Wales COVID-19 Evidence Centre (WCEC)
Rapid Review

What is the risk of SARS-CoV-2 transmission in vaccinated populations?
Report number – RR00012 (November 2021)

Rapid Review Details

Review conducted by:
Health Technology Wales

Review Team:
- Sasha Barrate, Lauren Elston, Tom Winfield, David Jarrom

Review submitted to the WCEC on:
29th November 2021

Stakeholder consultation meeting:
29th November 2021

Rapid Review report issued by the WCEC on:
8th, January 2022

WCEC Team:
- Adrian Edwards, Alison Cooper, Ruth Lewis, Micaela Gal, Becki Law and Jane Greenwell involved in drafting Topline Summary, review and editing.

This review should be cited as: A rapid review of the risk of Sars-CoV-2 transmission in vaccinated populations. RR_00012. Wales COVID-19 Evidence Centre, November 2021

http://www.primecentre.wales/resources/RR/Clean/RR00012_Wales_COVID-19_Evidence_Centre-Rapid_Review_What_is_the_risk_of_Sars-CoV-2_transmission_in_vaccinated_populations_November_2021.pdf

What is the risk of SARS-CoV-2 transmission in vaccinated populations?
Report number – RR00012 (November 2021)

TOPLINE SUMMARY

What is a Rapid Review?

Our rapid reviews use a variation of the systematic review approach, abbreviating or omitting some components to generate the evidence to inform stakeholders promptly whilst maintaining attention to bias. They follow the methodological recommendations and minimum standards for conducting and reporting rapid reviews, including a structured protocol, systematic search, screening, data extraction, critical appraisal, and evidence synthesis to answer a specific question and identify key research gaps. They take 1- 2 months, depending on the breadth and complexity of the research topic/ question(s), extent of the evidence base, and type of analysis required for synthesis.

Background / Aim of Rapid Review

Since COVID-19 vaccination programmes have been introduced, the focus of most research has been vaccine safety and efficacy, with large clinical trials confirming that vaccines are generally safe and effective against symptomatic COVID-19 infection and reducing hospitalisations and mortality. However, breakthrough infections can still occur, and the effectiveness of COVID-19 vaccines against transmission from infected vaccinated people to susceptible contacts is unclear.

This review aimed to examine evidence on the transmission risk of SARS-CoV-2 from vaccinated people to unvaccinated or vaccinated people.

Key Findings

Extent of the evidence base

- We identified a **robust rapid literature review by the University of Calgary Health Technology Assessment Unit** (via COVID-END) that reported on the transmissibility of COVID-19 among vaccinated individuals with a review period up to **August 23rd 2021.**
- We also searched for evidence published after this review and **identified an additional nine primary studies** that reported on direct transmission, cycle threshold (Ct) values or viral load with a review period up to **5th October 2021 (one post-hoc analysis of an RCT and eight observational)**
- In total, **35 studies** were included in this review: one randomised controlled trial (RCT), one post-hoc analysis of an RCT, 13 prospective cohort studies, 16 retrospective cohort studies and four case control studies.

Recency of the evidence base

- All studies were published in 2021 (preprints were included)
- The UK Health Security Agency, with whom we are collaborating in this ongoing work, is currently conducting a rapid review on the effect of COVID-19 vaccination on transmission of COVID-19.

Main findings

- Evidence shows a **reduction in SARS-CoV-2 transmission from vaccinated people**; however, the dominant variant at the time of these studies was B.1.1.7 (Alpha) rather than B.1.617.2 (Delta).

- Findings from more **recent studies are uncertain on the effects of vaccination on transmission**, which may be due to the replacement of the Alpha variant with Delta.
- Most **direct evidence is limited to transmission within household settings** therefore **there is a gap in the evidence on risk of transmission in other settings** such as schools, care homes, hospitals, workplaces and social venues, and in vulnerable populations.
- Overall, the **effectiveness of vaccination in reducing transmission appears to be higher in fully vaccinated individuals, compared with partial vaccination.**
- Protection against onward transmission **waned within 3 months post second vaccination**, for both Alpha and Delta (Eyre et al. 2021; preprint only).
- Although **cycle threshold (Ct) values are used as a proxy for viral load**, the relationship between viral load and infectiousness is not fully evidenced.

Best quality evidence

- University of Calgary (COVID-END) rapid literature review: https://sporevidencealliance.ca/key-activities/covid-19-evidence-synthesis/

Policy Implications

- The Delta variant is currently dominant in Wales, however most **studies focused on the Alpha variant,** with a relative **lack of evidence on the transmission of the Delta variant** (currently dominant in Wales) and settings other than households.
- Given limited evidence on the effectiveness of vaccination on transmission of Delta in households and other settings, **other preventative measures** to reduce transmission may still be required.
- **Further research is indicated** to better understand transmission, specifically – in this context – the effect of vaccination on transmission of the SARS-CoV-2 Delta variant and other variants of concern in different cohorts and settings.
- **Full immunisation** (rather than partial) should be encouraged.
- **Evidence of waning immunity** supports booster vaccines.

Strength of Evidence

- Most included studies were **observational,** where **confounding factors** were not always adjusted for, therefore the quality of the available evidence is assessed as 'low'.

Contents

Abbreviations:

Acronym	Full Description
AZ	AstraZeneca vaccine
CI	Confidence interval
COVID-19	Coronavirus disease 2019
Ct	Cycle threshold
HCW	Healthcare workers
IQR	interquartile range
mRNA	Messenger RNA
OR	Odds Ratio
PfBNT	Pfizer BioNTech vaccine
RoB	Risk of Bias
RT-PCR	Reverse transcription polymerase chain reaction test
VE	Vaccine Effectiveness
VOC	Variant of concern

1. BACKGROUND

This Rapid Review is being conducted as part of the Wales COVID-19 Evidence Centre Work Programme. The above question was developed through collaboration with a range of stakeholders including Welsh government, the WCEC core team and Health Technology Wales.

1.1 Purpose of this review

Since December 2020, infections with SARS-CoV-2 and the respective disease, COVID-19 (Coronavirus Disease 2019), have spread worldwide. On 11 March 2020, WHO declared the COVID-19 outbreak a pandemic (WHO 2021). COVID-19 has represented a serious threat to public health reporting nearly 5,151,643 deaths and 256,966,237 confirmed cases globally. As of 22 November 2021, approximately 7.4 billion vaccine doses have been administered (WHO 2021).

Since the vaccine roll out, much of the research has been focussed on vaccine safety and efficacy, with large clinical trials confirming that vaccines are generally effective against symptomatic COVID-19 infection. There are different types of vaccines that have been developed by different manufacturers; at the time of this report, Moderna, Oxford/AstraZeneca (AZ) and Pfizer/BioNTech (PfBNT) are used in the UK and all offer some protection against COVID-19 (Shapiro et al. 2021). However, breakthrough infections can still occur, and the effectiveness of vaccines against transmission from infected vaccinated people to susceptible contacts is unclear.

Vaccination aims to prevent onward transmission by at least two mechanisms: (i) preventing infection, thereby reducing the number of infectious individuals, and (ii) reducing transmission from vaccinated people who do become infected (Eyre et al.). Ct values have been referred to as indicative of viral load and infectiousness. A Ct value is defined as the number of amplification cycles required to reach a fixed background level of fluorescence at which the diagnostic result of the real-time polymerase chain reaction (PCR) changes from negative (not detectable) to positive (detectable) (PHE 2020). Public Health England (has since become the United Kingdom Health Security Agency (UKHSA)) have reported that a high Ct value indicates a low concentration of viral genetic material (viral load) which is typically associated with a lower risk of infectivity(PHE 2020) (PHE 2020). In the context of an upper respiratory tract sample, a high Ct may also represent scenarios where a higher risk of infection remains – for example, early infection, inadequately collected or degraded sample. Although, in the absence of clinical context, a single Ct value cannot be relied upon for decision making about a person's infectivity (PHE 2020). However, studies on direct transmission are lacking compared with studies on Ct values.

