. 'Effectiveness of BNT162b2 and ChAdOx1 against SARS-CoV-2 household transmission: a prospective cohort study in England' medRxiv 2021
4. Lyngse FP and others. 'SARS-CoV-2 Omicron VOC transmission in Danish households' medRxiv 2021
5. Lyngse FP and others. 'Effect of vaccination on household transmission of SARS-CoV-2 Delta VOC' medRxiv 2022
6. Bobdey S and others. 'Effectiveness of ChAdOx1 nCOV-19 vaccine: experience of a tertiary care institute' Medical Journal of the Armed Forces India 2021: volume 77, pages S271-S7
7. Hsu L and others. 'COVID-19 breakthrough infections and transmission risk: real-world data analyses from Germany's largest public health department (Cologne)' Vaccines (Basel) 2021: volume 9, issue 11
8. Martinez-Baz I and others. 'Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021' Eurosurveillance 2021: volume 26, issue 39
9. Ng OT and others. 'Impact of Delta Variant and Vaccination on SARS-CoV-2 Secondary Attack Rate Among Household Close Contacts' Lancet Regional Health Western Pacific 2021: volume 17, page 100,299
10. Singanayagam A and others. 'Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study' Lancet Infectious Disease 2021
11. Yi S and others. 'SARS-CoV-2 Delta variant breakthrough infection and onward secondary transmission in household' Journal of Korean Medical Science 2022: volume 37, issue 1, pages e12
12. Allen H and others. 'Household transmission of COVID-19 cases associated with SARS-CoV-2 delta variant (B.1.617.2): national case-control study' Lancet Regional Health - Europe 2021: pages 100252
13. de Gier B and others. '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' medRxiv 2021
14. Kang M and others. 'Transmission dynamics and epidemiological characteristics of Delta variant infections in China' medRxiv 2021
15. Eyre DW and others. 'The impact of SARS-CoV-2 vaccination on Alpha and Delta variant transmission' medRxiv 2021

16. Allen H and others. 'Increased household transmission of COVID-19 cases associated with SARS-CoV-2 Variant of Concern B.1.617.2: a national case control study'
17. de Gier B and others. 'Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021' Eurosurveillance 2021: volume 26, issue 31
18. Harris RJ and others. 'Effect of vaccination on household transmission of SARS-CoV-2 in England' New England Journal of Medicine 2021
19. Harris RJ and others. 'Impact of vaccination on household transmission of SARS-COV-2 in England' 2021
20. Layan M and others. 'Impact of BNT162b2 vaccination and isolation on SARS-CoV-2 transmission in Israeli households: an observational study' medRxiv 2021
21. Meyer E and others. '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 to March 2021' medRxiv 2021
22. Prunas O and others. 'Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel' medRxiv 2021
23. Shah ASV and others. 'Effect of Vaccination on Transmission of SARS-CoV-2' New England Journal of Medicine 2021
24. Braeye T and others. 'Vaccine effectiveness against infection and onwards transmission of COVID-19: Analysis of Belgian contact tracing data, January to June 2021' Vaccine 2021: volume 39, issue 39, pages 5,456-60
25. Acharya CB and others. 'No significant difference in viral load between vaccinated and unvaccinated, asymptomatic and symptomatic groups when infected with SARS-CoV-2 Delta variant' medRxiv 2021
26. Hirotsu Y and others. 'Active immunization by COVID-19 mRNA vaccine results in rapid antibody response and virus reduction in breakthrough infection by Delta (B.1.617.2)' Research Square 2021
27. Levine-Tiefenbrun M and others. 'Waning of SARS-CoV-2 booster viral-load reduction effectiveness' medRxiv 2021
28. Peña-Hernández MA and others. 'Comparison of infectious SARS-CoV-2 from the nasopharynx of vaccinated and unvaccinated individuals' medRxiv 2022
29. Salvatore PP and others. 'Transmission potential of vaccinated and unvaccinated persons infected with the SARS-CoV-2 Delta variant in a federal prison, July to August 2021' medRxiv 2021
30. Siddle KJ and others. 'Evidence of transmission from fully vaccinated individuals in a large outbreak of the SARS-CoV-2 Delta variant in Provincetown, Massachusetts' medRxiv 2021
31. Magalis BR and others. 'SARS-CoV-2 Delta vaccine breakthrough transmissibility in Alachua, Florida' medRxiv 2021
32. Puhach O and others. 'Infectious viral load in unvaccinated and vaccinated 1 patients infected with SARS-CoV-2 WT, Delta and Omicron' medRxiv 2022

33. Kale P and others. 'Vaccine breakthrough infections by SARS-CoV-2 variants after ChAdOx1 nCoV-19 vaccination in healthcare workers' Vaccines (Basel) 2021: volume 10, issue 1
34. Adamson PC and others. 'Lower severe acute respiratory syndrome coronavirus 2 viral shedding following coronavirus disease 2019 vaccination among healthcare workers in Los Angeles, California' Open Forum Infectious Disease 2021: volume 8, issue 11, pages ofab526
35. Boschi C and others. 'Isolation of 4000 SARS-CoV-2 shows that contagiousness is associated with viral load, not vaccine or symptomatic status' Emerging Microbes and Infections 2021: volume 10
36. Brunner-Ziegler S and others. 'Postvaccination infections among staff of a tertiary care hospital after vaccination with severe acute respiratory syndrome coronavirus 2 vector and mRNA-based vaccines' Clinical Microbiology and Infection 2021
37. Costa R and others. 'RNA viral loads of SARS-CoV-2 Alpha and Delta variants in nasopharyngeal specimens at diagnosis stratified by age, clinical presentation and vaccination status' Journal of Infection 2021
38. Smith DR and others. 'Genomic and virological characterization of SARS-CoV-2 variants in a subset of unvaccinated and vaccinated U.S. military personnel' Frontiers in Medicine 2022
39. Kolobukhina L and others. 'Assessment Of COVID-19 clinical course in patients vaccinated with Spitnik V, SARS-COV-2 S protein rbd domain variation and serum virus neutralizing activity' Bulletin of Russian State Medical University 2021
40. Chia PY and others. 'Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study' medRxiv 2021
41. Griffin JB and others. 'SARS-CoV-2 infections and hospitalizations among persons aged >/=16 years, by vaccination status - Los Angeles County, California, May 1 to July 25, 2021' Morbidity and Mortality Weekly Report 2021: volume 70, issue 34, pages 1,170-6
42. Kerwin H and others. 'An analysis of SARS-CoV-2 vaccine breakthrough infections and associated clinical outcomes' medRxiv 2021
43. Luo CH and others. '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' medRxiv 2021
44. Pouwels KB and others. 'Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK' Nature Medicine 2021
45. Riemersma KK and others. 'Shedding of infectious SARS-CoV-2 despite vaccination when the Delta variant is prevalent - Wisconsin, July 2021' medRxiv 2021
46. 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
47. Elliott P and others. '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' 2021

48. Kislaya I and others. 'Delta variant and mRNA Covid-19 vaccines effectiveness: higher odds of vaccine infection breakthroughs' medRxiv 2021
49. Levine-Tiefenbrun M and others. 'Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2' Nature Medicine 2021
50. Christensen PA and others. 'Delta variants of SARS-CoV-2 cause significantly increased vaccine breakthrough COVID-19 cases in Houston, Texas' American Journal of Pathology 2021
51. Hagan LM and others. 'Outbreak of SARS-CoV-2 B.1.617.2 (Delta) Variant Infections Among Incarcerated Persons in a Federal Prison - Texas, July to August 2021' Morbidity and Mortality Weekly Report 2021: volume 70, issue 38, pages 1,349-54
52. Abu-Raddad LJ and others. 'Effect of vaccination and of prior infection on infectiousness of vaccine breakthrough infections and reinfections' medRxiv 2021
53. Bailly B and others. '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' Clinical Infectious Diseases 2021
54. Blanquart F and others. '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' Eurosurveillance 2021: volume 26, issue 37
55. Emary KRW and others. '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 randomised controlled trial' Lancet 2021: volume 397, issue 10,282, pages 1,351-62
56. Ioannou P and others. 'Transmission of SARS-CoV-2 variant B.1.1.7 among vaccinated health care workers' Infectious Diseases (London) 2021: pages 1-4
57. Jacobson KB and others. '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' Clinical Infectious Diseases 2021: pages 1-8
58. Lumley S and others. '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' medRxiv 2021
59. 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, pages 26
60. 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
61. 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
62. Pajon R and others. 'Initial analysis of viral dynamics and circulating viral variants during the mRNA-1273 phase 3 COVE trial' medRxiv 2021

63. Regev-Yochay G and others. 'Decreased infectivity following BNT162b2 vaccination' The Lancet Regional Health, Europe 2021
64. 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
65. 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 320-9
66. Gazit S and others. 'BNT162b2 mRNA vaccine effectiveness given confirmed exposure: analysis of household members of coronavirus disease 2019 patients' Clinical Infectious Diseases 2021: pages 1-7
67. Luo CH and others. 'Infection with the SARS-CoV-2 Delta variant is associated with higher recovery of infectious virus compared to the Alpha variant in both unvaccinated and vaccinated individuals' Infectious Diseases Society of America 2021
68. Prunas O and others. 'Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel' Science 2022: volume 375, issue 6585, pages 1,151-4
69. Salo J and others. 'The indirect effect of mRNA-based COVID-19 vaccination on unvaccinated household members' medRxiv 2021
70. Gazit S and others. 'BNT162b2 mRNA vaccine effectiveness given confirmed exposure; analysis of household members of COVID-19 patients' medRxiv 2021
71. Chia PY and others. 'Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine breakthrough infections: a multicentre cohort study' Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2021
72. 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 1,751-9
73. Servellita V and others. 'Predominance of antibody-resistant SARS-CoV-2 variants in vaccine breakthrough cases from the San Francisco Bay Area, California' Nature Microbiology 2022: volume 7, issue 2, pages 277-88
74. Jones NK and others. 'Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection' Elife 2021: volume 10
75. Levine-Tiefenbrun M and others. 'Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine' Nature Medicine 2021: volume 27, issue 5, pages 790-2
76. Shrotri M and others. 'Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study' The Lancet Infectious Diseases 2021: volume 21, issue 11, pages 1,529-38
77. Public Health England. 'Transmission of COVID-19 within large events and interventions to minimise transmission: A rapid review' last updated Not yet published 2021 (viewed on 23 April 2021)

78. Page MJ and others. 'The PRISMA 2020 statement: an updated guideline for reporting systematic reviews' British Medical Journal 2021: volume 372, page n71
79. Academy of Nutrition and Dietetics. Evidence analysis manual: steps in the academy evidence analysis process 2016
80. Agency for Healthcare Research and Quality (AHRQ). Systems to rate the strength of scientific evidence. Evidence report/technology assessment (summary) 2002
81. Evidence Prime Inc. 'GRADEpro GDT: GRADEpro Guideline Development Tool last updated 2020
82. The GRADE Working Group. GRADE handbook for grading quality of evidence and strength of recommendations 2013
83. Murad M and others. 'Rating the certainty in evidence in the absence of a single estimate of effect' Evidence Based Medicine 2017: volume 22, issue 3, pages 85 to 87
84. NCT04811664. 'A Study of SARS CoV-2 Infection and Potential Transmission in University Students Immunized With Moderna COVID-19 Vaccine'. 2021
85. NCT04324606. 'A Study of a Candidate COVID-19 Vaccine (COV001)'. 2020
86. NCT04750356. 'SARS-CoV-2 (COVID-19) Longitudinal Study: Understanding Susceptibility, Transmission and Disease Severity (Legacy Study)'. 2021

Annexe A: Methods

This is an update to a previously published review (1) and 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 (2). 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 (77) and registered on PROSPERO (CRD42021257125). The review has been reported according to PRISMA guidelines (78).

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

1. What is the evidence on COVID-19 transmission from people who have had one or 2 doses of a COVID-19 vaccination?
2. 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 Social Science Research Network (SSRN) preprints, World Health Organization (WHO) COVID-19 Research Database.

Search strategy

Searches were conducted for papers published between 22 October 2021 and 12 January 2022. The previous review included the same search strategy for papers published between 1 January 2020 and 22 October 2021. Studies included in the previous review are also included in this review.

Search terms covered key 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. All that had been identified as preprints as of 12 January 2022 were last checked and updated (if necessary) on 9 February 2022.

Search strategy for 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.1.

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 as with the previous review, we focussed 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. As in the previous review, we have removed this exclusion criteria. We have also removed the need for contacts to be unvaccinated in transmission studies from the inclusion criteria.

Table A.1. Inclusion and exclusion criteria

	Included	**Excluded**
Population	People 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, exposure	Partial, full or booster (third dose) vaccination against COVID-19; any COVID-19 specific vaccination	
Outcomes	**Direct outcomes** 1. Secondary transmission 2. Transmission of laboratory-confirmed COVID-19 to contacts (secondary cases, assessed as transmission by genomic analysis or proximity, such as household members) **Indirect outcomes** 1. Viral load 2. Duration of infection (if presented with a direct outcome or viral load)	
Language	English	
Date of publication	22 October 2021 to 12 January 2022	
Study design	1. Randomised controlled trials 2. Cohort study 3. Case-control study	1. Systematic or narrative reviews

	Included	Excluded
		2. Other observational studies 3. Guidelines 4. Opinion pieces 5. 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 (79). 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) (80). In the QCC tool, 4 questions are considered critical (on selection bias, group comparability and confounding, interventions and 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 more than or equal to 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.

QCC ratings are reported in the data extraction tables, Supplementary Tables 1 and 2.
The certainty of the evidence was assessed using a variation of the GRADE framework for systematic reviews without meta-analysis (81 to 83). 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 both transmission of COVID-19 and viral load, separately for Wild-type and pre-Delta variant COVID-19, Delta variant COVID-19, and Omicron variant COVID-19.

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

GRADE assessment

GRADE assessments were conducted for each of the following outcomes, see Table A.2:

- transmission of Wild-type and pre-Delta variant COVID-19, Delta variant COVID-19, and Omicron variant COVID-19 to household and other contacts, comparing vaccinated (any number of doses) and unvaccinated index cases
- viral load (including Ct values) of Wild-type and pre-Delta variant COVID-19, Delta variant COVID-19, and Omicron variant COVID-19 cases, comparing vaccinated (any number of doses) and unvaccinated index 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:

- there was only one Omicron variant COVID-19 study, so inconsistency could not be assessed, and there was little evidence for large effects or dose response – as such, the evidence was judged as very low certainty
- for Delta variant COVID-19 studies, there was evidence of dose response, but little evidence for large effects – as such, the evidence was judged as low certainty
- for Wild-type and pre-Delta variant COVID-19 studies, there was evidence of dose response, as across the included studies fully vaccinated index cases transmitted COVID-19 less then partially vaccinated index cases, who transmitted COVID-19 less than unvaccinated index

cases, and evidence of large effects, as many studies had large effects (for example, >50% reduction in transmission) – as such, 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 in most studies, and a high risk that factors other than vaccination affected the results:

- there were no Omicron variant COVID-19 studies that looked at the difference in viral loads between vaccinated and unvaccinated cases, so a GRADE assessment was not performed
- for Delta variant COVID-19 studies, there was little evidence for dose response or large effects – as such, the evidence was judged as very low certainty
- for Wild-type and pre-Delta variant COVID-19 studies, there was evidence of large effects, but little evidence for dose response – as such, the evidence was judged as low certainty

Table A.2. 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	Omicron	Evidence suggests that booster vaccinated (3 doses) index cases transmit Omicron variant COVID-19 less than fully vaccinated index cases, who transmit less than unvaccinated index.	1	⨁◯◯◯ Very low
	Delta	Evidence suggests fully vaccinated cases transmit Delta variant COVID-19 less than unvaccinated cases.	10	⨁⨁◯◯ Low
	Wild-type and pre-Delta	Evidence suggests fully vaccinated cases transmit Wild-type and pre-Delta variant COVID-19 less than unvaccinated cases. This reduction was substantial in many studies.	14	⨁⨁⨁◯ Moderate
Viral load of COVID-19 positive cases, comparing vaccinated (any number of doses) and unvaccinated cases	Omicron	No studies provided evidence for this outcome (no studies compared viral loads between vaccinated and unvaccinated cases).	0	Not applicable
	Delta	Evidence suggests mixed evidence for a difference in viral load between fully vaccinated and unvaccinated cases, with 16 studies suggesting no difference and 8 studies suggesting higher Ct values in fully vaccinated cases (suggesting a lower viral load).	25	⨁◯◯◯ Very low
	Wild-type and pre-Delta	Evidence suggested fully vaccinated cases had higher Ct values than unvaccinated cases (suggesting a lower viral load).	28	⨁⨁◯◯ Low

Figure A.1. PRISMA diagram

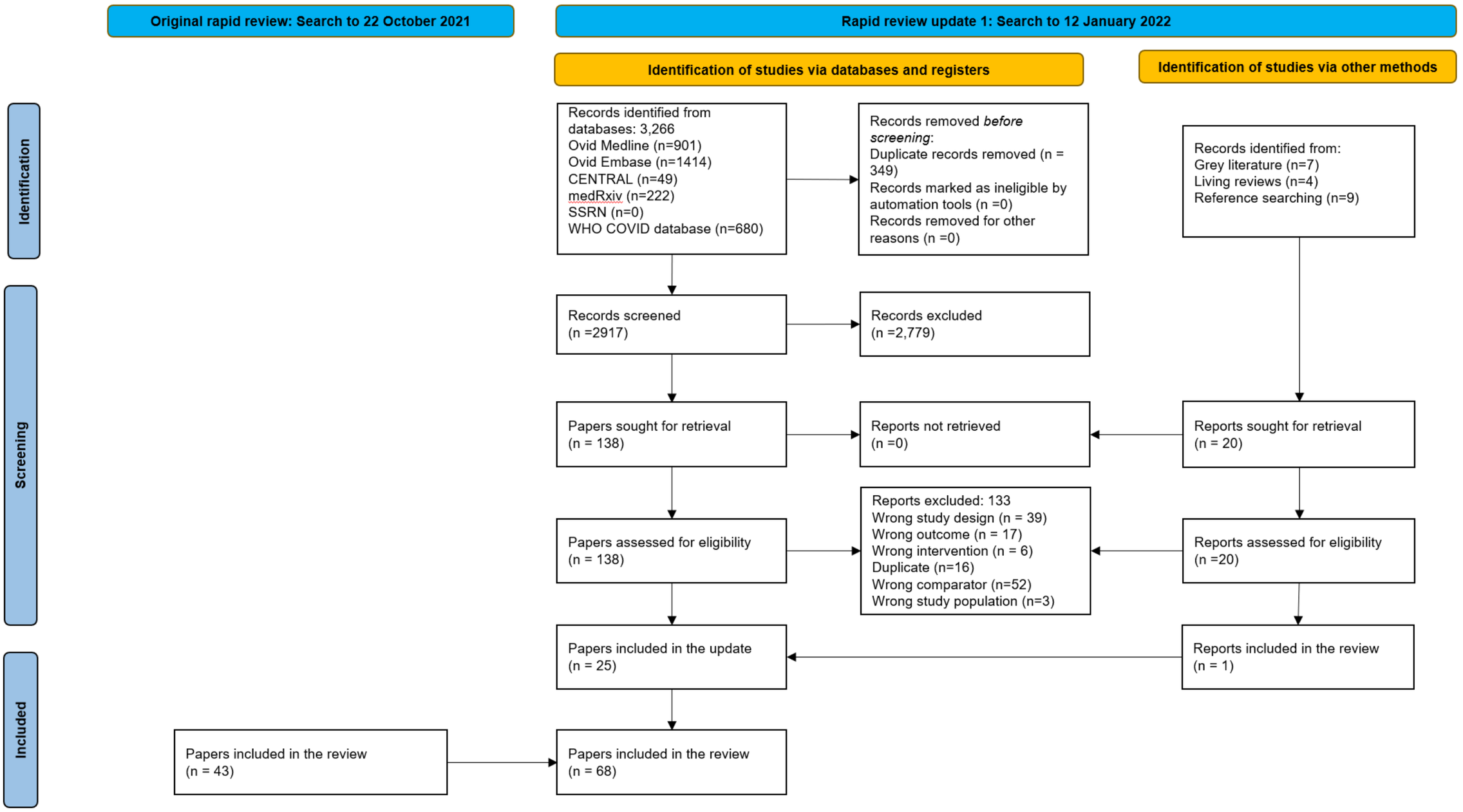

Figure A.1. PRISMA diagram – alt text

A PRISMA diagram showing the flow of studies through this review, including 43 studies from the original rapid review (search to 22 October 2021), 24 studies identified from databases and registers and 1 study identified via other methods, in a search up to 12 January 2022.

From the original rapid review (search to 22 October 2021), there were n=43 papers included in the review.

From rapid review update 1 (search to 12 January 2022):
From identification of studies via databases and registers, n=3,266 records identified from databases:

- Ovid Medline (n=901)
- Ovid Embase (n=1,414)
- CENTRAL (n=49)
- medRxiv (n=222)
- SSRN (n=0)
- WHO COVID database (n=680)

From these, records removed before screening:

- duplicate records removed (n=349)
- records marked as ineligible by automation tools (n=0)
- records removed for other reasons (n=0)

n=2,917 records screened, of which n=2,779 were excluded, leaving n=138 papers sought for retrieval

n=20 records identified from identification of studies via other methods, and all sought for retrieval:

- grey literature (n=7)
- living reviews (n=4)
- reference searching (n=9)

All identified reports were retrieved.

n=138 papers assessed for eligibility from identification of studies via databases and registers, and n=20 reports from identification of studies via other methods.

Of these, n=133 reports were excluded:

- wrong study design (n = 39)
- wrong outcome (n = 17)
- wrong intervention (n = 6)
- duplicate (n=16)
- wrong comparator (n=52)
- wrong study population (n=3)

n=25 papers included in the update (n=1 from identification of studies via other methods)

n=68 papers included in the review (n=43 from the original rapid review, n=25 from the updated search)

Annexe B. Supplementary Tables

Supplementary Table 1. Characteristics of included observational studies on transmission

Light grey rows indicate studies from the previous review (search to 22 October 2021)
Acronyms used: CPE = Cytopathic effect, 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, SIMD = Scottish index of multiple deprivation, VE = Vaccine effectiveness

Reference	Study design	Methods	Findings	Risk of bias
Allen and others, 2021 (12) 'Household transmission of COVID-19 cases associated with SARS-CoV-2 delta variant (B.1.617.2): national case-control study'	Study design: Matched case-control Objective: To estimate the differences in transmissibility between the Delta and Alpha variants. Participants: n=17,928 genomically sequenced index cases; n=5,976 index cases in households with secondary transmission (cases) matched with n=11,952 index cases in households without secondary transmission (controls). Cases (n=5,976): Age: less than 10 years: 6.9%; 10 to 19 years: 26.2%; 20 to 29 years: 17.5%; 30 to 39 years: 21.2%; 40 to 49 years: 15.2%; 50 to 59 years: 9.4%; 60 to 69 years: 2.5%; 70 years and over: 1.1% Sex: 49.3% Female Ethnicity: 77.3% White, 15.2% Asian, 2.5% Black, 2.5% Mixed, 2.4% Other Vaccination status: fully vaccinated: n=156 (2.6%); partially vaccinated: n=913 (15.3%); unvaccinated: n=3,990 (66.8%); less than 21 days post dose one (not included in these results): n=454 (7.6%); unknown (not included in these results): n=463 (7.8%) Controls (n=11,952): Age: less than 10 years: 5.5%; 10 to 19 years: 29.2%; 20 to 29 years: 24.4%; 30 to 39 years: 19.1%; 40 to 49 years: 10.9%; 50	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 vaccine (not specified) at least 14 days prior to testing positive. Partially vaccinated: one dose of vaccine at least 21 days prior to testing positive. Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: Households with a positive case in the preceding 90 days from the index case positive test date were excluded. Testing: Laboratory confirmed pillar 2 cases of COVID-19, secondary cases could be laboratory confirmed or confirmed by lateral flow tests. SARS-CoV-2 variant: Delta (n=2,586, 43.3%) and Alpha (n=4,824, 40.4%). 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, NHS summary care records, Laboratory Information Management System, self-	OR for household transmission, compared to unvaccinated index cases: • partially vaccinated: 0.94 (95% CI: 0.84 to 1.05) • fully vaccinated: 0.73 (95% CI: 0.58 to 0.90)	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
	to 59 years: 7.1%; 60 to 69 years: 2.8%; 70 years and above: 0.8% Sex: 51% Female Ethnicity: 79.7% White, 12.3% Asian, 2.8% Black, 3.3% Mixed, 2.0% Other Vaccination status: fully vaccinated: n=344 (2.9%); partially vaccinated: n=1,581 (13.2%); unvaccinated: n=8,198 (68.6%); less than 21 days post dose 1 (not included in these results): n=853 (7.1%); unknown (not included in these results): n=976 (8.2%) Index cases: First positive test between 18 March to 7 June 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 cases within 14 days Setting: England, March to June 2021	report, Contact Tracing Advisory Service, Cloud Infrastructure for Big Data Microbial Bioinformatics database, and the National Immunisation Management System. Statistical analysis: Conditional logistic regression to estimate the effect of vaccination on secondary transmission (split by variant), adjusted for age, sex, ethnicity, index of multiple deprivation, number of household contacts and matched on area of residence, test date and property type.		
Allen and others, 2021 (16) '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: 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%);	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%)	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
	<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 cases within 14 days Setting: England, March to May 2021	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 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		
Bobdey and others, 2021 (6) 'Effectiveness of ChAdOx1 nCOV-19 Vaccine: Experience of a tertiary care institute'	Study design: Retrospective cohort Objective: To estimate the incidence of COVID cases in the unvaccinated and vaccinated population of the institute of Western Maharashtra, India. Participants: Staff at a tertiary care institute. Index cases (n=3) and high risk contacts (n=47) who shared their dormitory or a washroom were included, from a total of n=3,196 staff and students and n=113 cases. Demographic information for the 3 index cases and 47 high risk contacts was not reported. Setting: India, February to April 2021	Outcomes: Positive COVID-19 test among staff sharing a dormitory or washroom with index cases. Exposure: Definition of vaccinated: Fully vaccinated: Received 2 doses of AstraZeneca vaccine more than 14 days before a positive test or analysis of results Partially vaccinated: Received a single vaccine dose more than 14 days before a positive test or analysis of results Definition of unvaccinated: No vaccine received or single vaccine dose received up to and including 14 days before a positive test or analysis of results Prior infections: NR Testing: RT-PCR of all symptomatic cases and all asymptomatic direct and high-risk contacts of a laboratory confirmed case, tested once between 5 and 10 days after contact. Additionally, staff sharing a dormitory or washroom with confirmed cases were quarantined for one week and tested	Secondary attack rate, by time period: • pre-vaccination period (June to October 2020): 21.4% (n=54 of 252) • post-vaccination period (February to April 2021): 4.3% (n=2 of 47) • p<0.05	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: The comparison was for two different time periods. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		one and 7 days after their last contact with the index case. SARS-CoV-2 variant: NR Data collection: Self report to researchers. Statistical analysis: Comparison of secondary attack rates to high risk contacts in the post-vaccination period (February to April 2021) was compared with a pre-vaccination period (June to October 2020): the quarantine period and housing conditions were similar between these periods.		
Braeye and others, 2021 (24) '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	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%)	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	• Janssen (n=74): 57% (95% CrI: 21% to 81%) 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%)	
Clifford and others, 2021 (3) 'Effectiveness of BNT162b2 and ChAdOx1 against SARS-CoV-2 household transmission: a prospective cohort study in England' PREPRINT (version 2)	Study design: Prospective cohort Objective: To estimate the effectiveness of Pfizer and AstraZeneca vaccines against acquisition and transmission of the Alpha and Delta variants. Participants: Index cases and their household contacts recruited after the initial case's positive RT-PCR test, identified from Pillar 2 (community) testing. Household contacts were considered positive if they had a positive RT-PCR COVID-19 test in the week after recruitment. Index cases weren't included if a household contact was symptomatic more than 2 days before the index case. Household contacts weren't included if they appeared to be infected elsewhere, given their sequencing results. Index cases: (n=195) Age: less than 18 years: 0%; 18 to 49 years: 53%; 50 to 64 years: 44%; 65 years and over: 4% Not vaccinated: n=45 (23.1%); partially vaccinated: n=72 (36.9%); fully vaccinated: n=78 (40.0%) Variant: Alpha: n=99 (57.9%); Delta: n=20	Outcomes: Positive COVID-19 test among household members of index cases. Exposure: Definition of vaccinated: Fully vaccinated: Received 2 doses of Pfizer or AstraZeneca vaccine more than 7 days before recruitment Partially vaccinated: Received a single vaccine dose more than 21 days before recruitment Definition of unvaccinated: No vaccine received or single vaccine dose received less than or equal to 21 days before recruitment Prior infections: NR Testing: Initial RT-PCR test for index cases, then all recruited index cases and household contacts RT-PCR tests at days 1, 3 and 7 after recruitment. SARS-CoV-2 variant: Likely Alpha (60%) and Delta (40%); percentages assumed by study authors: some cases had missing sequencing (30%) and variant was estimated given the prevalent variant at time of their PCR tests. Data collection:	Vaccine effectiveness against transmission, compared to unvaccinated index case (Alpha): Partially vaccinated index case: • AstraZeneca: -7% (95% CrI: -60% to 29%) • Pfizer: 26% (95% CrI: -11% to 54%) Fully vaccinated index case: • AstraZeneca: 35% (95% CrI: -26% to 74%) • Pfizer: 57% (95% CrI: 5% to 85%) Vaccine effectiveness against transmission, compared to unvaccinated index case (Delta): Partially vaccinated index case: • AstraZeneca: 14% (95% CrI: -11% to 52%) • Pfizer: 9% (95% CrI: -16% to 49%) Fully vaccinated index case: • AstraZeneca: 42% (95% CrI: 14% to 69%) • Pfizer: 31% (95% CrI: -3% to 61%) Vaccine effectiveness against infection, compared to unvaccinated contact (Alpha): Partially vaccinated contact:	Risk of bias: 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
	(11.7%); Unknown: n=52 (30.4%) Household contacts: (n=278) Age: less than 18 years: 24%; 18 to 49 years: 42%; 50 to 64 years: 29%; 65 years and over: 5% Not vaccinated: n=134 (48.2%); partially vaccinated: n=73 (26.3%); fully vaccinated: n=71 (25.5%) Setting: UK, February to September 2021	Initial RT-PCR test data from Pillar 2 community testing, vaccination status from the National Immunisation Management System, repeated self-swabbed RT-PCR at days 1, 3 and 7 after recruitment for all index cases and household contacts. Statistical analysis: Bayesian hierarchical linear model with Bernoulli likelihood for the probability that a household contact of an index case has a positive RT-PCR test within a week of recruitment, accounting for vaccination status of the contact, variant, and age of index case and contact.	• AstraZeneca: 3% (95% CrI: -38% to 39%) • Pfizer: 53% (95% CrI: 7% to 83%) Fully vaccinated contact: • AstraZeneca: 26% (95% CrI: -39% to 73%) • Pfizer: 71% (95% CrI: 12% to 95%) Vaccine effectiveness against infection, compared to unvaccinated contact (Delta): Partially vaccinated contact: • AstraZeneca: 2% (95% CrI: -19% to 31%) • Pfizer: 4% (95% CrI: -21% to 44%) Fully vaccinated contact: • AstraZeneca: 14% (95% CrI: -5% to 46%) • Pfizer: 24% (95% CrI: -2% to 64%)	
De Gier and others, 2021 (17) '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 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: 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: 1% Sex: 52% 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.	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%)	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
	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: 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: 2% Sex: 50% female 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: 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: 1% Sex: 52% female Setting: The Netherlands, 9 August 2021 to 24 September 2021	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. 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.	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: • unvaccinated household contacts: 55% (95% CI: 19% to 76%) • fully vaccinated household contacts: 28% (95% CI: -4% to 50%)	
De Gier and others, 2021 (13) 'Vaccine effectiveness against SARS-CoV-2 transmission to household contacts during dominance of Delta variant (B.1.617.2), August-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: 4% Sex: 50% female Partially vaccinated index cases (n=540, 11.0%):	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.	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:	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: 12 to 17 years: 32%; 18 to 29 years: 42%; 30 to 49 years: 19%; 50 to 74 years: 6%; 75+ years: 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: 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: 2% Sex: 50% female 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: 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: 1% Sex: 52% female Setting: The Netherlands, 9 August 2021 to 24 September 2021	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. 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: 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: • unvaccinated household contacts: 55% (95% CI: 19% to 76%) • fully vaccinated household contacts: 28% (95% CI: -4% to 50%)	
Eyre and others, 2021 (15) 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	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	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)	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
	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 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)	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. 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.	• 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) 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	