There are large household studies reporting on direct transmission that show vaccination reduces, but does not eliminate, onward transmission of the Alpha variant.(Harris et al. 2021, de Gier et al. 2021). However, whether vaccination reduces onward transmission of the Delta variant remains unclear. Despite the successful development and distribution of the vaccines, newly reported COVID-19 cases continue to rise globally (Elliott et al. 2021).

The purpose of this rapid review is to identify and examine evidence on the transmission risk of SARS-CoV-2 from vaccinated people to unvaccinated or vaccinated people.

2. RESULTS

2.1 Overview of the Evidence Base

For this review we updated evidence from a rapid literature review undertaken by the University of Calgary Health Technology Assessment unit and published by (Salmon et al. 2021), which was identified in our search. This rapid literature review include data on the following outcomes that are also of relevance to this review:

- Direct transmission from vaccinated people to both vaccinated and unvaccinated people,
- Ct values,
- Viral load.

We therefore used this review as a source of outcome data for studies up to the last date searched by the authors (23 August 2021). We then searched for additional evidence (published from 23 August 2021 until our last date of search, 5 October 2021) or earlier studies that were not included in the existing review. We identified an additional nine studies that reported on direct transmission, Ct values and viral load.

In total, 35 studies were included in this review: one randomised controlled trial (RCT), one post-hoc analysis of an RCT, 13 prospective cohort studies, 16 retrospective cohort studies and four case control studies

2.2 Vaccine Effectiveness against Direct Infection Transmission

The University of Calgary review included six studies that reported on the effectiveness of vaccines against disease transmission. We identified a further three relevant studies published after the Calgary review searches, resulting in a total of nine observational studies reporting direct transmission. All the included studies examined vaccine effectiveness against the B.1.1.7 (Alpha) variant, and only one included the B.1.617.2 (Delta) variant. The type of vaccines used varied (PfBNT, Moderna, J&J and AZ vaccines). Two studies, Shah et al. (2021) and Harris et al. (2021) had a moderate overall risk of bias, whilst the rest were scored as serious for overall risk of bias (Eyre et al. 2021, Braeye et al. 2021, Rovida et al. 2021, Gazit et al. 2021, de Gier et al. 2021, Layan et al. 2021, Salo et al. 2021).

A retrospective cohort study undertaken in the UK reported on the impact of mRNA-based (PfBNT or AZ) vaccination on transmission of both the Alpha and Delta variants (Eyre et al. 2021). The study, which used data from NHS Test and Trace, reported on the vaccination status of the index case and the contact, and included unvaccinated, partially vaccinated, and fully vaccinated people. Eyre et al. (2021) included 108,498 adult index cases (symptomatic and asymptomatic) and 146,243 contact cases (Alpha 41.3%, Delta 58.7%). Vaccination was found to reduce transmission of the Delta variant, but by less than the

Alpha variant. Compared with unvaccinated index cases, adjusted rate ratio for transmission of the Alpha variant from fully vaccinated index cases was 0.48 (95% confidence interval [CI] 0.30 to 0.78) with AZ and 0.32 (95% CI 0.21 to 0.48) with PfBNT. For the Delta variant, adjusted rate ratio was 0.76 (95% CI 0.70 to 0.82) with AZ and 0.50 (95% CI: 0.39 to 0.65) with PfBNT. There was no evidence of difference in transmission after two doses between vaccines for the Alpha variant (heterogeneity rate ratio, hRR=1.51[0.81 to 2.85]). Two BNT162b2 doses reduced transmission of Delta by more than ChAdOx1 (aRR=0.50[0.39-0.65] vs. aRR=0.76[0.70-0.82, respectively, hRR=1.51[1.15-1.97]) PCR-positivity was highest in unvaccinated contacts (52%) followed by those partially vaccinated (AZ: 32%, PfBNT: 32%) and lowest for the fully vaccinated (AZ: 22%, PfBNT: 17%).

Eyre et al. (2021) also found protection against onward transmission waned within three months post second vaccination. For Alpha, some protection against transmission remained, but for the Delta this eroded much of the protection against onward transmission, particularly for the AZ vaccine. For Delta and PfBNT, reductions at 2 and 12 weeks were 50% (35-61%) and 24% (20-28%), respectively, and 24% (18-30%) and 2% (−2-6%) for AZ. The authors adjusted for confounding factors including age, sex, local deprivation and time since vaccination.

A similar Belgian retrospective cohort study (Braeye et al. 2021) used contact tracing to report on vaccine effectiveness against onwards transmission from fully or partially vaccinated index cases to high-risk contacts (contacts for longer than 15 minutes at less than 1.5m without face masks, or direct physical contact). 80% of the strains identified in this study were the B.1.1.7 (Alpha) strain. Index cases (n=131,283) were confirmed COVID-19 positive using RT-PCR testing and contacts (n=301,741) were defined as someone without a positive COVID-19 test in the previous 90 days who had contact with an infected person. The vaccine effectiveness against onwards transmission was estimated at 62% (95% credibility intervals (CrI) 57 to 67) for PfBNT and 52% (95% CrI 33 to 69) for Moderna for full vaccination. No significant effect against onward transmission was found for the 'viral-vector'-vaccines (AZ and Janssen), but credibility intervals were large. This may be due to the small population size for these specific vaccines, meaning accurate conclusions cannot be made. Vaccination with mRNA-vaccines (PfBNT and Moderna) had a similar effect to previous infection, but two doses were required to achieve this effect.

Braeye et al. (2021) reported that the mRNA vaccines provided a level of high protection and had significant effects on transmission when both index cases and contacts were fully vaccinated. Although the sample size was large in this study, only a small proportion were vaccinated. Previous infections and household exposure were adjusted for.

Another study by Rovida et al. (2021) drew similar conclusions, however the sample size was smaller. The study reported on virus transmission of 33 fully vaccinated (PfBNT) COVID-19 positive individuals, with transmission to family members or close contacts being reported in two cases (6.1%). All individuals analysed were also infected with the Alpha variant.

The University of Calgary (Salmon et al. 2021) reported on six large household surveillance studies from the UK, Netherlands, Finland, and Israel suggesting that a full dose of PfBNT,

Moderna, AZ, or Johnson & Johnson (J&J) vaccines may prevent household transmission of wild-type or Alpha variant after 14 days of vaccination.

Shah et al. (2021) and Harris et al. (2021) both evaluated the risks of transmission after vaccination in UK households (Shah et al. 2021) included 194,363 household members of 144,525 healthcare workers, who had been vaccinated with either the PfBNT or the AZ vaccine. Household members of fully vaccinated healthcare workers had significantly lower risk of infection and hospitalisation (rate per 100 person-years of 9.40 versus 2.98, hazard ratio [HR]: 0.46 [95% CI: 0.30 to 0.70]; and 0.51 versus 0.22 per 100 person-years, HR: 0.68 [95% CI: 0.17-2.83], respectively).

Harris et al. (2021) also conducted a UK retrospective cohort study, to determine whether vaccinated individuals are less likely than unvaccinated cases to transmit COVID-19 to their unvaccinated household contacts. The study included 365,447 residential households of two to ten people with at least one index case, with 1,018,842 household contacts and 102,662 secondary cases. The authors concluded that there is evidence of reduced transmission to household contacts from index cases who have received one dose of either vaccine (PfBNT or AZ).