Reference	Study design	Methods	Findings	Risk of bias
	Sex: 68.8% Female 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 <u>Setting:</u> England, 1 January 2021 to 31 July 2021		• partially vaccinated (AstraZeneca): 0.69 (95% CI: 0.66 to 0.72) • partially vaccinated (Pfizer): 0.67 (95% CI: 0.65 to 0.69) • fully vaccinated (AstraZeneca): 0.42 (95% CI: 0.38 to 0.45) • fully vaccinated (Pfizer): 0.19 (95% CI: 0.16 to 0.23) <u>Reduction in transmission, compared to unvaccinated index cases, by variant of the index case and time since second dose:</u> <u>Alpha</u> • 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%) <u>Delta</u> • 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%) <u>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):</u> • AstraZeneca: 1.08 (95% CI: 1.05 to 1.11) • Pfizer: 1.13 (95% CI: 1.05 to 1.21)	

Reference	Study design	Methods	Findings	Risk of bias
Gazit and others. 2021 (66,70) 'BNT162b2 mRNA Vaccine Effectiveness Given Confirmed Exposure; Analysis of Household members of COVID-19 patients' Included in previous review, but updated results are presented here	Study design: Retrospective cohort Objective: Assessing vaccine effectiveness in preventing COVID-19 transmission within households of confirmed cases Study participants: n=4,024 households of 2 adults, no children and no prior infections, from a total of n=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, 20th December 2020 to 17 March 2021	Outcome: COVID-19 infection in adult household member less than or equal to 10 days after index case diagnosis 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).	Secondary attack rate, by vaccination status of household member: • 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: 80.3% (95% CI: 73.5% to 85.4%) • fully vaccinated vs recently vaccinated: 82.0% (95% CI: 75.6% to 86.8%) 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: 76.4% (95% CI: 67.5% to 82.8%) • fully vaccinated vs recently vaccinated: 78.4% (95% CI: 69.9% to 84.4%)	Confounding: There is a very high risk of bias from confounding as the analysis was 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 (18,19) '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) 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: 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: 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.	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
Hsu and others, 2021 (7) 'COVID-19 Breakthrough Infections and Transmission Risk: Real-World Data Analyses from Germany's Largest Public	Study design: Matched case-control Objective: To estimate the effect of vaccination of close contacts on transmission from fully vaccinated index cases. Participants: n=357 fully vaccinated index	Outcomes: Secondary cases within close contacts within 14 days of an index case's positive test result Exposure: Definition of vaccinated: NR, though partially vaccinated cases were excluded (80.1% Pfizer,	Secondary attack rate, by vaccination status of index case: • unvaccinated: 37.8% (n=303 of 802) • fully vaccinated: 10.1% (n=99 or 979) OR for transmission, compared to unvaccinated index cases:	Risk of bias: Confounding: There is a high risk of bias from confounding, particularly as deprivation was not accounted for.

Reference	Study design	Methods	Findings	Risk of bias
Health Department (Cologne)'	cases (cases) with n=979 close contacts, matched with n=357 unvaccinated index cases (controls) with n=802 close contacts. Vaccinated index cases (n=357, cases): Mean age: 48.6 years (SD: 22.1 years) Sex: 64.7% female COVID-19 symptoms: 41.2% Mean vaccination interval: 62.4 days (SD: 35.2 days, range: 14 to 188 days) Unvaccinated index cases (n=357, controls): Mean age: 46.7 years (SD: 21.0 years) Sex: 64.7% female COVID-19 symptoms: 77.9% Setting: Germany, December 2020 to August 2021	8.4% Janssen, 3.9% AstraZeneca, 3.1% Moderna, 0.6% Sputnik or Sinopharm, 3.9% combination). Definition of close contact: Any person who had close exposure to a confirmed index case (less than 1.5 m) for more than 10 minutes without a mask, within 2 days before to 14 days after symptom onset in the index case. Prior infections: NR Testing: RT-PCR. Close contacts of index cases were contacted, and RT-PCR provided if COVID-19 symptoms developed. From April 2021, all index cases and contacts had an RT-PCR at the end of quarantine. SARS-CoV-2 variant: Alpha (n=404, 56.6%), Delta (n=286, 40.1%), Wild-type (n=18, 2.5%) and Beta (n=6, 0.8%) Data collection: All people living in Cologne with positive RT-PCR tests were contacted by telephone by the Cologne public health department. Matching of index cases was 1:1 (vaccinated index cases to unvaccinated index cases) in the same observation period on age, sex and variant. Statistical analysis: Logistic regression to estimate the effect of vaccination of the index case on secondary transmission, adjusted for age, sex, and vaccination status of close contacts.	• fully vaccinated index case: 0.21 (95% CI: 0.16 to 0.27) OR for transmission, compared to unvaccinated contacts: • fully vaccinated contact: 1.26 (95% CI: 0.90 to 1.77)	Other bias: No specific biases to report. QCC rating: Medium
Kang and others, 2021 (14) 'Transmission dynamics and epidemiological characteristics of Delta variant infections in China'	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	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).	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%)	Confounding: There is a high risk of bias from residual confounding even after adjustment, particularly as deprivation was not accounted for.

Reference	Study design	Methods	Findings	Risk of bias
PREPRINT (version 1)	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	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 of contact, exposure on the day of symptom onset of the index case, and duration of exposure as covariables.	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.	Other bias: No specific biases to report. QCC rating: Medium
Layan and others, 2021 (20) '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)	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.	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)	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

Reference	Study design	Methods	Findings	Risk of bias
	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) 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	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 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.	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%) • 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)	members was self-reported. QCC rating: Medium
Lyngse and others, 2021 (4) 'SARS-CoV-2 Omicron VOC Transmission in Danish Households'	Study design: Retrospective cohort Objective: To estimate the transmission dynamics of Omicron variant COVID-19. Participants: n=11,937 households (2 to 6 person) with a COVID-19 positive index	Outcomes: Secondary cases within the household within one to 7 days of an index case' positive test result Exposure: Definition of vaccinated:	Secondary attack rate, by vaccination status of secondary cases and variant: Omicron: • unvaccinated: 29% • fully vaccinated: 32% • booster vaccinated: 25% Delta:	Risk of bias: Confounding: There is a high risk of bias from confounding, particularly as deprivation was not accounted for.

Reference	Study design	Methods	Findings	Risk of bias
PREPRINT (version 1)	case, followed for 1 to 7 days for infections in household members. Index cases - Omicron (n=2,225): Age: less than 10 years: 5.9%; 10 to 20 years: 20.4%; 20 to 30 years: 32.5%; 30 to 40 years: 13.4%; 40 to 50 years: 12.7%; 50 to 60 years: 10.7%; 60 to 70 years: 3.5%; 70 years and over: 1.0% Sex: 48.4% Female Vaccination status: booster vaccinated: n=105 (4.7%); fully vaccinated/previous infection: n=1,752 (78.7%); unvaccinated: n=368 (16.5%) Index cases - Delta (n=9,712): Age: less than 10 years: 24.9%; 10 to 20 years: 19.4%; 20 to 30 years: 12.8%; 30 to 40 years: 10.2%; 40 to 50 years: 12.9%; 50 to 60 years: 11.5%; 60 to 70 years: 5.9%; 70 years and over: 2.4% Sex: 48.7% Female Vaccination status: booster vaccinated: n=286 (2.9%); fully vaccinated/previous infection: n=4,797 (49.4%); unvaccinated: n=4,629 (47.7%) Time since vaccination: The time since vaccination was very similar for the Omicron and Delta variant secondary cases. Index cases: First positive test between 9 and 12 December 2021 Secondary cases: Any positive test (including antigen) within one to 7 days of index case in same household Setting: Denmark, December 2021	Booster vaccinated: a booster vaccination dose taken 7 days before positive test results Fully vaccinated: all doses of any vaccine, with the final dose received some days before positive test results (Pfizer [85%]: 7 days; AstraZeneca [0%]: 15 days; Moderna [14%]: 14 days; Janssen [1%]: 14 days) or 14 days after previous infection Definition of unvaccinated: no vaccine received prior to positive test results, or only partial vaccination (1 dose of a 2 dose vaccine). Prior infections: Included in the definition of fully vaccinated. Testing: RT-PCR for index cases, RT-PCR or antigen test for secondary cases. SARS-CoV-2 variant: Delta (n=9,712, 81%) and Omicron (n=2,225, 19%). Data collection: Danish Vaccination Register and Danish Microbiology Database. Statistical analysis: Adjusted odds ratios (OR) for transmission to secondary cases, including variant (Omicron or Delta), age and sex of index and secondary cases, and household size as covariables, as well as an interaction term between vaccination status of primary and secondary cases and the variant to test for differential protection from vaccination against transmission of each variant. Standard errors were adjusted to account for clustering at the household levels.	• unvaccinated: 28% • fully vaccinated: 19% • booster vaccinated: 11% OR for household transmission, compared to fully vaccinated index cases: • unvaccinated index cases: 1.41 (95% CI: 1.27 to 1.57) • booster vaccinated index cases: 0.72 (95% CI: 0.56 to 0.92) • there was no observed difference in the OR of transmission for the Omicron and Delta variants OR for household transmission, compared to fully vaccinated secondary cases, by variant: Omicron: • unvaccinated secondary cases: 1.04 (95% CI: 0.87 to 1.24) • booster vaccinated secondary cases: 0.54 (95% CI: 0.40 to 0.71) Delta: • unvaccinated secondary cases: 2.31 (95% CI: 2.09 to 2.55) • booster vaccinated secondary cases: 0.38 (95% CI: 0.32 to 0.46)	Other bias: No specific biases to report. QCC rating: Medium
Lyngse and others, 2022 (5)	Study design: Retrospective cohort Objective: To estimate the vaccine effectiveness against susceptibility and	Outcomes: Secondary cases within the household within one to 14 days of an index case' positive test result	Secondary attack rate, by vaccination status of household contacts: • unvaccinated: 28% • fully vaccinated: 15%	Risk of bias: Confounding: There is a high risk of bias from

Reference	Study design	Methods	Findings	Risk of bias
‘Effect of Vaccination on Household Transmission of SARS-CoV-2 Delta VOC’ PREPRINT (version 1)	transmissibility of Delta variant COVID-19. Participants: n=24,693 households (2 to 6 person) with a COVID-19 positive index case, followed for 1 to 14 days for infections in household members. Index cases - vaccinated (n=8.262): Age: less than 10 years: 0%; 10 to 20 years: 8.7%; 20 to 30 years: 16.6%; 30 to 40 years: 13.7%; 40 to 50 years: 20.3%; 50 to 60 years: 19.4%; 60 to 70 years: 13.1%; 70 to 80 years: 8.2% Sex: 51.6% Female Index cases - unvaccinated (n=16,431): Age: less than 10 years: 22.3%; 10 to 20 years: 29.6%; 20 to 30 years: 25.1%; 30 to 40 years: 14.1%; 40 to 50 years: 5.6%; 50 to 60 years: 2.5%; 60 to 70 years: 0.7%; 70+ years: 0.1% Sex: 49.5% Female Index cases: First positive test between 21 June and 26 October 2021 Secondary cases: Positive RT-PCR test within one to 14 days of index case in same household Setting: Denmark, June to November 2021	Exposure: Definition of vaccinated: Fully vaccinated: all doses of any vaccine, with the final dose received some days before positive test results (Pfizer [83%]: 7 days; AstraZeneca [6.2%]: 15 days; Moderna [4.4%]: 14 days; Janssen [6.4%]: 14 days). Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: All households with a previous infection (positive RT-PCR test) were excluded. Testing: RT-PCR for all participants. SARS-CoV-2 variant: Delta (100%) Data collection: Danish Vaccination Register and Danish Microbiology Database. Statistical analysis: Relative risk reductions for vaccine effectiveness against susceptibility and against transmissibility were both estimated using a generalised linear model (Poisson distribution response and log link function), with age and sex of index cases and household contacts, household size and calendar week as covariables. Standard errors were clustered at the household level. Vaccine effectiveness against susceptibility estimated as 1 minus the secondary attack rate (SAR) in vaccinated household contacts divided by the SAR in unvaccinated household contacts. Vaccine effectiveness against transmissibility estimated as 1 minus the SAR from vaccinated index cases divided by the SAR from unvaccinated index cases. Both estimates were also estimated among only unvaccinated and vaccinated index cases (for susceptibility) and household contacts (for transmissibility).	Vaccine effectiveness against transmissibility, by vaccination status of household contacts: • unvaccinated: 31% (95% CI: 26% to 36%) • fully vaccinated: 10% (95% CI: 0% to 15%) • all: 42% (95% CI: 49% to 45%) Vaccine effectiveness against susceptibility, by vaccination status of index cases: • unvaccinated: 61% (95% CI: 59% to 63%) • fully vaccinated: 46% (95% CI: 40% to 52%) • all: 61% (95% CI: 59% to 63%) Vaccine effectiveness against susceptibility and transmissibility, comparing fully vaccinated index cases and household contacts with unvaccinated index cases and household contacts: • 66% (95% CI: 63% to 68%)	confounding, 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

Martinez-Baz and others, 2021 (8)
 	
'Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021'
	Study design: Retrospective cohort
	
	Objective: To assess vaccine effectiveness against COVID-19 infection and hospitalisation amongst close contacts of COVID-19 cases
	
	Participants: n=30,240 adult close contacts of n=12,263 adult index cases
	
	Close contacts (n=30,240)
	Vaccination status of close contacts:
	Unvaccinated n=14,248 (47.1%), partially vaccinated n=4,135 (13.7%),
	fully vaccinated n=11,754 (38.9%)
	
	Setting: Spain, April to August 2021
		Outcomes: Secondary cases amongst close contacts of COVID-19 cases (within 2 days before to 10 days after symptom onset or positive test)
		
		Exposure:
		Definition of vaccinated:
		Fully vaccinated: 2 doses of vaccine (AstraZeneca, Moderna or Pfizer) or one dose of Janssen, at least 14 days prior to testing positive
		Partially vaccinated: one dose of vaccine at least 14 days prior to testing positive
		Definition of unvaccinated: no vaccine received prior to positive test results.
		