A retrospective cohort study in the Netherlands by de Gier et al. (2021) assessed vaccine effectiveness against transmission to household members and close contacts of index cases. The study had a large sample size of 113,582 index cases, 142,540 household contacts and 110,628 other close contacts. Fully vaccinated individuals were associated with the reduction of transmission of COVID-19 to any household contact by 71% (95% CI: 63 to 77), 73% (95% CI: 65 to 79) to any unvaccinated household contact, 22% (95% CI: −5 to 43) to any other close contact, and 24% (95% CI: −5 to 43) to any unvaccinated close contact. The authors did not adjust for confounding factors such as sex and deprivation, which may have introduced bias into the results.

Another retrospective cohort study was conducted in Finland, that investigated vaccine effectiveness (PfBNT or Moderna) for vaccinated and unvaccinated healthcare workers to unvaccinated household members. At 10 weeks post first vaccination, Salo et al. (2021) reported the highest reduction in transmission to unvaccinated spouses (42.9% [95% CI: 22.3 to 58.1]) and to unvaccinated children between the ages of 3 and18 years old, 32.9% (95% CI: 4.1 to 53.0).

Salmon et al. (2021) also reported on two studies from Israel that found fully vaccinated individuals had a reduced transmission to their household contacts. Both studies examined the PfBNT vaccine, Gazit et al. (2021) found reduced infection transmission of the wild-type strain by 80.0% (95% CI: 73.0 to 85.1) compared to those who were unvaccinated. Layan et al. (2021) reported the risk of transmission from vaccinated cases was 0.22 times (95% CI: 0.06 to 0.70) the risk of transmission from unvaccinated cases. It should be noted that the COVID-19 status of healthcare workers was confirmed through RT-qPCR, while the status of household members was self-reported.

2.2.1 Bottom line results for Vaccine Effectiveness against Transmission

All studies reported a reduction in transmission of the Alpha variant from partial and fully vaccinated individuals. Overall, vaccine effectiveness on transmission appears to increase with fully vaccinated individuals, compared with partial vaccination.

Further research is needed on vaccine effectiveness on transmission of variants of concerns, in particular the Delta variant. Also, the addition of further studies that adequately address relevant confounding variables would provide more certainty to the evidence reported.

2.3 Cycle Threshold (Ct) Values

Cycle threshold (Ct) values are an inverse proxy for viral load (PHE 2020). In total there were 22 observational studies and one RCT that reported Ct values of vaccinated individuals. All studies included either the PfBNT, Moderna or AZ vaccines.

Nine UK studies reported on the Ct values of vaccinated people (Emary et al. 2021, Pritchard et al. 2021, Shrotri et al. 2021, Baltas et al. 2021, Lumley et al. 2021, Jones et al. 2021, Singanayagam et al. 2021, Elliott et al. 2021, Pouwels et al. 2021).

Emary et al. (2021) reported results from a Phase 2/3 trial where participants were randomised 1:1 to receive the AZ vaccine or a meningococcal vaccine as a comparator. Participants provided routine weekly swabs during the trial and were also required to provide swab samples if they developed suspected COVID-19 at any time. Nasal and throat swabs were sequenced from 256 participants and the group that received the AZ vaccine showed significantly lower viral load compared with the control group, as represented by minimum PCR Ct value ($p<0.0001$). Furthermore, participants vaccinated against COVID-19 were PCR-positive for a shorter period of time ($p<0.0001$). Emary et al. (2021) recruited early in the pandemic between October 2020 and January 2021, therefore the Delta (B.1.617) variant was not reported on in this study. The study also scored high risk of bias overall, with high bias in missing outcome data and some concerns with randomisation, deviation from intended intervention and selection of reported results.

A longitudinal UK study assessed Ct values of vaccinated people against the Alpha and Delta variant (Pouwels et al. 2021). The study ran from December 2020 to August 2021, with the Delta variant being assessed from the May 2021 to August 2021. For the Alpha variant, Pouwels et al. (2021) reported significantly higher Ct values (median 33.3) from individuals vaccinated with a single dose compared with seronegative unvaccinated individuals (median 28.7; $p=0.02$) but not compared with seropositive unvaccinated individuals (median 32.8, $p=0.72$). For the Delta variant, infections occurring despite either vaccine have similar peak viral burden to those in unvaccinated individuals, however exact figures were not reported.

Baltas et al. (2021) and Lumley et al. (2021), two UK studies, reported no significant difference in the median Ct values of vaccinated people compared with unvaccinated (see Table 9). However, a longitudinal UK household survey by (Pritchard et al. 2021) found a statistically significant increase in the median Ct values of partially or fully vaccinated people ($p<0.001$). Similarly, in another UK study from Elliott et al. (2021), Ct values were analysed

and compared for positive vaccinated and unvaccinated individuals as a proxy for infectiousness. Median Ct values were higher for vaccinated participants at 27.6 (95% CI 25.5 to 29.7) compared with unvaccinated at 23.1 (95% CI 20.3 to 25.8). The Delta variant completely replaced the Alpha variant during the period of the study.

In another UK study, Ct values were analysed for vaccinated healthcare workers (n=3535) and unvaccinated healthcare workers (HCWs) (n=3252). Jones et al. (2021) reported a non-significant trend towards increase between unvaccinated and vaccinated HCWs after 12 days post-vaccination (median 20.3 versus 30.3), suggesting that samples from infected vaccinated individuals had lower viral loads. However, a further UK longitudinal study conducted between September 2020 and September 2021 compared viral load (VL) trajectories from fully-vaccinated cases of Delta infection (n=19) with unvaccinated Delta (n=10), Alpha (n=39) and pre-Alpha (n=49) infections. The authors reported that fully vaccinated individuals with breakthrough infections had peak upper respiratory tract viral load similar to unvaccinated cases and could efficiently transmit infection in household settings, including to fully vaccinated contacts (Singanayagam et al. 2021).

In a different UK study, Shrotri et al. (2021) initially found no significant difference (p=0.158) in the mean Ct values of unvaccinated individuals (26.6 [95% CI: 26-27.1]) compared with partially vaccinated individuals (26·6 [95% CI: 25.19-26.62]). However, after 28 days, there was a statistically significant decrease in the mean Ct between vaccinated and unvaccinated persons (mean Ct 26.6 [95% CI: 26-27.1] vs 31·3 [95% CI: 29.6-32.9], p<0·001), which could be indicative of reduced risk of transmission.

Three USA studies reported similar findings of no significant difference in Ct values of vaccinated and unvaccinated people (Jacobson et al. 2021, Riemersma et al. 2021, Mostafa et al. 2021). Jacobson et al. (2021) investigated the Ct values of healthcare workers within 14 days of partial vaccination and after 14 days of partial vaccination (See Table 9). Riemersma et al. (2021) included the Ct values of RT-PCR SARS-CoV-2 positive people from a single Wisconsin commercial laboratory with self-reported vaccination status between June 28 and July 24, 2021. Forty-two people were identified with the Delta infection and the authors reported no significant difference in Ct values (p=0.61). Mostafa et al. (2021) conducted a longitudinal cohort study of healthcare workers who were offered voluntary PCR testing every two weeks. The authors found no difference in median Ct values for the vaccinated (n=49) and the unvaccinated (n=96) groups (19.26 [interquartile range, IQR: 16.56-21.96] vs 19.6 [IQR: 16.28-22.66], respectively).

Different findings were reported in a study among community living residents in the USA, Ct values were analysed from five cases of asymptomatic infections. The median Ct values for unvaccinated residents (12.8, IQR: 12.4-14.9) were significantly lower (p=0.009) than vaccinated residents (19.4, IQR: 18.9-25.5). The authors also reported that viral load was statistically lower among the vaccinated cohort (p=0.004) (McEllistrem et al. 2021). Also, in a retrospective study in Israel, vaccinated individuals were compared with a demographically matched control group of unvaccinated individuals. Between 12 and 28 days after the first dose, Ct values were significantly higher for vaccinated people than the controls (Levine-Tiefenbrun et al. 2021). In another large cohort study in Israel, Ct values amongst fully vaccinated healthcare workers were significantly higher than unvaccinated healthcare workers (mean difference 5.09, 95% CI: 2.8-7.4, p<0.001) (Regev-Yochay et al. 2021).

A small study, set in a legal gold mine in French Guiana, reported low Ct values (Ct <28) for vaccinated miners that had become infected with the Gamma variant (18/23 (78.2%). Vignier et al. (2021) suggested that full vaccination was not sufficient to prevent symptomatic SARS-CoV-2 infection and its transmission in this context of communal life without masks. However, this study did not include an unvaccinated cohort for comparison, and the occupation of participants may reduce the generalisability of the findings. Similarly, Shitrit et al. (2021) reported low (median 19.9 [IQR: 17.8, 25.1]) Ct values for vaccinated patients in a nosocomial outbreak caused by the Delta variant in Israel, however, unvaccinated individuals were not included.

Another US study reported no significant difference in viral RNA loads using Ct values between fully vaccinated breakthrough cases and unvaccinated cases (p=0.99). Venice et al. (2021) reported higher viral loads for the following variants of concern: Gamma (p=0.00076, Δ Ct = 2.5), Delta (p=0004, Δ Ct = 2.1), and Epsilon (p=0.047, Δ Ct = 1.2) variants, but not for the Alpha, Beta, and Iota variants.

A study conducted in Greek healthcare workers found no statistically significant differences between the median Ct values for those that were vaccinated and unvaccinated (18 [15.5-25.5] vs 18.5 [13.5-24]) (Ioannou et al. 2021). Similarly, long-term care residents in France showed no difference in median Ct values of the unvaccinated residents, (Median=21 [IQR:13-32] vs 15 [IQR: 12-17]; p=0.05) (Bailly et al. 2021). However, a matched case-control study evaluating Ct values of fully vaccinated individuals with breakthrough infections, conducted by Abu-Raddad et al. (2021) in Qatar, did find a difference. When compared with the matched unvaccinated individuals, median Ct values were statistically significantly higher in the vaccinated cohort (p<0.001).

2.4 Viral load

The University of Calgary (Salmon et al. 2021) reported on two USA studies that examined viral load of vaccinated and unvaccinated people. A prospective cohort study by Thompson et al. (2021) investigated nasal swab viral loads of healthcare workers across Arizona. The authors found a lower presence of virus in partially and fully vaccinated people compared with the unvaccinated cohort (2.3+1.7 Log10 copies/mL vs. 3.8+1.7 Log10 copies/mL). This represented a 40.2% lower viral RNA load after at least partial vaccination. The second was a small retrospective cohort study of vaccinated (n=5) and unvaccinated (n=5) residents with asymptomatic COVID-19 (virus variant not reported) at a single nursing home. The study found that the viral load was significantly lower in the vaccinated cohort with at least one dose of the vaccine (p=0.004) (McEllistrem et al. 2021).

We identified two relevant viral load studies published after the University of Calgary review (Rovida et al. 2021, Rolando et al. 2021). Rolando et al. (2021) reported a post-hoc analysis of a randomised controlled trial (RCT) in the US. In the analysis, viral variants were sequenced, and viral copy number and shedding were assessed in 799 adjudicated COVID-19 cases in the per-protocol set from the blinded portion of the RCT. The authors found that vaccination significantly reduced SARS-CoV-2 viral copy number on the day of diagnosis

compared with placebo (4.1, [95% CI 3.4 to 4.8] versus 6.2 [95% CI 6.0 to 6.4] log10 copies/ml).

Rovida et al. (2021) analysed cell cultures in 21 of 33 vaccinated individuals with breakthrough infections. Virus isolation was not performed in the unvaccinated control group, so comparable data was not reported. The authors could only detect infectious virus in half of the cases. Rovida et al. (2021) suggested that the low detections of infectious virus relate to lower contagiousness, along with the lower severity, of the vaccine breakthrough infections.

2.4.1 Bottom line results for Ct values and viral load

There is evidence that Ct values are higher in vaccinated people, including from a UK RCT and a US post-hoc analysis of a RCT, though these trials did not include evidence on the Delta variant. Of the studies that did include the Delta variant, findings were more variable, with three studies reporting a significant difference between vaccinated and unvaccinated people, and four reporting a nonsignificant difference. There were a small number of studies found that reported directly on viral load, although all these reported similar findings of a significant reduction in viral load for vaccinated people. It should be noted that none of the viral load studies included evidence on the Delta variant.

2.5 Risk of Bias Assessment

We used the ROBIS tool to undertake the risk of bias assessment on the University of Calgary review (Salmon et al. 2021) that we have adapted. The review scored low across all domains except for synthesis and findings. This was due to the heterogeneity of the studies.

We extracted risk of bias scores for the relevant studies from the University of Calgary review and conducted risk of bias assessments on the additional studies identified using the same tools (RoB2 for RCTs and ROBINS-I for non-randomised studies) for consistency (see Tables 2-4). The one RCT identified had a high overall bias score due to missing outcome data. The post-hoc analysis of an RCT scored low across all domains. Across the 33 observational studies, 17 were rated as moderate on risk of bias due to confounding, with 10 rated as high and six rated as low. On risk of bias for participant selection, 12 were rated as low, 15 as moderate and six were rated as serious. On bias in classification of interventions, all studies were rated as low, apart from two that were rated as moderate. With respect to bias due to deviations from intended interventions, none were rated as serious, one was no information, 21 were rated as low and 11 were rated as moderate. For bias due to missing data, 16 studies scored low, nine were rated as moderate, three were serious and five did not have sufficient information. Across the outcome measurement domain, one was rated as serious, 28 were scored as low and the rest were moderate. On bias in selection of reported results, the majority of studies did not have sufficient information (17), 13 were rated as low and 3 were rated as moderate. On the overall risk of bias domain, 17 studies were rated serious, 14 were rated as moderate risk of bias and two were critical.

2.6 Ongoing research

The UK Health Security Agency (UKHSA) are currently setting up a living review on the effect of COVID-19 vaccination on transmission of COVID-19. The Wales COVID-19 Evidence Centre (and Health Technology Wales) are collaborating with the UKHSA on this ongoing work but the exact scope and timelines for this work, including frequency of updates, are yet to be finalised.

We also identified four ongoing studies of relevance: one randomised controlled trial, two systematic reviews and one rapid review (Table 1). The purpose of the RCT is to assess SARS CoV-2 infection, viral shedding, and subsequent potential transmission in individuals immunised with the Moderna COVID-19 vaccine. A primary outcome of the trial is peak viral load in nasal samples from participants diagnosed with SARS-CoV-2 infection. The variant of concern (VOC) has not been specified and the trial is currently still in the recruiting stage (National Institute of Allergy and Infectious Diseases (NIAID) 2021).

One of the systematic reviews is planning on conducting meta-analyses and the main outcomes include prevalence of variants of concern, the mutations, transmissibility, severity of illness, and effectiveness of vaccination (Ahmed et al.). This review may address some of the gaps in the evidence around variants of concern, however the review is only including observational studies (case reports, case series, cohort studies). The anticipated completion date for the review is Jan 2022. McIntosh et al. (2021) are conducting a systematic review to answer the question: does the COVID-19 vaccine reduce onward transmission of COVID-19 infection in people who have been vaccinated. Outcomes of the study include viral loads from nasopharyngeal swabs in the form of Ct values and incidence of asymptomatic covid cases. Hooper et al. (2021) are doing a rapid review which also has viral load as a main outcome, along with secondary transmission and transmission of laboratory-confirmed COVID-19 to unvaccinated contacts. Neither study specific whether variants of concern will be identified or reported.