		Definition of close contact: Any person who had high-risk exposure to a confirmed COVID-19 case from 2 days before the onset of symptoms in the index case to 10 days after the onset of symptoms,
		or in the 2 days before to 10 days after a positive test (for asymptomatic cases).
		
		Prior infections: Close contacts with a previous infection were excluded.
		
		Testing: Close contacts encouraged to test immediately after exposure and 7 to 10 days after last exposure with RT-PCR. A positive LFD within 5 days of symptom onset was also considered a confirmed infection for symptomatic close contacts.
		
		SARS-CoV-2 variant: Alpha (52%), Delta (40%), other (9%)
		
		Data collection: Demographic and vaccination data collected from the enhanced epidemiological surveillance of COVID-19.
		
		Statistical analysis: Relative risk (RR) for vaccine effectiveness against infection estimated using a Cox regression model, adjusted for age, sex,
			Secondary attack rate (SAR), by vaccination status of the index case
			• unvaccinated index cases (n=6,237 of 25,024): 25%
			• partially vaccinated index cases (n=328 of 1,729): 19%
			• fully vaccinated index cases (n=612 of 3,487): 18%
			
			Secondary attack rate (SAR), by vaccination status of close contacts
			• unvaccinated close contacts (n=4,811 of 14,348): 34%
			• partially vaccinated close contacts (n=723 of 4,138): 18%
			• fully vaccinated close contacts (n=1,643 of 11,754): 14%
			
			Secondary attack rate (SAR) and adjusted vaccine effectiveness (VE), by vaccination status of close contacts
			
			Unvaccinated close contacts (n=4,811 of 14,348):
			• SAR: 34%
			
			Partially vaccinated close contacts:
			• Moderna (n=70 of 517):
			  ○ SAR: 14%
			  ○ VE: 66 (95% CI: 56 to 73)
			• Pfizer (n=351 of 2,022):
			  ○ SAR: 17%
			  ○ VE: 57 (95% CI: 52 to 61)
			• AstraZeneca (n=302 of 1,599):
			  ○ SAR: 19%
			  ○ VE: 41 (95% CI: 34 to 48)
			
			Fully vaccinated close contacts
			• Janssen (n=209 of 997):
			  ○ SAR: 21%
			  ○ VE: 50 (95% CI: 42 to 57)
			• Moderna (n=85 of 1,127):
				Risk of bias:
				
				Confounding: There is a very high risk of bias from confounding for the secondary attack rate analyses as the analyses were unadjusted. There is a high risk of bias from confounding for the vaccine effectiveness analyses, 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
		chronic conditions, contact setting, month and COVID-19 status of the index case. Vaccine effectiveness estimated as 1 minus adjusted RR) x 100.	○ SAR: 8% ○ VE: 82 (95% CI: 78 to 86) • Pfizer (n=1,070 of 7,972) ○ SAR: 13% ○ VE: 69% (95% CI: 66 to 72) • AstraZeneca (n=272 of 1,539): ○ SAR: 18% ○ VE: 54 (95% CI: 48 to 60) <u>Secondary attack rate (SAR) and adjusted vaccine effectiveness (VE) for close contacts of unvaccinated index cases, by vaccination status of the close contact</u> <u>Unvaccinated close contacts (n=4,559 of 13,485)</u> • SAR: 34% <u>Partially vaccinated close contacts</u> • Moderna (n=55 of 393): ○ SAR: 14% ○ VE: 65 (95% CI: 54 to 73) • Pfizer (n=272 of 1,569): ○ SAR: 17% ○ VE: 57 (95% CI: 51 to 62) • AstraZeneca (n=246 of 1,277): ○ SAR: 19% ○ VE: 42 (95% CI: 33 to 49) <u>Fully vaccinated close contacts</u> • Janssen (n=151 of 779): ○ SAR: 19% ○ VE: 54 (95% CI: 46 to 62) • Moderna (n=55 of 850): ○ SAR: 6% ○ VE: 85 (95% CI: 80 to 88) • Pfizer (n=716 of 5,606): ○ SAR: 13% ○ VE: 70 (95% CI: 67 to 73) • AstraZeneca (n=176 of 982): ○ SAR: 18%	

Reference	Study design	Methods	Findings	Risk of bias
			○ VE: 55 (95% CI: 47 to 62) • AstraZeneca & Pfizer (1 dose of each) (n=7 of 83): ○ SAR: 8% ○ VE: 80 (59 to 91) <u>Secondary attack rate (SAR) and adjusted vaccine effectiveness (VE) for close contacts of fully vaccinated index cases, by vaccination status of the close contact</u> <u>Unvaccinated close contacts (n=118 of 394)</u> • SAR: 30% <u>Partially vaccinated close contacts</u> • Moderna (n=8 of 77): ○ SAR: 10% ○ VE: 64 (95% CI: 26 to 83) • Pfizer (n=38 of 216): ○ SAR: 18% ○ VE: 43 (95% CI: 18 to 61) • AstraZeneca (n=18 of 124): ○ SAR: 15% ○ VE: 43 (95% CI: 2 to 67) <u>Fully vaccinated close contacts</u> • Janssen (n=47 of 167): ○ SAR: 28% ○ VE: 23 (95% CI: -14 to 48) • Moderna (n=24 of 220): ○ SAR: 11% ○ VE: 70 (95% CI: 52 to 81) • Pfizer (n=286 of 1,839): ○ SAR: 16% ○ VE: 59 (95% CI: 45 to 69) • AstraZeneca (n=73 of 420): ○ SAR: 17% ○ VE: 41 (95% CI: 16 to 58) • AstraZeneca & Pfizer (1 dose of each) (n=0 of 30):	

Reference	Study design	Methods	Findings	Risk of bias
			○ SAR: 0% ○ VE: NA <u>Secondary attack rate (SAR) and adjusted vaccine effectiveness (VE) for household contacts, by contact vaccination status</u> <u>Unvaccinated household contacts (n=2,869 of 6,494)</u> • SAR: 44% <u>Partially vaccinated household contacts</u> • Moderna (n=42 of 254): ○ SAR: 17% ○ VE: 62 (95% CI: 49 to 72) • Pfizer (n=248 of 1,152): ○ SAR: 22% ○ VE: 51 (95% CI: 44 to 58) • AstraZeneca (n=232 of 913): ○ SAR: 25% ○ VE: 35 (95% CI: 25 to 43) <u>Fully vaccinated household contacts</u> • Janssen (n=179 of 741): ○ SAR: 24% ○ VE: 42 (95% CI: 32 to 51) • Moderna (n=68 of 769): ○ SAR: 9% ○ VE: 79 (95% CI: 73 to 84) • Pfizer (n=811 of 5,048): ○ SAR:16% ○ VE: 65 (95% CI: 62 to 69) • AstraZeneca (n=185 of 863): ○ SAR: 21% ○ VE: 50 (95% CI: 41 to 58) • AstraZeneca & Pfizer (1 dose of each) (n=5 of 71): ○ SAR: 7% ○ VE: 84 (61 to 93)	

Reference	Study design	Methods	Findings	Risk of bias

			Secondary attack rate (SAR) and adjusted vaccine effectiveness (VE) for non-household contacts, by contact vaccination status
			
			Unvaccinated non-household contacts (n=1,942 of 7,854)
			• SAR: 25%
			
			Partially vaccinated non-household contacts
			• Moderna (n=28 of 263):
			  ○ SAR: 11%
			  ○ VE: 66 (95% CI: 50 to 76)
			• Pfizer (n=103 of 870):
			  ○ SAR: 12%
			  ○ VE: 56 (95% CI: 46 to 64)
			• AstraZeneca (n=70 of 686):
			  ○ SAR: 10%
			  ○ VE: 45 (95% CI: 29 to 57)
			
			Fully vaccinated non-household contacts
			• Janssen (n=30 of 256):
			  ○ SAR: 12%
			  ○ VE: 54 (95% CI: 33 to 68)
			• Moderna (n=17 of 358):
			  ○ SAR: 5%
			  ○ VE: 83 (95% CI: 72 to 90)
			• Pfizer (n=259 of 2,924):
			  ○ SAR: 9%
			  ○ VE: 68 (95% CI: 62 to 73)
			• AstraZeneca (n=87 of 676):
			  ○ SAR: 13%
			  ○ VE: 54 (95% CI: 42 to 63)
			• AstraZeneca & Pfizer (1 dose of each) (n=2 of 48):
			  ○ SAR: 4%
			  ○ VE: 86 (43 to 96)	

Meyer and others, 2021 (21)	Study design: Retrospective cohort Objective: To describe the epidemiology of an outbreak of COVID-19 in a German	Outcome: Secondary cases of COVID-19 in household members of staff index cases one to 14 days after diagnosis of the corresponding index case.	Secondary attack rate, by index case vaccination status: • unvaccinated: n=12 of 18 (67%) • vaccinated: n=2 of 9 (22%)	Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted.

Reference	Study design	Methods	Findings	Risk of bias
'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)	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	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%). 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.	• p value for difference = 0.046	Other bias: No specific biases to report. QCC rating: Medium
Ng and others, 2021 (9) 'Impact of Delta Variant and Vaccination on SARS-CoV-2 Secondary Attack Rate Among Household Close Contacts'	Study design: Retrospective cohort Objective: To estimate the risk of infection by the Delta variant compared to other variants, vaccine efficacy against any infection and symptomatic or severe infection, and risk factors associated with COVID-19 acquisition and symptomatic disease. Participants: n=753 household contacts of confirmed COVID-19 index cases (n=228) with the Delta variant in Singapore.	Outcomes: Positive COVID-19 test among household members of index cases. Exposure: Definition of vaccinated: Fully vaccinated: Received 2 doses of Pfizer (83.0% of contacts) or Moderna (17.0% of contacts) vaccine over 14 days before quarantine Partially vaccinated: Received a single vaccine dose before quarantine Definition of unvaccinated: No vaccine received Prior infections: NR	Secondary attack rate, by vaccination status of household contacts: Delta variant • unvaccinated: 25.8% (95% bootstrapped CI: 20.6 to 31.5) (n=137 of 530) • fully vaccinated: 11.3% (95% bootstrapped CI: 6.1 to 17.3) (n=15 of 133) Non-Delta variant • unvaccinated: 12.9% (95% bootstrapped CI: 7.0 to 20.0%) (n=31 of 241)	Risk of bias: Confounding: There is a high risk of bias from confounding, particularly as deprivation was not accounted for. Other bias: It is unclear why only 74% of index cases and 78% of household contacts were analysed.

Reference	Study design	Methods	Findings	Risk of bias
	Non-Delta variant Index cases (n=73) Median age: 36 years (IQR: 28 to 48 years) Sex: 23.3% female Vaccination status: unvaccinated: n=70 (95.9%); partially vaccinated: n=3 (4.1%); fully vaccinated: n=3 (4.1%) Household contacts (n=248) Median age: 35 (IQR: 27 to 47) Sex: 36.3% female Vaccination status: unvaccinated: n=241 (97.2%); partially vaccinated: n=4 (1.6%); fully vaccinated: n=3 (1.2%) Delta variant Index cases (n=228): Median age: 40 years (IQR: 28 to 53 years) Sex: 39.9% female Vaccination status: unvaccinated: n=156 (68.4%); partially vaccinated: n=21 (9.2%); fully vaccinated: n=51 (22.4%) Household contacts (n=753): Median age: 36 years (IQR: 25 to 51 years) Sex: 47.0% female Vaccination status: unvaccinated: n=530 (70.4%); partially vaccinated: n=90 (12.0%); fully vaccinated: n=133 (17.7%) Setting: Singapore, September 2020 to May 2021	Testing: RT-PCR testing was offered to all people aged 13 years and older presenting with symptoms of febrile or non-febrile acute respiratory infection. Contact tracing was performed by the ministry of health for all diagnosed index cases. All close contacts (including household contacts) of positive cases were quarantined for 14 days, with entry and exit RT-PCR tests. Quarantined persons were monitored daily for symptoms, and symptomatic contacts were transported to hospital for COVID-19 testing and clinical evaluation. SARS-CoV-2 variant: Delta (76%), Alpha (24%) Data collection: All data from the ministry of health contact tracing database. Statistical analysis: Logistic regression to estimate vaccine effectiveness, adjusted for age and gender of the index case and contact, vaccine status of index case, number of days of exposure from symptom onset to isolation, using bootstrapping at the cluster level.	• fully vaccinated: 33.3% (NR) (n=1 of 3) OR for transmission, compared to unvaccinated index cases: Delta variant • partially vaccinated index case: 0.62 (95% CI: 0.22 to 1.69), p=0.35 • fully vaccinated index case: 0.73 (95% CI: 0.38 to 1.40), p=0.34 OR for transmission, compared to unvaccinated contacts: Delta variant • partially vaccinated contact: 0.61 (95% CI: 0.33 to 1.12), p=0.11 • fully vaccinated contact: 0.33 (95% CI: 0.17 to 0.63), p=0.0009	QCC rating: Medium
Prunas and others, 2021 (22,68) 'Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel'	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	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.	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.