Table 1. Design and characteristics of ongoing research

Study title/ID	Design	Intervention	Outcomes	Estimated Completion Date
NCT04811664 National Institute of Allergy and Infectious Diseases (NIAID) (2021)	Randomised controlled trial (RCT) Up to 12,000 participants will be randomized 1:1 to Immediate Vaccination Group 1 (at Months 0 and 1) or Standard of Care Group 2, with vaccination given at Months 4 and 5 if not received off-study previously. Up to an additional 6,000 participants will be enrolled into the Vaccine Declined Group 3 and will also	Moderna COVID-19 Vaccine (mRNA-1273)	Efficacy of Moderna COVID-19 Vaccine against SARS-CoV-2 infection. SARS-CoV-2 infection diagnosed by PCR among participants who were SARS-CoV-2 seronegative at enrolment Effect of Moderna COVID-19 Vaccine on peak nasal viral load as a measure of infection and a proxy of infectiousness, peak viral load in nasal samples from participants diagnosed with SARS-CoV-2 infection among participants who were SARS-CoV-2 seronegative at enrolment.	22 December 2021

	be offered vaccine at Months 4 and 5.			
Ahmed et al. (2021) Prevalence and Impact of SARS-COV-2 Variant of concern (VOC) on disease transmissibility and effectiveness of vaccination: A systematic review and meta-analysis	Systematic review and meta-analysis Types of studies to be included: case reports, case series, possibly cohort studies, and cross-sectional studies.	Mutations in Variant of Concerns/COVID-19	The main outcome is to report the prevalence of VOC, the mutations, transmissibility, severity of illness, and effectiveness of vaccination. Measures of effect • association between VOC and the transmissibility • association between the VOC and severity of illness • association between VOC and the effectiveness of the vaccine	26 January 2022
McIntosh et al. (2021) Systematic review of the efficacy of the COVID-19 vaccine in reducing disease transmission	Systematic review Types of study to be included Exclusion: Not clinical trial, not RCT, not cohort study, not cross-sectional study, not case study, not observational study Will include epidemiological models if not simulating real-world data that has not yet been presented Will exclude molecular modelling drug-design studies.	COVID-19 vaccination. This includes any of the currently available COVID-19 vaccines (examples include Pfizer, Moderna, Janssen, AstraZeneca). The exposure may be after the first or second dose of the COVID-19 vaccine.	Included studies will have reported outcomes on COVID-19 vaccine effects on onward disease transmission of COVID-19. These reported outcomes will be measured in viral loads from nasopharyngeal swabs in the form of Ct values. These reported outcomes may also measure the incidence of asymptomatic covid cases (measured from COVID-19 positive nasopharyngeal swabs) post vaccination Viral load: Ct values/cycles (1 Ct unit/cycle is equal to 1.94 viral particles per sample), IQR (where available), 95% confidence intervals Asymptomatic nasopharyngeal swabs: number of cases, person-years, vaccine efficacy percentage, 95% confidence intervals, IRR (where available), p-values (where available)	31 May 2021
Hooper et al. (2021) Transmission of COVID-19 following COVID-19 vaccination: protocol for a rapid review	Rapid Review Types of study to be included Randomised controlled trial, cohort study or case-control study	Intervention or Exposure: part or full vaccination against COVID-19, any COVID-19 specific vaccination	Secondary transmission, transmission of laboratory-confirmed COVID-19 to unvaccinated contacts (assessed as direct transmission by genomic analysis or proximity, such as household members), (secondary cases) Indirect outcomes: • viral load • illness severity	31 August 2021

Table 2: ROBIS Risk of Bias for Systematic Reviews

Author	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Overall Bias
Salmon et al. (2021)	Low	Low	Low	Serious	Low

Table 3: Cochrane Risk of Bias Assessment for RCT

Author	Randomization	Deviation from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported results	Overall Bias
Rolando et al. (2021)	Low	Low	Low	Low	Low	Low
Emary et al. (2021)	Some concerns	Some concerns	High	Low	Some concerns	High

Table 4: ROBINS-I Risk of Bias for non-RCTs

Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall Risk of Bias
Abu-Raddad et al. (2021)	Low	Low	Low	Low	Low	Low	NI	Moderate
Singanayagam et al. (2021)	Serious	Serious	Low	Low	Low	Low	Low	Serious
Baltas et al. (2021)	Moderate	Serious	Low	Moderate	Low	Low	Low	Serious
Bailly et al. (2021)	Serious	Moderate	Low	Moderate	Moderate	Moderate	NI	Serious
Braeye et al. (2021)	Moderate	Moderate	Low	Low	Serious	Low	Low	Serious
de Gier et al. (2021)	Serious	Serious	Low	Low	Low	Moderate	NI	Serious
Duerr et al. (2021)	Low	Low	Low	Low	Serious	Serious	NI	Critical

Elliott et al. (2021)	Moderate	Low	Low	Low	NI	Low	Low	Moderate
Eyre et al. (2021)	Moderate	Moderate	Low	Low	Serious	Low	Low	Serious
Gazit et al. (2021)	Moderate	Serious	Low	Moderate	Low	Low	NI	Serious
Harris et al. (2021)	Moderate	Low	Low	Low	Moderate	Low	NI	Moderate
Ioannou et al. (2021)	Moderate	Moderate	Low	Moderate	Low	Low	NI	Moderate
Jacobson et al. (2021)	Moderate	Serious	Low	Moderate	Moderate	Moderate	Low	Serious
Jones et al. (2021)	Moderate	Low	Low	Low	NI	Low	NI	Moderate
Layan et al. (2021)	Serious	Serious	Low	Moderate	Low	Low	NI	Serious
Levine-Tiefenbrun et al. (2021)	Moderate	Low	Low	Low	NI	Low	NI	Moderate
Lumley et al. (2021)	Low	Low	Low	Low	Moderate	Low	Moderate	Moderate
McEllistrem et al. (2021)	Moderate	Low	Low	Low	Low	Low	NI	Moderate
Mostafa et al. (2021)	Moderate	Serious	Low	NI	Low	Low	NI	Serious
Muhsen et al. (2021)	Moderate	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
Pouwels et al. (2021)	Moderate	Serious	Low	Moderate	Low	Low	Low	Serious
Pritchard et al. (2021)	Low	Low	Low	Low	Moderate	Low	Moderate	Moderate
Regev-Yochay et al. (2021)	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Riemersma et al. (2021)	Serious	Serious	Low	Moderate	Moderate	Low	NI	Critical
Rovida et al. (2021)	Serious	Serious	Low	Low	NI	Low	Low	Serious
Salo et al. (2021)	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	NI	Serious
Shah et al. (2021)	Moderate	Moderate	Low	Low	Low	Low	NI	Moderate
Shitrit et al. (2021)	Serious	Serious	Low	Low	Low	Low	Low	Serious
Shrotri et al. (2021)	Moderate	Low	Low	Low	Moderate	Low	NI	Moderate
de Souza et al. (2021)	Low	Low	Low	Low	Low	Low	NI	Moderate
Thompson et al. (2021)	Serious	Serious	Moderate	Moderate	Low	Low	Low	Serious
Venice et al. (2021)	Serious	Serious	Low	Low	NI	Low	Low	Serious
Vignier et al. (2021)	Serious	Serious	Low	Low	Low	Low	Low	Serious

Table 5: Observation Studies of Vaccine Effectiveness Against Transmission to Household Contacts (Salmon et al. 2021)

Vaccine	Author	Country	Dose	Follow-up days*	Outcomes*	Vaccine Effectiveness (95% CI)+
	Harris et al. (2021)	England	1	14-16	Transmission to household contact	OR: 0.73 (0.62-0.83) [Estimated VE: 25%]
	Harris et al. (2021)	England	1	≥21	Transmission to household contact	aOR: 0.51 (0.44, 0.59) [Estimated VE: 46%]
	Harris et al. (2021)	England	1	28-34	Transmission to household contact	OR: 0.62 (0.52-0.74) [Estimated VE:35%]
	de Gier et al. (2021)	Netherlands	1	>14	Transmission to household contact	Adjusted VE 26% (95% CI: 12-37)
	de Gier et al. (2021)	Netherlands	2	>7	Transmission to household contact	Adjusted VE 70% (95% CI: 61-77)
	Gazit et al. (2021)	Israel	1	0-7	Transmission to vaccinated household contact	94% (95% CI: 90.8-95.7)
	Gazit et al. (2021)	Israel	2	>7	Transmission to vaccinated household contact	70.1% (95% CI: 61.3-76.9)
	Layan et al. (2021)	Israel	2	>7	HCW transmission to household contact	78% (95% CI: 30-94)
	Singanayagam et al. (2021)	UK	2	>14	Transmission to household contact	45% (bootstrap 95% CI: - 84% to 77%)
Pfizer, BioNTech (BNT162b2)	Braeye et al. (2021)	Belgium	1 or 2	>7	Transmission to any high-risk contact	62% (95% CrI 57–67)
	de Gier et al. (2021)	Netherlands	1	>14	Transmission to household contact	Adjusted VE 51% (95% CI: 8-74)
	de Gier et al. (2021)	Netherlands	2	>7	Transmission to household contact	Adjusted VE 88% (95% CI: 50-97)
Moderna (mRNA-1273)	Braeye et al. (2021)	Belgium	1 or 2	>7	Transmission to any high-risk contact	52% (95% CI 33–69)
Janssen (Ad26.COV2.S)	de Gier et al. (2021)	Netherlands	1	>14	Transmission to household contact	Adjusted VE 77% (95% CI: 6-94)
	Harris et al. (2021)	England	1	14-16	Transmission to household contact	OR: 0.78 (0.66-0.92) [Estimated VE: 21%]
AstraZeneca (ChAdOx1 nCoV-19)	Harris et al. (2021)	England	1	≥21	Transmission to household contact	aOR: 0.53 (95% CI 0.43-0.63) [Estimated aVE: 44%]

	Harris et al. (2021)	England	1	28-34	Transmission to household contact	OR: 0.44 (0.34-0.58) [Estimated VE: 54%]
	de Gier et al. (2021)	Netherlands	1	>14	Transmission to household contact	Adjusted VE 15% (95% CI: 4-26)
	de Gier et al. (2021)	Netherlands	2	>7	Transmission to household contact	Adjusted VE 58% (95% CI: -12-84)
BNT162b2 or ChAdOx1 nCoV-19	Shah et al. (2021)	Scotland	1	7-13	HCW Transmission to household	-8% (95% CI: -25 - 6)
	Shah et al. (2021)	Scotland	1	14-20	HCW Transmission to household	15% (95%CI:1-27)
	Shah et al. (2021)	Scotland	1	>28	HCW Transmission to household	36% (95% CI: 27-44)
	Shah et al. (2021)	UK	2	>14	HCW Transmission to household	54%(95% CI: 30-70)
Pfizer, BioNTech or Moderna, mRNA-1273	Salo et al. (2021)‡	Finland	1	14	Transmission to household contact (unvaccinated spouse)	8.7% (95% CI: -28.9-35.4)
	Salo et al. (2021)‡	Finland	1	70	Transmission to household contact (unvaccinated spouse)	42.9% (95% CI: 22.3-58.1)
	Salo et al. (2021)‡	Finland	1	14	Transmission to household contact (unvaccinated child 3-18 years)	-1% (95% CI: -53.9-33.7)
	Salo et al. (2021)‡	Finland	1	70	Transmission to household contact (unvaccinated child 3-18 years)	32.9% (95% CI: 4.1-53.0)
	Salo et al. (2021)‡	Finland	1	42	Transmission to household contact (unvaccinated child 3-12 years)	12.3% (95% CI: -37.4-44.0)
	Salo et al. (2021)‡	Finland	1	70	Transmission to household contact (unvaccinated child 3-12 years)	22.3% (95%CI: -34.4-55.2)
	Salo et al. (2021)‡	Finland	1	42	Transmission to household contact	16.7% (95% CI: -17.7-41.0)

					(unvaccinated child 13-18 years)	
	Salo et al. (2021)‡	Finland	1	70	Transmission to household contact (unvaccinated child 13-18 years)	38% (95% CI: 1.2-61.1)
Pfizer, BioNTech or Moderna, mRNA-1273 or AstraZeneca, ChAdOx1 nCoV-19 or Janssen, Ad26.COV2.S	de Gier et al. (2021)	Netherlands	1	>14	Transmission to household contact	Adjusted VE 21% (95% CI: 12-28)
	de Gier et al. (2021)	Netherlands	1	>14	Transmission to unvaccinated household contact	Adjusted VE 23% (95% CI: 14-32)
	de Gier et al. (2021)	Netherlands	1	>14	Transmission to any other close contact	Adjusted VE 22% (95% CI: 9-33)
	de Gier et al. (2021)	Netherlands	1	>14	Transmission to any unvaccinated close contact	Adjusted VE 22% (95% CI: 8-34)
	de Gier et al. (2021)	Netherlands	2	>7	Transmission to household contact	Adjusted VE 71% (95% CI: 63-77)
	de Gier et al. (2021)	Netherlands	2	>7	Transmission to unvaccinated household contact	Adjusted VE 73% (95% CI: 65-79)
	de Gier et al. (2021)	Netherlands	2	>7	Transmission to any other close contact	Adjusted VE 22% (95% CI: -5-43)
	de Gier et al. (2021)	Netherlands	2	>7	Transmission to any unvaccinated close contact	Adjusted VE 24% (95% CI: -5-43)

Table extracted and adapted from the University of Calgary review (Salmon et al. 2021). None of the studies excluded other sources of exposure.
Abbreviations: CI: confidence intervals; CrI: credibility intervals; OR: odds ratio; aOR: adjusted odds ratio, VE: vaccine effectiveness.
[+] VE =1-RR (or HR) x100%, where RR is the reported relative risk or Hazard ratio; or derived from reported baseline prevalence in unvaccinated group and OR
All studies included participants with unknown baseline serology except for Salo et al. who included participants who were seronegative

Table 6 Ct values (Salmon et al. 2021)

Vaccine	Author	Country	Virus type	Baseline Serology	1st or 2nd dose	Follow-up days	Sub-population	Ct Values (Vaccinated), Median (IQR), unless otherwise specified	Ct Values (Unvaccinated), Median (IQR), unless otherwise specified	Effect size/p-values
BNT162b2	Abu-Raddad et al. (2021)	Qatar	Wild type and B.1.1.7, B.1.351, B.1.617.2	Unknown	2	≥14	Breakthrough infection vs primary infection in unvaccinated	27.8 (21.1-32.7)	25.8 (19.5-31.4)	p <0.001
								Mean=26.8 (95% CI: 26.5-27.2)	Mean=25.5 (95% CI: 25.2-25.8)	Mean difference (95% CI): 1.3 (0.9-1.8), p<0.001
					2	≥14	Breakthrough infection vs reinfection in unvaccinated	28.2 (21.1-33.1)	31.2 (24.3-33.9)	p <0.001
								Mean=27 (95% CI: 26.3-27.6)	Mean=28.9 (95% CI: 28.3-29.5)	Mean difference (95% CI): 2.0 (1.1-2.8), p <0.001
	Bailly et al. (2021)	France	501Y.V2	Both	2	NR		21 (13-32)	15 (12-17)	p=0.05
	Ioannou et al. (2021)	Greece	B.1.1.7		2	>14		18 (15.5-25.5)	18.5 (13.5-24)	NR
	Eyre et al. (2021)	UK	B.1.1.7 and B.1.617.2	Unknown	2	NR		27.4(19.7-32.1)	18.4(15.7-22.5)	NR
	Jones et al. (2021)	UK	Wild-type and B.1.1.7	Unknown	1	≥12		30.3 (25.5-35.1)	23.3 (13.5-33)	ns
	Shitrit et al. (2021)	Israel	B.1.617.2	Unknown	2	NR		19.9 (IQR: 17.8–25.1)	NR	NR
	Levine-Tiefenbrun et al. (2021)	Israel	Wild type	Unknown	1	<12		NR	NR	no significant differences in the Ct values for any of the 3 genes