Reference	Study design	Methods	Findings	Risk of bias
	COVID-19 case and at least 2 household members. Setting: Israel, 15 June 2020 to 24 March 2021	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, vaccination status and characteristics of household transmission.		QCC rating: Medium
Salo and others, 2021 (69) '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)	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.	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
	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	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 risk reduction, adjusting for week of infection, age, age-squared and sex.		
Shah and others, 2021 (23) '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%	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	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:	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
	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: 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	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 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.	• 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) 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)	
Singanayagam and others, 2021 (10) ‘Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study’	Study design: Prospective cohort Objective: To estimate transmission and viral load kinetics in vaccinated and unvaccinated individuals with the Delta variant. Participants: n=19 symptomatic index cases and n=602 community contacts recruited to the Assessment of Transmission and Contagiousness of COVID-19 in Contacts study, after notification to the UK contact-tracing system (NHS test and trace). Of the 602 contacts recruited, 144 (24%) tested positive for COVID-19. Including index cases, 71 participants were infected with the Delta variant and included in this analysis. Unvaccinated participants infected with the	Outcomes: Positive COVID-19 test among epidemiologically linked contacts of index cases (89% household contact, 11% non-household contact). Exposure: Definition of vaccinated: Fully vaccinated: Received 2 doses of Pfizer or AstraZeneca vaccine at least 7 days before recruitment Partially vaccinated: Received a single vaccine dose at least 7 days before recruitment Definition of unvaccinated: No vaccine received, or single vaccine dose received less than 7 days before recruitment Prior infections: NR	Secondary attack rate, by vaccination status of index cases: • unvaccinated: 23% (95% CI: 15% to 32%, n=23 of 100) • partially vaccinated: 37% (n=13 of 35) • fully vaccinated: 25% (95% CI: 15% to 35%, n=17 of 69) Time between second vaccination and recruitment: • PCR-negative: 64 days (IQR: 32 to 97 days) • PCR-positive (n=53): 101 days (IQR: 74 to 120 days) • p<0.01 Secondary attack rate, by vaccination status of contacts (all):	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
	Delta variant (n=23): Median age: 13 years (IQR: 11 to 17 years) Sex: 30% female Ethnicity: 61% White; 30% Non-White; 9% Unknown Vaccinated participants infected with the Delta variant (n=38): Median age: 49 years (IQR: 41 to 55 years) Sex: 67% female Ethnicity: 68% White; 24% Non-White; 8% Unknown Setting: UK, September 2020 to September 2021	Testing: RT-PCR. Time from vaccination to infection: Median (Delta, n=53): 101 days (IQR: 74 to 120 days) SARS-CoV-2 variant: Delta (100%) Data collection: Self-report to study team, PHE, UK National Immunisation Management System, and general practice records. Statistical analysis: Secondary attack rates reported by vaccination status of index cases.	• unvaccinated: 34% (95% CI: 22% to 49%, n=15 of 44) • partially vaccinated: 15% (95% CI: 7% to 28%, n=7 of 47) • fully vaccinated: 22% (95% CI: 16 to 30%, n=31 of 140) • p=0.16 Secondary attack rate, by vaccination status of household contacts: • unvaccinated: 38% (95% CI: 24% to 53%, n=15 of 40) • partially vaccinated: 18% (95% CI: 9% to 33%, n=7 of 39) • fully vaccinated: 25% (95% CI: 18% to 33%, n=31 of 126)	
Yi and others, 2022 (11) 'SARS-CoV-2 Delta Variant Breakthrough Infection and Onward Secondary Transmission in Household'	Study design: Retrospective cohort Objective: To assess the incidence of COVID-19 breakthrough infections and onwards transmission to household contacts following an outbreak an adult day service centre Participants: n=42 service users and n=16 staff at an adult day service centre, of which n=25 were COVID-19 positive, and n=46 household contacts Index cases (n=25) Mean age: 78.9 years (SD: 14.3 years) Sex: 72.0% female Vaccination status: 4% unvaccinated, 96% fully vaccinated Mean interval after second vaccine dose: 140.0 days (range: 80 to 117 days) Household contacts (n=46) Vaccination status: 39% unvaccinated, 43% partially vaccinated, 17% fully vaccinated Setting: South Korea, 3 to 10 August 2021	Outcomes: RT-PCR confirmed COVID-19 infections and secondary infections Exposure: Definition of vaccinated: Fully vaccinated: 2 doses of Pfizer vaccine at least 14 days prior to testing positive Partially vaccinated: not stated Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: RT-PCR testing of all service users, staff and household contacts, regardless of symptom status SARS-CoV-2 variant: Delta (100% of the 13 samples sequenced) Data collection: Vaccination, demographic, symptom status and exposure data collected by the Korea Disease Control and Prevention Agency and Jeju Special Self-Governing Provincial Government. Participants and staff	Secondary attacked rate from fully vaccinated index cases, by household contact vaccination status • Unvaccinated: 27.8% • Partially vaccinated: 25% • Fully vaccinated: 12.5%	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
		were interviewed to assess symptoms in the previous 14 days. Statistical analysis: NR		

Supplementary Table 2. Characteristics of included studies on viral load

Light grey rows indicate studies from the previous review (search to 22 October 2021)
Acronyms used: CPE = Cytopathic effect, 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, SIMD = Scottish index of multiple deprivation, VE = Vaccine effectiveness

Reference	Study design	Methods	Findings	Risk of bias
Abu-Raddad and others, 2021 (52) '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: • all infections • symptomatic infections (tested because of clinical suspicion)	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	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
		asymptomatic infections (random testing, routine care testing, or through travel)	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) • Mean difference: 3.2 (95% CI: 1.8 to 4.5), p<0.001	
Acharya and others, 2021 (25) 'No Significant Difference in Viral Load Between Vaccinated and Unvaccinated, Asymptomatic and Symptomatic Groups When Infected with SARS-CoV-2 Delta Variant' PREPRINT (version 2)	Study design: Retrospective cohort Objective: To compare the viral load of COVID-19 positive cases according to their vaccination and symptom status Study participants: n=869 individuals who voluntarily sought COVID-19 testing in two locations in California: Healthy Yolo Together (HYT) provided asymptomatic testing, and Unidos en Salud (UeS) provided testing to those with or without symptoms. HYT testing centre (n=500): Age: more than 2 years Vaccination status: 75% unvaccinated Symptom status: 100% asymptomatic UeS testing centre (n=369): Age: at least one year Vaccination status: 54% unvaccinated, 46% fully vaccinated Symptom status: 64% symptomatic, 36% asymptomatic Setting: US, 17 June to 31 August 2021	Outcomes: RT-qPCR confirmed COVID-19 infections, symptom status and CT values Exposure: Definition of vaccinated: Fully vaccinated: completion of vaccination course at least 14 days prior to testing positive (vaccine type not specified) Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: RT-qPCR testing with CT values for the detection of the N and E genes. Whole genome sequencing also conducted. Asymptomatic cases tested at the UeS testing centre, were initially tested with lateral flow tests. Positive cases were also RT-qPCR tested. SARS-CoV-2 Variants: UeS: Delta (96.4%) HYT: Delta (95.1%) Data collection: Demographic data during registration at testing site. Vaccination status data collected via contract tracing and confirmed in the California Vaccine Registry Statistical analysis: Ct values stratified by vaccination status, symptom status and by testing site, and compared with a two sided t-test.	Median Ct values (data extracted from figure), by vaccination status HYT: Asymptomatic cases • unvaccinated (n=375): 25.7 (IQR: 22.9 to 28.2) • fully vaccinated (n=125): 26.1 (IQR: 22.7 to 28.8) • p=0.80 UeS: All cases • unvaccinated (n=198): 22.7 (IQR: 19.1 to 27.3) • fully vaccinated (n=171): 22.2 (IQR: 18.9 to 26.6) • p=0.54 UeS: Symptomatic cases • unvaccinated (n=117): 21.9 (IQR: 18.9 to 26.1) • fully vaccinated (n=120): 21.2 (IQR: 18.9 to 25.8) • p=0.62 UeS: Asymptomatic cases • unvaccinated (n=81): 23.6 (IQR: 19.8 to 28.7) • fully vaccinated (n=51): 24.0 (IQR: 20.3 to 29.1) • p=0.89	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: Only participants with positive lateral flow tests received an RT-PCR test in the UeS testing centre, excluding any COVID-19 cases with negative lateral flow tests. QCC rating: Medium.
Adamson and others, 2021 (34)	Study design: Retrospective cohort Objective: To compare Ct values of confirmed	Outcomes: RT-PCR confirmed COVID-19 infections and associated Ct values	Median Ct values, by vaccine type and vaccination status, (IQR)	Risk of bias: Confounding: There is a

Reference	Study design	Methods	Findings	Risk of bias
'Lower Severe Acute Respiratory Syndrome Coronavirus 2 Viral Shedding Following Coronavirus Disease 2019 Vaccination Among Healthcare Workers in Los Angeles, California'	COVID-19 cases by vaccination status. Study participants: n=11,930 healthcare workers (HCWs) tested at the University of California, Los Angeles, of which n=880 had a positive RT-PCR test Vaccination status: 32.5% unvaccinated, 67.5% received at least 1 dose of vaccine during the study period Setting: US, December 2020 to March 2021	Exposure: Definition of vaccinated: Fully vaccinated: 2 doses of vaccine (Pfizer [62.0%], Moderna [34.5%], Janssen [3.5%]) at least 7 days prior to testing positive Partially vaccinated (2 doses): second dose 0 to 6 days prior to testing positive Partially vaccinated (one dose): one dose at least 12 days prior to testing positive Partially vaccinated (one dose): one dose 1 to 11 days prior to testing positive Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: RT-PCR testing. Asymptomatic surveillance screening (optional) and symptomatic testing conducted. SARS-CoV-2 Variants: NR. Study conducted prior to the emergence of the Delta variant in the local area. Data collection: Testing data collected from UCLA laboratories. Vaccination data collected from the employee health record database. Statistical analysis: Kruskal-Wallis test used to measure differences in Ct values by vaccination status.	• unvaccinated (n=510): 20.1 (IQR: 16.9 to 25.1) • one to 11 days after first dose (n=126): 20.6 (IQR: 16.9 to 26.3) • at least 12 days after dose one and before dose 2 (n=67): 21.9 (IQR: 17.5 to 27.1) • 0 to 6 days after dose 2 (n=14): 24.9 (IQR: 16.4 to 32.4) • fully vaccinated (n=25): 30.4 (IQR: 20.8 to 34.1) • p<0.01 for a difference in Ct values by vaccination status	very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific bias to report. QCC rating: Medium
Bailly and others, 2021 (53) '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	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.	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

Reference	Study design	Methods	Findings	Risk of bias
	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	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.		
Blanquart and others, 2021 (54) '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'	Study design: Retrospective cohort Objective: To assess and compare the viral load (Ct values) of COVID-19 positive individuals 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	Outcomes: COVID-19 infections and associated Ct values. Exposure: 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.	Comparison of Ct values (all variants), fully vaccinated compared to unvaccinated: • 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), $p < 10^{-6}$	Risk of bias Confounding: There is a high risk of bias from 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

Reference	Study design	Methods	Findings	Risk of bias
		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.		
Boschi and others, 2021 (35) 'Isolation of 4000 SARS-CoV-2 shows that contagiousness is associated with viral load, not vaccine or symptomatic status'	Study design: Retrospective cohort Objective: To assess the viral load and infectiousness of confirmed COVID-19 positive samples according to their vaccination and symptom status. Study participants: n=6722 patients, of which n=3,637 patient's samples were isolated. Mean age: 60.5 years (SD: 21 years) Fully vaccinated (n=309) Unvaccinated (n=433) Setting: France, January to July 2021	Outcomes: Confirmed COVID-19 infections and associated Ct value and cell culture findings Exposure: Definition of vaccinated: Fully vaccinated: one dose of a vaccine (Pfizer, AstraZeneca, Moderna, Janssen) at least 15 days prior to testing positive Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: RT-PCR testing, virus isolation by cell culture and sequencing. SARS-CoV-2 Variants: Alpha and Delta (proportions not reported) Data collection: NR Statistical analysis: One-Way Anova or Mann-Whitney tests	Mean Ct value, by vaccination status • unvaccinated: 21.5 (SD: 4.5) • fully vaccinated: 23.4 (SD: 5.4) Mean Ct value, by culture positivity • positive culture: 23.2 (SD: 4.83) • negative culture: 28.3 (SD: 4.9) • p<0.0001 Proportion of samples successfully isolated, by vaccination status • unvaccinated: 66% (n=287 of 433) • fully vaccinated: 80% (n= 249 of 309) • p<0.0001	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: It is unclear from where the samples for the analysis came. QCC rating: Medium
Brunner-Ziegler and others, 2021 (36) 'Postvaccination infections among staff of a tertiary care hospital after vaccination with severe acute respiratory syndrome coronavirus 2 vector and mRNA-based vaccines'	Study design: Retrospective cohort Objective: To assess the incidence of COVID-19 breakthrough infections and associated viral load amongst hospital employees. Study participants: n=8,553 healthcare workers (HCWs) at a tertiary care hospital, of which n=78 had breakthrough infections. Insufficiently vaccinated (n=23) Median age: 36.0 years (IQR: 19 to 57 years) Sex: 60.9%	Outcomes: Confirmed COVID-19 infections and associated Ct values Exposure: Definition of vaccinated: Fully vaccinated: 2 vaccine doses (69.7% AstraZeneca, 32.1% Pfizer) at least 14 days prior to testing positive Partially vaccinated: one dose of vaccine more than 21 days prior to testing positive, and less than 14 days before second dose Insufficiently vaccinated: one dose less than 22 days prior to testing positive	Mean Ct values of first positive sample, by vaccination status • insufficiently vaccinated: 22.55 (SD: 7.12) • partially vaccinated: 25.49 (SD: 7.42) • fully vaccinated: 24.78 (SD: 6.37)	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific bias to report. QCC rating: Medium.