Vaccine	Author	Country	Virus type	Baseline Serology	1st or 2nd dose	Follow-up days	Sub-population	Ct Values (Vaccinated), Median (IQR), unless otherwise specified	Ct Values (Unvaccinated), Median (IQR), unless otherwise specified	Effect size/p-values
										(RdRp, N and E)
					1	12-28		NR	NR	the Ct values for the 3 genes were significantly higher among infected vaccinated persons than controls ($p<10^{-8}$)
	McEllistrem et al. (2021)	USA	Wild type	Unknown	1	NR	Asymptomatic COVID-19	19.4 (18.9-22.5)	12.8 (12.4-14.9)	p=0.009
	Muhsen et al. (2021)	Israel	Wild type	Seronegative	2	>14		32 (14.5)	26.7 (8.8)	p=0.008
	Vignier et al. (2021)	French Guiana	Gamma	Unknown	2	NR		78.2% had Ct <28	NR	NR
	Regev-Yochay et al. (2021)	Israel	Wild type	Both	2	≥11		Mean=27.3 (SD=2.2)	Mean=22.2 (SD=1.0)	Mean difference (95% CI): 5.09 (2.8-7.4), p<0.001
BNT162b2 or ChAdOx1	Baltas et al. (2021)	UK	Wild type and B.1.1.7	Unknown	1	9-24		30.8 (25.9-35.4)	28.8 (25.3-33.7)	P=0.053
	Lumley et al. (2021)	England	Wild type and B.1.1.7 (35% of unvaccinated seronegative;	Seronegative	NR	NR		Change in median: 2.7 (-0.5 to 6.7)		NR

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

Vaccine	Author	Country	Virus type	Baseline Serology	1st or 2nd dose	Follow-up days	Sub-population	Ct Values (Vaccinated), Median (IQR), unless otherwise specified	Ct Values (Unvaccinated), Median (IQR), unless otherwise specified	Effect size/p-values
					2	>14		33.3 (Q1, Q3: 31.6 to 34.0)		significantly higher than in those unvaccinated and not previously PCR/antibody-positive, age/sex-adjusted p=0.02).
					1	0 to 20	Delta (17 May 2021 to 13 Jun 2021)	29.93 (Q1, Q3: 22 to 34.21)	21.5 (Q1, Q3: 16.5 to 31.64) for not previously PCR positive; 30.86 (Q1, Q3: 29.5 to 34.28) for previously PCR positive	NR
					1 or 2	>21 for dose 1 or 0-13 for dose 2		30.07 (Q1, Q3: 18.64 to 33.64)		
					2	>14		32.29 (Q1, Q3: 26.07 to 33.93)		
					1	0 to 20	Delta (14 Jun 2021 to 1 Aug 2021)	25.64 (Q1, Q3: 21.64 to 30.79)	25.71 (Q1, Q3: 19.07 to 30.71) for not previously PCR positive; 22.29 (Q1, Q3: 16.57 to 30.29) for	NR
					1 or 2	>21 for dose 1 or 0-13 for dose 2		24.64 (Q1, Q3: 18.86 to 31.29		

Vaccine	Author	Country	Virus type	Baseline Serology	1st or 2nd dose	Follow-up days	Sub-population	Ct Values (Vaccinated), Median (IQR), unless otherwise specified	Ct Values (Unvaccinated), Median (IQR), unless otherwise specified	Effect size/p-values
					2	>14		25.29 (Q1, Q3: 19.21 to 31.29)	previously PCR positive	
BNT162b2 or Moderna mRNA-1273	Jacobson et al. (2021)	USA	Wild type and B.1.427/B.1.429 (34.3%)	Both	1	≤ 14	Early post vaccination vs. unvaccinated	Mean=22.6 (SD=7)	Mean=23 (SD=7.4)	NR
					1 or 2	up to 14 after 2nd dose	Partially vaccinated vs unvaccinated	Mean=27.7 (SD=8.7)	Mean=23 (SD=7.4)	NR
					2	>14	Fully vaccinated vs unvaccinated	Mean=28.5 (SD=7.4)	Mean=23 (SD=7.4)	NR
BNT162b2, Moderna, or Janssen	Duerr et al. (2021)	USA	Wild type, B.1.1.7, B.1.526, P1, and others	Unknown	1 or 2	≥14	Vaccination breakthrough infections	27 (13-42)	≤30	NR
					1 or 2	≥14	Vaccination breakthrough infections that passed quality control	24 (13-36)	≤30	NR
ChAdOx1	Eyre et al. (2021)	UK	B.1.1.7 and B.1.617.2	Unknown	2	NR		23.9(18.1-32.5)	18.4(15.7-22.5)	NR
	Emary et al. (2021)	UK	Wild type and B.1.1.7	Unknown	2	≥14	Asymptomatic	30.25 (24.81-34.20)	28.15 (19.51-32.35)	p=0.0040
					2	≥14	Symptomatic	20.49 (15.43-24.44)	17.9 (15.06-25.06)	p=0.1534
					2	≥14	Symptomatic and	19.34 (15.39-21.62)	15.03 (12.51-16.59)	p=0.0113

Vaccine	Author	Country	Virus type	Baseline Serology	1st or 2nd dose	Follow-up days	Sub-population	Ct Values (Vaccinated), Median (IQR), unless otherwise specified	Ct Values (Unvaccinated), Median (IQR), unless otherwise specified	Effect size/p-values
							asymptomatic B1.1.7			
					2	≥14	Symptomatic and asymptomatic not sequenced	29.52 (23.29-33.59)	25.57 (19.22-31.44)	p=0.0164
					2	≥14	Symptomatic and asymptomatic non-B.1.1.7 only	22.93 (17.54-29.4)	18.26 (15.15-25.57)	p=0.0201
Moderna (mRNA-1273)	Abu-Raddad et al. (2021)	Qatar	Wild type and B.1.1.7, B.1.351, B.1.617.2	Unknown	2	≥14	Breakthrough infection vs primary infection in unvaccinated	33.3 (29.6-34.8)	30.5 (23.5-33.7)	p<0.001
								Mean=31.2 (95% CI: 30.4-32.1)	Mean=28 (95% CI: 27-29.1)	Mean difference (95% CI): 3.2 (1.8-4.5), p<0.001
					2	≥14	Breakthrough infection vs reinfection in unvaccinated	33.1 (26.5-34.8)	33.1 (31.1-34.6)	p=0.104
								Mean=30 (95% CI: 28.3-31.7)	Mean=31.7 (95% CI: 30.5-32.9)	Mean difference: (95% CI): 1.7 (-0.4-3.8), p=0.104
NR	Riemersma et al. (2021)	USA	Wild type and B.1.617.2	NR	2	≥14		NR	NR	p=0.84
					2	≥14		NR	NR	p=0.99
					2	≥14		NR	NR	p=0.85
					2	≥14		NR	NR	p=0.61

Vaccine	Author	Country	Virus type	Baseline Serology	1st or 2nd dose	Follow-up days	Sub-population	Ct Values (Vaccinated), Median (IQR), unless otherwise specified	Ct Values (Unvaccinated), Median (IQR), unless otherwise specified	Effect size/p-values
	Elliott et al. (2021)	UK	B.1.1.7 and B.1.617.2	NR	2	>7		27.6 (25.5, 29.7)	23.1 (20.3, 25.8)	NR

This table was extracted and updated from the University of Calgary rapid review. (Salmon et al. 2021)

Abbreviations: CI: confidence intervals; IQR: interquartile range; NR: not reported; SD: standard deviation.