Reference	Study design	Methods	Findings	Risk of bias
	Partially vaccinated (n=37) Median age: 43.0 years (IQR: 21 to 60 years) Sex: 67.6% Fully vaccinated (n=18) Median age: 40.0 years (IQR 24 to 55 years) Sex: 77.8% female Setting: Austria, January to July 2021	 Prior infections: NR Testing: Weekly asymptomatic screening with lateral flow devices (LFD). Positive LFDs confirmed with RT-PCR testing of nasopharyngeal samples. SARS-CoV-2 Variants: Alpha (81%), Beta (5%), Delta (14%) Data collection: Demographic, testing and vaccination status data collected from the General Hospital of Vienna COVID-19 contact tracing team. Statistical analysis: Chi-square test, independent samples t test, and variance analysis used for comparative group analysis.		
Chia and others, 2021 (40,71) 'Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study' PREPRINT (version 1)	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) 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	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 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	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 (18.8-31.2) • fully vaccinated: 19.2 (IQR: 16.6 to 21.5) • p = 0.279 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).	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: Singapore, 1 April to 14 June 2021	status using a generalised additive mixed model with a random intercept.		
Christensen and others, 2021 (50) '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%) Janssen: 147 (4%) Setting: US, 15 March to 20 September 2021	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.	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
Costa and others, 2021 (37) 'RNA viral loads of SARS-CoV-2 Alpha and Delta variants in nasopharyngeal specimens at diagnosis stratified by age, clinical presentation and vaccination status'	Study design: Retrospective cohort Objective: To assess the SARS-CoV-2 viral load of confirmed COVID-19 cases according to the infecting variant, vaccination status, symptom status and age. Study participants: Convenience sample of n=545 COVID-19 positive cases Delta infections (n=250): Median age: 39 years (range: 1 to 93 years) Sex: 51% male Vaccination status: 20.4% fully vaccinated Alpha infections (n=295):	Outcomes: Confirmed COVID-19 infection and associated viral load (log10 copies/ml) Exposure: Definition of vaccinated: Fully vaccinated: 2 doses of vaccine (Pfizer, AstraZeneca, Moderna or Janssen) at least 14 days prior to testing positive Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: RT-PCR testing and whole genome sequencing.	Median viral load (log_{10} copies/ml), by vaccination and symptom status All infections • unvaccinated (n=128): 8.1 • fully vaccinated (n=51): 7.8 • p=0.31 Asymptomatic infections • unvaccinated: 8.4 • fully vaccinated: 8.7 • p=0.85 Median viral load (log_{10} copies/ml) of symptomatic cases, by vaccination status (matched for time since symptom onset)	Risk of bias: Confounding: There is a high risk of bias from confounding, particularly as deprivation was not accounted for. Other bias: It is unclear from where the samples for the analyses came. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	Median age: 22 years (range: 0 to 96 years) Sex: 50% male Vaccination status: 100% unvaccinated Time since full vaccination: 51 days (range: 14 to 177 days) Setting: Spain, February to July 2021	SARS-CoV-2 Variants: Alpha (54%), Delta (46%) Data collection: Not reported Statistical analysis: Participants matched on sex.	• unvaccinated: 8.1 • fully vaccinated: 7.4 • p=0.12	
Elliott and others, 2021 (47) '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.	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 (55) '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.	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:	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)	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

Reference	Study design	Methods	Findings	Risk of bias
randomised controlled trial' Clinical trial number: NCT04400838, ISRCTN: 15281137	Vaccinated group (n=4,244) 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	Symptomatic testing: Clinical assessment and NAAT 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)	• p=0.07 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	risk of bias from confounding, 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 (15) '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%) Median age: 49 years (IQR: 36 to 57 years) Sex: 50% Female	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. Prior infections: NR	Median Ct values, symptomatic index cases, by variant type and vaccination status: Alpha • unvaccinated: 18.4 (IQR: 15.7 to 22.5) • fully 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
	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	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 (41) ‘SARS-CoV-2 Infections and Hospitalizations Among Persons Aged ≥16 Years, by Vaccination Status —	Study design: Retrospective cohort Objective: To assess vaccine effectiveness of the Moderna, Janssen and Pfizer vaccines against COVID-19 infection and hospitalisation.	Outcomes: Confirmed COVID-19 infections and associated Ct values. 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.	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	Risk of bias Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias:

Reference	Study design	Methods	Findings	Risk of bias
Los Angeles County, California, May 1–July 25, 2021'	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	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).	• 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	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 (51) '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. 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	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. 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.	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 providing samples for viral cultures, were selected randomly. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	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	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.		
Hirotsu and others, 2021 (26) 'Active immunization by COVID-19 mRNA vaccine results in rapid antibody response and virus reduction in breakthrough infection by Delta (B.1.617.2)' PREPRINT (version 1)	Study design: Prospective cohort Objective: To compare the viral load, antigen and antibody levels, and serological kinetics of COVID-19 positive cases according to their vaccination status and infecting variant. Study participants: n=697 patients (outpatients and hospitalised), of which n=176 had Delta variant COVID-19 and were included in the viral load analysis. Patient characteristics (n=697) Mean age: 42.1 years (range: 0 to 102 years) Sex: 45% female Setting: Japan, February to September 2021	Outcomes: RT-PCR confirmed COVID-19 infections and associated viral load Exposure: Definition of vaccinated: Fully vaccinated: 2 doses of vaccine (Pfizer, Moderna, unknown) at least 14 days prior to testing positive Partially vaccinated: at least 14 days after the first dose to less than 13 days after the second dose of vaccine Recently vaccinated: less than or equal to 13 days after the first dose of vaccine Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: RT-qPCR testing and whole genome sequencing of nasopharyngeal swabs. SARS-CoV-2 Variants: Delta (100% of samples included in the analysis) Data collection: Vaccination status data collected from patient interviews. Viral load data collected from hospital laboratories. Statistical analysis: Mean Ct values presented by vaccination status and compared with t tests.	Mean log_{10} copies/ml viral load of Delta variant cases, by vaccination status • unvaccinated (n=147): 6.0 (SD: 1.6) • recently vaccinated (n=14): 6.2 (SD: 1.4) • partially vaccinated (n=8): 5.5 (SD: 2.2) • fully vaccinated (n=7): 6.5 (SD: 0.8) • p>0.05 Time to reach a viral antigen level of 1.0 log pg/ml, by vaccination status • unvaccinated: 11.9 days • fully vaccinated: 10.1 days	Risk of bias: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific bias to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
Hsu and others, 2021 (7) 'COVID-19 Breakthrough Infections and Transmission Risk: Real-World Data Analyses from Germany's Largest Public Health Department (Cologne)'	Study design: Matched case-control Objective: To estimate the differences in transmissibility and viral load between the Delta and Alpha variants. Study participants: n=357 fully vaccinated index cases (cases) with n=979 close contacts, matched with n=357 unvaccinated index cases (controls) with n=802 close contacts. Vaccinated index cases (n=357, cases): Mean age: 48.6 years (SD: 22.1 years) Sex: 64.7% female COVID-19 symptoms: 41.2% Mean vaccination interval: 62.4 days (SD: 35.2 days, range: 14 to 188 days) Unvaccinated index cases (n=357, controls): Mean age: 46.7 years (SD: 21.0 years) Sex: 64.7% female COVID-19 symptoms: 77.9% Close contacts (n=1,781) unvaccinated close contacts (n=1,182) fully vaccinated close contacts (n=439) Setting: Germany, December 2020 to August 2021	Outcomes: Viral load (Ct values) of confirmed COVID-19 cases Exposure: Definition of vaccinated: NR, though partially vaccinated cases were excluded (80.1% Pfizer, 8.4% Janssen, 3.9% AstraZeneca, 3.1% Moderna, 0.6% Sputnik or Sinopharm, 3.9% combination). Definition of close contact: Any person who had close exposure to a confirmed index case (<1.5 m) for more than 10 minutes without a mask, within 2 days before to 14 days after symptom onset in the index case. Prior infections: NR Testing: RT-PCR. Close contacts of index cases were contacted, and RT-PCR provided if COVID-19 symptoms developed. From April 2021, all index cases and contacts had an RT-PCR at the end of quarantine. SARS-CoV-2 Variants: Alpha (n=404, 56.6%), Delta (n=286, 40.1%), Wild- type (n=18, 2.5%) and Beta (n=6, 0.8%) Data collection: All people living in Cologne with positive RT-PCR tests were contacted by telephone by the Cologne public health department. Matching of index cases was 1:1 (vaccinated index cases to unvaccinated index cases) in the same observation period on age, sex and variant. Statistical analysis: Means and standard deviations calculated for Ct values.	Mean Ct values of index cases by variant and vaccination status Alpha • unvaccinated (n=154): 26.9 (SD: 6.4) • fully vaccinated (n=156): 33.1 (SD: 6.0) • p<0.001 Delta • unvaccinated (n=124): 24.1 (SD: 6.4) • fully vaccinated (n=133): 25.0 (SD: 6.7) • p<0.001 Mean CT values of close contacts by vaccination status (variant unclear) • unvaccinated: 25.6 (SD: 6.5) • fully vaccinated: 26.2 (SD: 7.3) • p=0.599	Risk of bias: Confounding: There is a high risk of bias from confounding, particularly as deprivation was not accounted for. Other bias: Selection bias: It is unclear why 21% of index cases and 82% of close contacts were not included in the Ct value analyses. QCC rating: Medium
Ioannou and others, 2021 (56) 'Transmission of SARS-CoV-2 variant B.1.1.7	Study design: Prospective cohort Objective: To compare the viral load, incidence and exposure type of COVID-19 positive vaccinated and unvaccinated healthcare workers (HCWs).	Outcomes: RT-PCR confirmed infections and associated Ct values Exposure: Definition of fully vaccinated:	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.

Reference	Study design	Methods	Findings	Risk of bias
among vaccinated health care workers'	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) 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	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%) Data collection: Data collected by study staff for each HCW infected during the hospital outbreak. Statistical analysis: NR		Other bias: No specific biases to report. QCC rating: Medium
Jacobson and others, 2021 (57) '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	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:	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

Reference	Study design	Methods	Findings	Risk of bias
	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	• 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		
Jones and others, 2021 (74) 'Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection'	Study design: Prospective cohort 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	Outcome: COVID-19 cases confirmed with RT-PCR and associated Ct values 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	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
Kale and others, 2021 (33) 'Vaccine Breakthrough Infections by SARS-CoV-2 Variants after ChAdOx1 nCoV-19 Vaccination in Healthcare Workers'	Study design: Prospective cohort Objective: To compare the viral load, humoral response and clinical presentation of COVID-19 positive cases, according to the infecting variant and vaccination status. Study participants: n=1,858 healthcare workers (HCWs), of which n=203 were infected with	Outcomes: Confirmed COVID-19 infections and Ct values Exposure: Definition of vaccinated: Fully vaccinated: 2 doses of vaccine (AstraZeneca) at least 14 days prior to testing positive Partially vaccinated: one dose of vaccine prior to testing positive	Median Ct value, by vaccination status • partially vaccinated: 21.1 (IQR: 12.0 to 29.5) • fully vaccinated: 23.2 (IQR: 0.0 to 33.1) • p=0.82	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: Unclear whether all positive

Reference	Study design	Methods	Findings	Risk of bias
	COVID-19. Median age: 34 years (IQR: 21 to 67 years) Sex: 45% male Vaccination status: Unvaccinated n=219 (11.8%), partially vaccinated n=293 (15.8%), fully vaccinated n=1346 (72.4%). Vaccination status: Median time since full vaccination to positive test: 51 days (IQR: 32 to 61 days) Median time since partial vaccination to positive test: 26 days (IQR: 9 to 51.25 days) Setting: India, January to May 2021	Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: 2% of cases were reinfections. Testing: RT-PCR testing and whole genome sequencing of nasopharyngeal and oral swab samples. SARS-CoV-2 Variants: Delta (70% of n=46 samples), Kappa (24%) Data collection: NR Statistical analysis: Categorical data analysed with Chi-square or Fisher's exact test.	Ct values were similar for vaccinated and unvaccinated participants (data not reported in paper).	samples were included in the Ct value analysis. QCC rating: Medium
Kang and others, 2021 (14) '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: 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. 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.	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 • unvaccinated: 34.6 (IQR: 34.0 to 36.6) • vaccinated: 36.1 (35.9 to 36.5)	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
Kerwin and others, 2021 (42) '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.	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
Kislaya and others, 2021 (48) '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	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).	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)	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.

Reference	Study design	Methods	Findings	Risk of bias
	Partially vaccinated: n=198 Early post-vaccination: n=229 Unvaccinated: n=777 Setting: Portugal, 17 May 2021 to 4 July 2021	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.	• 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)	QCC rating: Medium
Kolobukhina and others, 2021 (39) 'Assessment of COVID-19 clinical course in patients vaccinated with Sputnik V, SARS-CoV-2 S protein RBD domain variation and serum virus'	Study design: Case-control Objective: To assess the clinical presentation and viral load of COVID-19 positive patients vaccinated with Sputnik V, compared of unvaccinated patients. Study participants: n=116 COVID-19 cases, previously vaccinated with the Sputnik V vaccine, compared with 135 unvaccinated COVID-19 cases Age: 30 to 50 years: 17.1%; more than 50 years: 82.8% Sex: 48.3% male Setting: Russia, December 2020 to April 2021	Outcomes: Confirmed COVID-19 infections and associated Ct values. Exposure: Definition of vaccinated: 2 doses of vaccine (Sputnik V) at least 14 days prior to testing positive Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: RT-PCR testing and virus isolation with cell culture of nasopharyngeal swab samples. SARS-CoV-2 Variants: Unclear for Ct value analysis. Data collection: Testing and vaccination status data collected from the Infectious disease hospital. Statistical analysis: Mann-Whitney U test used to compare Ct values by vaccination status.	Mean Ct values, by vaccination status • unvaccinated (n=34): 31.45 (IQR: 27.20 to 33.72) • fully vaccinated (n=8): 34.78 (IQR: 31.41 to 36.48) • p=0.026	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted Other bias: Unclear whether all positive samples were included in the Ct analysis. QCC rating: Medium
Levine-Tiefenburn and others, 2021 (49)	Study design: Retrospective cohort Objective: To compare the viral loads (Ct values) of fully vaccinated, booster vaccinated	Outcomes: RT-PCR positive COVID-19 infections and associated Ct values. Exposure:	Mean Ct values (*RdRp* gene): • unvaccinated: 27.7 (SD: 5.0) • fully vaccinated (all): 26.9 (SD: 5.0)	Risk of bias Confounding: There is a high risk of bias from

Reference	Study design	Methods	Findings	Risk of bias
'Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2'	and unvaccinated COVID-19 (Delta) positive cases 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 (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	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
Levine-Tiefenburn and others, 2021 (75) 'Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine'	Study design: Retrospective cohort and matched case-control 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	Outcomes: RT-PCR positive COVID-19 infections and associated Ct values. Exposure: 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.	Difference in mean Ct values (*RdRp*), compared unvaccinated (data extracted from figure): • 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)	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
Levine-Tiefenbrun and others, 2021 (27) 'Waning of SARS-CoV-2 booster viral-load reduction effectiveness' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To compare the viral loads (Ct values) of fully vaccinated, booster vaccinated and unvaccinated COVID-19 (Delta variant) positive cases Study participants: n=22,657 adults aged at least 20 years Sex: 43% male Vaccination status: Unvaccinated n=5,229 (23%), fully vaccinated n=16,038 (70.8%), booster vaccinated n=1,390 (6.1%). Setting: Israel, June to November 2021	Outcomes: RT-PCR confirmed COVID-19 infections and associated Ct values. Exposure: 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 Prior infections: People with previous positive samples excluded.	Mean Ct values (*RdRp* gene): Unvaccinated (n=5,229) • 26.8 (SD: 5.0) Fully vaccinated • 7 to 30 days after second dose (n=25): 30.8 (SD: 4.5) • 31 to 60 days after second dose (n=43): 28.4 (SD: 5.0) • 61 to 120 days after second dose (n=456): 27.2 (SD: 4.8) • 121 to 180 days after second dose (n=8,076): 26.9 (SD: 5.0) • 180 days after second dose (n=7,438): 26.8 (SD: 5.0) Booster vaccinated	Risk of bias: Confounding: There is a high risk of bias from 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
		Testing: RT-qPCR testing at central laboratory. Ct values for *E, N* and *RdRp* genes determined for each sample. SARS-CoV-2 Variants: Delta (more than 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 difference in Ct values between participants with different vaccination statuses over time, adjusting for sex, age, and calendar date.	• 7 to 30 days after booster dose (n=934): 29.4 (SD: 4.7) • 31 to 60 days after booster dose (n=318): 28.5 (SD: 4.4) • 61 to 120 days after booster dose (n=138): 28.9 (SD: 4.5) Difference in booster vaccinated Ct values (*RdRp* gene), compared with unvaccinated cases • 7 to 30 days after booster dose: 2.7 (95% CI: 2.3 to 3.0) • 31 to 60 days after booster dose: 1.3 (95% CI: 0.7 to 1.9) • 61 to 120 days after booster dose: 0.8 (95% CI: -0.1 to 1.8)	
Luo and others, 2021 (67) 'Infection with the SARS-CoV-2 Delta Variant is Associated with Higher Recovery of Infectious Virus Compared to the Alpha Variant in both Unvaccinated and Vaccinated Individuals' Included in previous review, but updated results are presented here	Study design: Retrospective cohort Objective: To compare the infectious viral load between Alpha and Delta variant COVID-19 cases Study participants: n=2,644 patients, of which n=737 were included in the Ct value analyses Alpha variant cases (n=1,482) Median age: 36 years (SD: 21.3) Sex: 58.4% female Ethnicity: 58% Black, 28% White, 12% Other/unknown, 2% Asian Delta variant cases (n=785) Median age: 38 years (SD: 22.4) Sex: 57.3% female Ethnicity: 63% Black, 42% White, 14% Other/unknown, 6% Asian Setting: US, January to September 2021	Outcomes: Confirmed COVID-19 infections and associated Ct values and cell culture (cytopathic effects, CPE) findings Exposure: Definition of vaccinated: Fully vaccinated: vaccine (72.6% Pfizer, 26.8% Moderna, 0.6% Janssen) dose completion at least 14 days prior to testing positive Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: qPCR testing, cell culture and sequencing. Symptomatic patients: Nasopharyngeal swab samples Asymptomatic patients: Lateral mid-turbinate nasal swab samples SARS-CoV-2 Variants: B.1.2 (14%), Alpha (56%), Delta (30%). Data collection: Demographic and symptom data collected from John Hopkins Medical Institutions data warehouse. Vaccination data collected via local	Mean Ct values (data extraction from figure), by vaccination status and variant Alpha • unvaccinated (n=470): 21.7 • fully vaccinated (n=46): 22.7 Delta • unvaccinated (n=134): 21.1 • fully vaccinated (n=87): 20.2 Mean Ct values (data extraction from figure), by days since symptom onset, vaccination status and variant 5 days or less after symptom onset Alpha • unvaccinated: 21.3 • fully vaccinated: 21.5 Delta • unvaccinated: 20.3 • fully vaccinated: 20.3 More than 5 days after symptom onset Alpha • unvaccinated: 24.6 • fully vaccinated: 24.2 Delta • unvaccinated: 24.6 • fully vaccinated: 21.1	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: Unclear whether all positive samples were included in the Ct analysis. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
		data sources and electronic medical records/insurance registries. Statistical analysis: Chi-square and Fisher Exact tests used for categorical variable comparisons. T-test and Kruskal-Wallis one-way Anova used for comparative analysis of continuous independent variables.	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=77): 74.4% • fully vaccinated (n=39): 76.6% Samples (Ct values less than 20) with recoverable infectious virus (CPE positive), by variant and vaccination status Alpha (n=51) • fully vaccinated: 38.9% • unvaccinated: 72.7% • p < 0.00001 Delta (n=47) • fully vaccinated: 100% • unvaccinated: 96.7% • p < 0.00001	
Li and others, 2021 (72) '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 Setting: China, 18 May to 20 June 2021	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.	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
		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 (58) '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. Statistical analysis: Quantile (median) regression used to compare Ct values between symptomatic and asymptomatic infections by vaccination and	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
		serostatus; it is unclear which, if any, variables were adjusted for in the analysis.		
Luo and others, 2021 (43) '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 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	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.	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% • fully vaccinated (n=27): 70.4% • p>0.05	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
	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			
Lyngse and others, 2021 (4) 'SARS-CoV-2 Omicron VOC Transmission in Danish Households' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To estimate the transmission dynamics of Omicron variant COVID-19. Participants: n=11,937 households (2 to 6 person) with a COVID-19 positive index case, followed for one to 7 days for infections in household members. Index cases - Omicron (n=2,225): Age: less than 10 years: 5.9%; 10 to 20 years: 20.4%; 20 to 30 years: 32.5%; 30 to 40 years: 13.4%; 40 to 50 years: 12.7%; 50 to 60 years: 10.7%; 60 to 70 years: 3.5%; 70 years and over: 1.0% Sex: 48.4% Female Vaccination status: booster vaccinated: n=105 (4.7%); fully vaccinated/previous infection: n=1,752 (78.7%); unvaccinated: n=368 (16.5%) Index cases - Delta (n=9,712): Age: less than 10 years: 24.9%; 10 to 20 years: 19.4%; 20 to 30 years: 12.8%; 30 to 40 years: 10.2%; 40 to 50 years: 12.9%; 50 to 60 years: 11.5%; 60 to 70 years: 5.9%; 70 years and over: 2.4% Sex: 48.7% Female Vaccination status: booster vaccinated: n=286 (2.9%); fully vaccinated/previous infection: n=4,797 (49.4%); unvaccinated: n=4,629 (47.7%)	Outcomes: To compare the viral load of Omicron and Delta variant COVID-19 cases. Exposure: Definition of vaccinated: Booster vaccinated: a booster vaccination dose taken 7 days before positive test results Fully vaccinated: all doses of any vaccine, with the final dose received some days before positive test results (Pfizer [85%]: 7 days; AstraZeneca [0%]: 15 days; Moderna [14%]: 14 days; Janssen [1%]: 14 days) or 14 days after previous infection Definition of unvaccinated: no vaccine received prior to positive test results, or only partial vaccination (one dose of a 2 dose vaccine). Prior infections: Included in the definition of fully vaccinated. Testing: RT-PCR for index cases, RT-PCR or antigen test for secondary cases. SARS-CoV-2 variant: Delta (n=9,712, 81%) and Omicron (n=2,225, 19%). Data collection: Danish Vaccination Register and Danish Microbiology Database. Statistical analysis: Comparison of median Ct values between Omicron and Delta variants.	Median Ct values, by variant: • Delta: 28.29 • Omicron: 27.24	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
	Time since vaccination: The time since vaccination was very similar for the Omicron and Delta variant secondary cases. Index cases: First positive test between 9 and 12 December 2021 Secondary cases: Any positive test (including antigen) within one to 7 days of index case in same household Setting: Denmark, December 2021			
Lyngse and others, 2022 (5) 'Effect of Vaccination on Household Transmission of SARS-CoV-2 Delta VOC' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To estimate the vaccine effectiveness against susceptibility and transmissibility of Delta variant COVID-19. Participants: n=24,693 households (2 to 6 person) with a COVID-19 positive index case, followed for one to 14 days for infections in household members. Secondary cases (n=11,611): Positive RT-PCR test within one to 14 days of index case in same household. 32.9% fully vaccinated. Setting: Denmark, June to November 2021	Outcomes: Laboratory confirmed COVID-19 cases and associated Ct values Exposure: Definition of vaccinated: Fully vaccinated: all doses of any vaccine, with the final dose received some days before positive test results (Pfizer [83%]: 7 days; AstraZeneca [6.2%]: 15 days; Moderna [4.4%]: 14 days; Janssen [6.4%]: 14 days). Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: All households with a previous infection (positive RT-PCR test) were excluded. Testing: RT-PCR for all participants. SARS-CoV-2 variant: Delta (100%) Data collection: Danish Vaccination Register and Danish Microbiology Database. Statistical analysis: Ct values compared for vaccinated and unvaccinated cases testing positive on the same day after exposure.	• Fully vaccinated secondary cases had a 1.6 higher mean Ct value compared to unvaccinated secondary cases	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
Magalis and others, 2021 (31) 'SARS-CoV-2 Delta vaccine breakthrough	Study design: Prospective cohort Objective: To assess the impact of COVID-19 variants on the incidence of breakthrough infections and associated viral load.	Outcomes: Confirmed COVID-19 infections and associated viral load. Exposure:	Mean viral load of COVID-19 Delta cases, by vaccination status • unvaccinated (n=36): 7.36 log copies/ml (IQR: 3.29 to 10.81)	Risk of bias: Confounding: There is a high risk of bias from confounding, particularly

Reference	Study design	Methods	Findings	Risk of bias
transmissibility in Alachua, Florida' PREPRINT (version 1)	Study participants: n=4,439 sequenced COVID-19 positive patients, including n=109 breakthrough cases were matched to unvaccinated cases. Fully vaccinated (n=109): Age: 36.7 (SD: 14.2) Sex: 62.4% female Ethnicity: 73.4% White, 9.2% Black, 10.1% Asian/Pacific Islander Mean time interval between vaccination and COVID-19 diagnosis: 104.0 days (SD: 57.5) Mean time-interval between disease onset and sample collection date: 4.2 days (SD: 2.4) Setting: US, October 2020 to August 2021	Definition of vaccinated: at least 14 days after completion of Pfizer (76.1%), Moderna (10.1%) or Janssen (12.8%) vaccination course Definition of unvaccinated: No vaccine received prior to infection Prior infections: NR Testing: qPCR testing of saliva samples and nasopharyngeal swabs. Standard curve generated using N1 quantitative standards 10-fold diluted to determine viral copies. Genome sequencing conducted for all samples. SARS-CoV-2 Variants: Fully vaccinated: Delta (53%), unknown (31%). Data collection: Testing and vaccination status data collected from the Alachua County Department of Health and associated laboratories and hospitals. Statistical analysis: Breakthrough cases matched on age and gender to unvaccinated cases. Linear regression with viral load as a dependent variable was conducted, with vaccination status, variant, sex, and days since January 2021 as covariables.	• fully vaccinated (n=56): 4.66 log copies/ml (IQR:1.2 to 10.62) • difference: fully vaccinated had a 38% reduced viral load compared with unvaccinated (p<0.00001) Mean viral load of COVID-19 non-Delta cases, by vaccination status • unvaccinated (n=75): 6.15 log copies/ml (IQR: 3.56 to 10.92) • fully vaccinated (n=13): 5.39 log copies/ml (IQR: 1.41 to 8.36) • difference: fully vaccinated had a 34% reduced viral load compared with unvaccinated (p<0.00001)	as deprivation was not accounted for. Other bias: No specific bias to report. QCC rating: Medium
McEllistrem and others, 2021 (59) '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%	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.	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)	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: US, 2 December 2020 to 6 February 2021	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 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.	• mean difference = -2.4, p=0.004	
Mostafa and others, 2021 (60) '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:	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
		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. 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 (61) '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.	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

Reference	Study design	Methods	Findings	Risk of bias
Pajon and others, 2021 (62) 'Initial Analysis of Viral Dynamics and Circulating Viral Variants During the mRNA-1273 Phase 3 COVE Trial 2021' PREPRINT (version 1)	Study design: RCT (secondary analysis) Objective: To assess the impact of vaccination on the viral kinetics of confirmed COVID-19 infections 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	Outcomes: Confirmed COVID-19 infections and associated viral load, viral shedding, and time to viral clearance (viral log10 copies per ml). Exposure: 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.	Median viral copies per ml (log10), by vaccination status and day of illness: Day 1 • unvaccinated: 6.7 • 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	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, as the analysis was unadjusted. Other bias: No specific biases to report. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
			• 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) <u>Day 9</u> • 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) <u>Day 14</u> • 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).	

Reference	Study design	Methods	Findings	Risk of bias
			Median time to viral clearance • unvaccinated 7 days • fully vaccinated: 4 days • difference: 3 days	
Pena-Hernandez and others, 2021 (28) 'Comparison of infectious SARS-CoV-2 from the nasopharynx of vaccinated and unvaccinated individuals' PREPRINT (version 2)	Study design: Case-control Objective: To compare virus titres and levels of infectious virus in vaccinated and unvaccinated COVID-19 patients (Delta variant) Study participants: n=125 COVID-19 cases; n=72 vaccinated cases matched with n=53 unvaccinated cases (matched on Ct value, age and sex). Mean age: 46.9 years (IQR:29.8 to 60.6) Sex: 41.6% male Setting: US, July to August 2021	Outcomes: Confirmed COVID-19 infections and associated viral load and cell culture (infectious virus) findings Exposure: Definition of vaccinated: Fully vaccinated: 2 doses of Pfizer or Moderna vaccines, or one dose with Janssen vaccine Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: RT-qPCR testing of nasopharyngeal samples. Samples from positive cases were assessed with plaque assays to determine virus titre and infectious viral load. SARS-CoV-2 Variants: Delta (dominant during study period) Data collection: Vaccination and testing data collected from the Yale New Haven Health system. Statistical analysis: Relative risk estimated for the association between vaccination and culturable virus, adjusting for age, sex and relative days from symptom onset (in addition to matching).	Samples with culturable virus, by vaccination status • unvaccinated: 40% • fully vaccinated: 21% • relative risk: 0.49 (95% CI: 0.27 to 0.91) Effectiveness against infectious viral load: probability of recovering infectious virus from fully vaccinated samples, by time since final dose • 5 months post full vaccination: 11% (95% CI: 4.5% to 25.4%) • 6 months post full vaccination: 40.3% (95% CI: 22.0% to 65.6%)	Risk of bias: Confounding: There is a high risk of bias from confounding, particularly as deprivation was not accounted for. Other bias: No specific bias to report. QCC rating: Medium
Pouwels and others, 2021 (44) 'Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections	Study design: Prospective cohort Objective: To assess the effectiveness of vaccination against COVID-19 infections and associated symptoms and viral load Participant visits: Adults (at least 18 years) Alpha dominant period: 2,580,021 visits with 384,543 adults from 221,909 households	Outcomes: Confirmed COVID-19 infections and associated Ct values. Exposure: Fully vaccinated: at least 14 days after second dose of Pfizer or AstraZeneca vaccine. Partially vaccinated: at least 21 days after first dose	Median Ct values, by variant and vaccine status 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)	Risk of bias Confounding: There is a high risk of bias from residual confounding even after adjustment, particularly as deprivation was not accounted for.

Reference	Study design	Methods	Findings	Risk of bias
in the UK' Office for National Statistics (ONS) COVID-19 Infection Survey (CIS) ISRCTN21086382	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 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	Definition of unvaccinated: at least 21 days before first vaccine dose. Testing: 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 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.	• 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) • 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	Other bias: No specific biases to report. QCC rating: Medium
Puhach and others, 2022 (32) 'Infectious viral load in unvaccinated and vaccinated patients infected with SARS-CoV-2 WT, Delta and Omicron'	Study design: Retrospective cohort Objective: To analyse the viral load characteristics in the upper respiratory tract of unvaccinated and vaccinated individuals (to quantify infectious viral particles from patient specimens) Study participants: n=384 patients with Ct	Outcomes: Confirmed COVID-19 infections and associated quantitative infectious viral titres during the first 5 symptomatic days, virus isolation and RNA genome copies. Exposure: Definition of vaccinated:	• infectious viral load for Delta variant COVID-19 was 9.33-fold lower for fully vaccinated compared with unvaccinated patients (0.97 $\log_{10}$, p<0.0001) • fully vaccinated Omicron cases had similar genome copy numbers to fully vaccinated Delta cases (p=0.33)	Risk of bias: Confounding: There is a high risk of bias from confounding, particularly as deprivation was not accounted for. Other bias: Unclear

Reference	Study design	Methods	Findings	Risk of bias
PREPRINT (version 2)	values of less than 27 at an outpatient testing centre of the Geneva University Hospital Unvaccinated (n=245) Pre-VOC: (n=118) Median age: 36 years (range: 17 to 82 years) Sex: 42.4% female Delta (n=127) Median age: 37 years (range: 16 to 83 years) Sex: 51.2% female Vaccinated (n=139) Delta (n=121) Median age: 40 years (range: 16 to 83 years) Sex: 51.2% female Time since second dose: 79.5 days (IQR: 40.5 to 139 days) Omicron (n=18) Median age: 35 years (range: 14 to 58 years) Sex: 50% female Time since second dose: 136 days (IQR: 85 to 176 days) Setting: Switzerland, April 2020 to December 2021	Fully vaccinated: 2 doses of vaccine (Pfizer, Moderna, CoviVac, other) at least 14 days prior to testing positive Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: RT-PCR, virus isolation (cell culture) and whole genome sequencing of nasopharyngeal samples. SARS-CoV-2 Variants: Pre-VOC (n=118), Delta (n=248), Omicron (n=18) Data collection: Testing data collected from symptomatic individuals in the outpatient testing centre of the Geneva university Hospital. Clinical data collected via a standardised questionnaire in the testing centre and/or through the Cantonal Health Service Statistical analysis: Infectious viral load analysis matched for age, sex and days post symptom onset.	• fully vaccinated Omicron cases had 4.9-fold lower infectious viral loads than fully vaccinated Delta cases (0·69 log_{10}, p=0.10) Percentage of sample with positive culture/virus isolated, by vaccination status Unvaccinated: • pre-VOC: 91.9% • Delta: 91.7% Vaccinated: • Delta: 83.8% Infectious virus recovery at 5 days after symptom onset, by vaccination status (Delta variant) • unvaccinated: (n=11 of 13) 84.6% • fully vaccinated: (n=7 of 13) 53.8%	whether all positive samples were included in the all analyses. QCC rating: Medium
Regev-Yochay and others, 2021 (63) ‘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): Age: 65% 18 to 45 years, 35% 46 to 65 years, 0% more than 65 years Sex: 32% male	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: 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.	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 • fully vaccinated: 25.8 • p<0.001	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
	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	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 two sample t-tests.		
Riemersma and others, 2021 (45) '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). 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.	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: • 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)	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
			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)	
Salvatore and others (29) 'Transmission potential of vaccinated and unvaccinated persons infected with the SARS-CoV-2 Delta variant in a federal prison, July—August 2021' PREPRINT (version 1)	Study design: Prospective cohort Objective: To assess the infectiousness and duration of positivity of COVID-19 cases by vaccination status. Study participants: n=95 incarcerated individuals situated in four housing units. Fully vaccinated (n=78) Age: 18 to 29 years: 4%, 30 to 39 years: 24%, 40 to 49 years: 28%, 50 to 59 years: 26%, 60 years and over: 18% Sex: 100% male Ethnicity: White: 73%, Hispanic: 13%, Black: 10% Baseline health: overweight: 31%, obesity or severe obesity: 62%, smoking history: 54%, hypertension: 49%, diabetes: 18%, moderate or severe asthma: 10% Prior COVID-19 infection: n=2 (3%) Time since second dose: up to 120 days: 33%, over 120 days: 61% Unvaccinated (n=17) Age: 18 to 29 years: 12%, 30 to 39 years: 18%, 40 to 49 years: 35%, 50 to 59 years: 29%, 60 years and over: 6% Sex: 100% male Ethnicity: White: 41%, Hispanic: 12%, Black: 47% Baseline health: overweight: 41%, obesity or severe obesity: 35%, smoking history: 24%,	Outcomes: Confirmed COVID-19 infections, duration of RT-PCR positivity, viral load (Ct values) and cell culture positivity. Exposure: Definition of vaccinated: at least 14 days after completion of Pfizer (73%), Moderna (18%) or Janssen (9%) vaccination course Definition of not fully vaccinated: No vaccine received or only partial vaccination prior to positive test Prior infections: Data collected and reported. Testing: Daily RT-PCR tests for 10 consecutive days after first positive test. Contacts of positive cases underwent asymptomatic screening tests every 2 days while in isolation. Genomic sequencing and cell culture testing also conducted. SARS-CoV-2 Variants: Delta (100%) Data collection: Vaccination status, demographic and prior infection collected via questionnaires. Baseline health data collected from electronic medical records. Statistical analysis: Disease onset defined as date of first COVID-19 related symptom or first positive test (whichever occurred first). Longitudinal analysis of RT-PCR positivity and viral culture positivity conducted.	Median duration of RT-PCR positivity by vaccination status • not fully vaccinated: 12 days • fully vaccinated (any vaccine): 13 days • fully vaccinated (Pfizer): 13 days • fully vaccinated (Moderna): 10 days • fully vaccinated (Janssen): 13 days • p=0.50 Median Ct values, by day after onset (first positive test or symptom onset, whichever came first) and vaccination status Day of onset • unvaccinated: 28.5 (24.8 to 31.8) • fully vaccinated: 26.4 (IQR: 23.5 to 28.4) Day 10 after onset • unvaccinated: 34.5 (29.4 to 35.2) • fully vaccinated: 32.9 (30.5 to 34.6) No statistical difference observed by vaccination status on any day after onset, all p values above 0.0026 Viral culture findings • viral culture testing conducted on 29% of samples. • infectious virus recovered from 8% of fully vaccinated samples compared to 12% of unvaccinated samples (p=0.16)	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: Selection bias: Unclear why only 29% of samples were tested for viral culture positivity. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
	hypertension: 29%, diabetes: 6%, moderate or severe asthma: 12% Prior COVID-19 infection: n=2 (12%) Setting: US, 12 July to 9 August 2021	Ct values were compared non-parametrically with the Mann-Whitney U test (dichotomous variables) or Kruskal-Wallis test (categorical variables).	• for samples from vaccinated people, no statistical difference in duration of viral culture positivity by time since second dose (p=0.79) or confirmed prior infection (p=0.99) Median duration of viral culture positivity, by vaccination status • unvaccinated: 5 days • fully vaccinated: 5 days • p=0.29	
Servellita and others, 2021 (46,73) '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 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.	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 • 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	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
			• 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 (76) 'Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study' ISRCTN: 14447421	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): 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	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. 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.	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 used to determine Ct values. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
Siddle and others, 2021 (30) 'Evidence of transmission from fully vaccinated individuals in a large outbreak of the SARS-CoV-2 Delta variant in Provincetown, Massachusetts' PREPRINT (version 1)	Study design: Retrospective cohort Objective: To assess the genetic epidemiology of a COVID-19 outbreak. Study participants: n=467 individuals identified during an outbreak investigation Median age: 43 years Sex: 80% male Vaccination status: 84% vaccinated, 16% unvaccinated Average time since vaccination course completion: 111 days Setting: US, July to August 2021	Outcomes: Confirmed COVID-19 infections and associated Ct values Exposure: Definition of vaccinated: at least 14 days after completion of Pfizer (48%), Moderna (37%) or Janssen (14%) vaccination course Partially vaccinated: at least one day after receipt of first dose. Definition of unvaccinated: No vaccine received prior to positive test. Prior infections: NR Testing: RT-qPCR testing and whole genome sequencing. Asymptomatic screening not conducted. SARS-CoV-2 Variants: Delta (99%) Data collection: Travel history and exposure data collected from the state COVID-19 surveillance system. Vaccination status data obtained from documentation of the state immunization registry of COVID-19 vaccination completion or self-reported vaccination status. Statistical analysis: Descriptive statistics reported only.	Mean Ct values (data extracted from figure), by symptoms and vaccination status Asymptomatic • unvaccinated: 24.1 (SD: 2.25) • fully vaccinated: 24.0 (SD: 6.0) Symptomatic • unvaccinated: 24.3 (SD: 6.7) • fully vaccinated: 24.4 (SD: 6.1)	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted. Other bias: No specific bias to report. QCC rating: Medium
Singanayagam and others, 2021 (10) 'Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study'	Study design: Prospective cohort Objective: To estimate COVID-19 transmission and viral load kinetics in vaccinated and unvaccinated individuals infected with the Delta variant. Study participants: n=19 symptomatic index cases and n=602 community contacts recruited to the Assessment of Transmission and Contagiousness of COVID-19 in Contacts study, after notification to the UK contact-tracing system (NHS test and trace). Of the 602 contacts recruited, 144 (24%) tested	Outcomes: Confirmed COVID-19 infections and associated viral load (log_{10} copies/ml) Exposure: Definition of vaccinated: Fully vaccinated: Received 2 doses of Pfizer or AstraZeneca vaccine at least 7 days before recruitment Partially vaccinated: Received a single vaccine dose at least 7 days before recruitment Definition of unvaccinated: No vaccine received, or single vaccine dose received less than 7 days before recruitment	ORF1ab gene Ct value data (within sample) Median peak log_{10} viral load/ml in 50-year-olds, by vaccination status • unvaccinated: 8.09 (2.5% and 97.5% percentiles: 7.74 to 8.42) • vaccinated: 8.19 (2.5% and 97.5% percentiles: 7.99 to 8.41) Median viral load growth rate per day, by vaccination status • unvaccinated: 4.16 (2.5% and 97.5% percentiles: 2.19 to 11.78) • vaccinated: 4.43 (2.5% and 97.5% percentiles: 3.01 to 10.19)	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
	positive for COVID-19. Including index cases, 71 participants were infected with the Delta variant and included in this analysis. Unvaccinated participants infected with the Delta variant (n=23): Median age: 13 years (IQR: 11 to 17 years) Sex: 30% female Ethnicity: 61% White; 30% Non-White; 9% Unknown Vaccinated participants infected with the Delta variant (n=38): Median age: 49 years (IQR: 41 to 55 years) Sex: 67% female Ethnicity: 68% White; 24% Non-White; 8% Unknown Setting: UK, September 2020 to September 2021	Prior infections: NR Testing: Sequential quantitative RT-PCR. SARS-CoV-2 Variants: Delta (100%) Data collection: Self-report to study team, PHE, UK National Immunisation Management System, and general practice records. Statistical analysis: ORF1ab and E gene Ct values converted to viral genome copies. Viral load kinetics modelled with a phenomenological model of viral titre, and viral kinetic parameters estimated per study participant with a Bayesian hierarchical model, separately for vaccinated and unvaccinated participants.	Median viral load decline rate per day, by vaccination status • unvaccinated: 1.81 (2.5% and 97.5% percentiles: 1.54 to 2.2) • vaccinated: 2.18 (2.5% and 97.5% percentiles: 1.88 to 2.57) E gene Ct value data (within sample) Median peak log_{10} viral load/ml in 50-year-olds, by vaccination status • unvaccinated: 8.16 (2.5% and 97.5% percentiles: 7.82 to 8.5) • vaccinated: 8.27 (2.5% and 97.5% percentiles: 8.06 to 8.48) Median viral load growth rate per day, by vaccination status • unvaccinated: 4.15 (2.5% and 97.5% percentiles: 2.36 to 10.01) • vaccinated: 4.33 (2.5% and 97.5% percentiles: 3.07 to 8.47) Median viral load decline rate per day, by vaccination status • unvaccinated: 1.65 (2.5% and 97.5% percentiles: 1.42 to 1.97) • vaccinated: 2.05 (2.5% and 97.5% percentiles: 1.76 to 2.4)	
Smith and others, 2021 (38) 'Genomic and Virological Characterization of SARS-CoV-2 Variants in a Subset of Unvaccinated and Vaccinated U.S. Military Personnel'	Study design: Retrospective cohort Objective: To provide genomic and virological characteristics of SARS-CoV-2 isolates Study participants: n=2,300 nasal swabs collected from USA military personnel and beneficiaries stationed worldwide aged between 18 and 40 years. Subset of samples were selected to determine if viable virus was present. Setting: US and Worldwide, March 2020 to November 2021	Outcomes: Confirmed COVID-19 infection and associated viral load (log_{10} PFU/ml) Exposure: Definition of vaccinated: NR Definition of unvaccinated: NR Prior infections: NR Testing: qRT-PCR, genomic sequencing and cell culture (plaque assay) SARS-CoV-2 Variants: Unvaccinated: non-Delta (100%); vaccinated: Delta (85%) Data collection: NR Statistical analysis: Mean amount of viable virus detected reported by vaccine status and variant.	Mean viable viral load (log_{10} PFU/ml) by vaccination status: Unvaccinated (n=25): • all variants: 3.2 log_{10} PFU/ml • Delta: NR Vaccinated (n=55): • non-Delta: 3.1 log_{10} PFU/ml • Delta: 4.6 log_{10} PFU/ml	Risk of bias: Confounding: There is a very high risk of bias from confounding, as the analysis was unadjusted Other bias: Proportion of CPE positive samples was not reported. QCC rating: Medium

Reference	Study design	Methods	Findings	Risk of bias
Tande and others, 2021 (64) '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 Ethnicity: 86% white, 2%African descent, 2% Asian, 5% Hispanic COVID-19 positive: n=1436 Setting: US, 17 Dec 2020 to 8 Feb 2021	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 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.	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) • more than 10 days after first dose, before second dose (n=1): 30.9	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
Thompson and others, 2021 (65) '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	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	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:	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

Reference	Study design	Methods	Findings	Risk of bias
	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	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.	• 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)	
Yi and others, 2022 (11) 'SARS-CoV-2 Delta Variant Breakthrough Infection and Onward Secondary Transmission in Household'	Study design: Retrospective cohort Objective: To assess the incidence of COVID-19 breakthrough infections and onwards transmission to household contacts following an outbreak an adult day service centre Participants: n=42 service users and n=16 staff at an adult day service centre, of which n=25 were COVID-19 positive, and n=46 household contacts Index cases (n=25) Mean age: 78.9 years (SD: 14.3 years) Sex: 72.0% female Vaccination status: 4% unvaccinated, 96% fully vaccinated Mean interval after second vaccine dose: 140.0 days (range: 80 to 117 days) Household contacts (n=46) Vaccination status: 39% unvaccinated, 43% partially vaccinated, 17% fully vaccinated	Outcomes: RT-PCR confirmed COVID-19 infections and secondary infections, with associated Ct values Exposure: Definition of vaccinated: Fully vaccinated: 2 doses of Pfizer vaccine at least 14 days prior to testing positive Partially vaccinated: not stated Definition of unvaccinated: no vaccine received prior to positive test results. Prior infections: NR Testing: RT-PCR testing of all service users, staff and household contacts, regardless of symptom status SARS-CoV-2 variant: Delta (100% of the 13 samples sequenced) Data collection: Vaccination, demographic, symptom status and exposure data collected by the Korea Disease Control and Prevention Agency and Jeju Special Self-Governing Provincial Government.	Mean Ct values of COVID-19 cases, by symptom and vaccination status Asymptomatic • unvaccinated: 17.2 • fully vaccinated: 18.1 Symptomatic • unvaccinated: 15.1 • fully vaccinated: 20	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: South Korea, 3 to 10 August 2021	Participants and staff were interviewed to assess symptoms in the previous 14 days. Statistical analysis: NR		

Supplementary Table 3. Characteristics of ongoing studies

Reference	Study description	Methodology
NCT04811664 (84) '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 **Setting:** US, March 2021 to December 2021	**Intervention/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 (85) '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/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 (86) '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 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

About the UK Health Security Agency

UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation heath secure.

UKHSA is an executive agency, sponsored by the Department of Health and Social Care.

Prepared by Sean Harrison, Zalaya Simmons, Amrita Ghataure, Nicola Pearce-Smith, Rachel Clark.

For queries relating to this document, please contact enquiries@ukhsa.gov.uk

Published: April 2022