3. DISCUSSION

3.1 Summary of the findings

In this review we identified evidence from a rapid literature review conducted by the University of Calgary HTA unit, that reported on the transmissibility of COVID-19 among vaccinated individuals (Salmon et al. 2021). We also searched for evidence published after this review and identified one post-hoc analysis of an RCT and eight observational studies that reported on direct transmission, Ct values or viral load.

In total, we included nine studies for vaccine effectiveness against direct transmission from vaccinated people. All studies reported a reduction in transmission of the Alpha variant from partial and fully vaccinated individuals. Vaccine effect on transmission increased with fully vaccinated individuals, compared with partial vaccination. However, only one of the nine studies reported on the Delta variant, which is currently the dominant variant of concern in Wales. Eyre et al. (2021) conducted a large UK retrospective cohort study using the NHS Test and Trace database and reported a small reduction in transmission of the Delta variant from vaccinated people, but also reported that immunity substantially waned within three months post-vaccination. Further research is needed on vaccine effect on transmission of variants of concerns, in particular the Delta variant. There were also confounding factors that were not controlled or adjusted for in some of the studies, such as age, sex and previous COVID-19 infections. Further research that adequately addressed such confounders would add certainty and strengthen the conclusions that could be drawn around the risk of transmission in vaccinated populations.

We also included 19 studies for Ct values and four studies reporting directly on viral load, nine of which were conducted in the UK. There is evidence that Ct values are higher in vaccinated people; a well conducted RCT in the UK showed significantly lower viral load represented by Ct values for the vaccinated cohort. They also found that vaccinated people were PCR-positive for a shorter period of time. Another analysis of a US randomised controlled trial reported similar findings, however neither of these trials included the Delta variant. Not all studies reported the variant of concern that was investigated; however, the results from the studies that included the Delta variant varied. This increases the level of uncertainty around the relationship between vaccinated people, Ct values and transmission of the Delta variant. Also, although Ct values are used as a proxy for viral load, the relationship between viral load and infectiousness is not fully evidenced.

There were a small number (n=4) of studies identified that reported directly on viral load, which all reported similar findings of a significant reduction in viral load for vaccinated people. As with much of the evidence identified for direct transmission and Ct values, the Delta variant was not the variant of concern investigated in any of the viral load studies.

In conclusion, it seems that earlier findings show a reduction in transmission from vaccinated people. However, these findings relate to the dominant variants of concern present in the study populations at that time. For more recent evidence where the Delta variant is reported,

or may be the unreported primary variant, the effects of vaccination on transmission is less certain.

3.2 Areas of Uncertainty

The majority of direct transmission evidence is limited to transmission in household settings. Therefore, there is a gap in the evidence on the risk of transmission in other settings or vulnerable populations that would be of value, such as schools, care homes, hospitals, workplaces, or social venues. Also, the heterogeneity of the identified evidence makes comparing the findings difficult.

Confounding factors such as age, sex and previous COVID-19 infections were not adjusted for in lot of the studies identified, resulting in many of the studies scored as having moderate or serious risk bias. Some studies did not include baseline PCR assessments, so the possibility of persistent PCR positivity after a covid infection cannot be ruled out.

Evidence on transmission of the Delta variant in vaccinated populations is lacking and requires further research. There is some evidence on Ct values and viral load with Delta, and Ct values are used as a proxy for viral load. However, the relationship between viral load and infectivity is not fully evidenced. Furthermore, Ct values can be inaccurate; the number of cycles required for detectable amplification of viral RNA is dependent on a long list of variables beyond simply how much viral RNA is present in a patient specimen (PHE 2020).The relative impacts of these variables on the Ct value differs between test platforms and can vary widely. Variables such as time of collection of specimens after infection onset, efficiency of the collection of the specimen and storage and transport conditions of the specimen prior to testing can all have an impact (PHE 2020).

Evidence of waning immunity against variants of concern, in particular Delta, also requires further investigation.

3.3 Implications for policy and practice

- The Delta variant is currently dominant in Wales, however most studies focused on the Alpha variant, with a relative lack of evidence on the transmission of the Delta variant (currently dominant in Wales) and settings other than households.
- Given limited evidence on the effectiveness of vaccination on transmission of Delta in households and other settings, other preventative measures to reduce transmission may still be required.
- Further research is indicated to better understand transmission, specifically – in this context – the effect of vaccination on transmission of the SARS-CoV-2 Delta variant and other variants of concern in different cohorts and settings.
- Full immunisation (rather than partial) should be encouraged.
- Evidence of waning immunity supports booster vaccines.

3.4 Strengths and limitations of this Rapid Review

As this is a rapid review, search concepts and strategies were developed to fit in with the rapid nature of this type of review. This may have resulted in studies not being included or identified in the search, also, different variants of concern (e.g. Alpha and Delta) were not specified in the search. Additionally, as this review adapted evidence from the University of Calgary rapid literature review, their methodology and processes were highly relied upon. Some of the included studies were based on preprints which are published prior to peer-review.

HTW conducted Risk of Bias assessments using the ROBINS-I tool and the RoB2, which was consistent with the University of Calgary's approach, we did not undertake GRADE scoring for this review. The majority of the evidence included were observational studies, where confounding factors were an issue and not always adjusted for.

4. REFERENCES

Abu-Raddad L, J., Chemaitelly H, Ayoub H, H. , et al. (2021). Effect of vaccination and of prior infection on infectiousness of vaccine breakthrough infections and reinfections. medRxiv. 2021.07.28.21261086. doi: https://doi.org/10.1101/2021.07.28.21261086

Ahmed N, Yean CY, Yusof W, et al. (2021). Prevalence and impact of SARS-COV-2 variant of concern (VOC) on disease transmissibility and effectiveness of vaccination: a systematic review and meta-analysis. PROSPERO. CRD42021276481. doi: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=276481

Bailly B, Guilpain L, Bouiller K, et al. (2021). BNT162b2 messenger RNA vaccination did not prevent an outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 variant 501Y.V2 in an elderly nursing home but reduced transmission and disease severity. Clinical Infectious Diseases. ciab446. doi: https://doi.org/10.1093/cid/ciab446

Baltas I, Boshier FAT, Williams CA, et al. (2021). Post-vaccination COVID-19: a case-control study and genomic analysis of 119 breakthrough infections in partially vaccinated individuals. Clinical Infectious Diseases. ciab714. doi: https://doi.org/10.1093/cid/ciab714

Braeye T, Cornelissen L, Catteau L, et al. (2021). Vaccine effectiveness against infection and onwards transmission of COVID-19: analysis of Belgian contact tracing data, January-June 2021. Vaccine. 39(39): 5456-60. doi: https://doi.org/10.1016/j.vaccine.2021.08.060

de Gier B, Andeweg S, Joosten R, et al. (2021). Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. Euro Surveillance. 26(31): 2100640. doi: https://doi.org/10.2807/1560-7917.ES.2021.26.31.2100640

de Souza W, Muraro SP, Souza GF, et al. (2021). Clusters of SARS-CoV-2 lineage B.1.1.7 infection after vaccination with adenovirus-vectored and inactivated vaccines: a cohort study. SSRN. 3883263. doi: https://doi.org/10.2139/ssrn.3883263

Duerr R, Dimartino D, Marier C, et al. (2021). Dominance of Alpha and Iota variants in SARS-CoV-2 vaccine breakthrough infections in New York City. medRxiv. 2021.07.05.21259547. doi: https://doi.org/10.1101/2021.07.05.21259547

Elliott P, Haw D, J. , Wang H, et al. (2021). 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. medRxiv. 2021.09.02.21262979. doi: https://doi.org/10.1101/2021.09.02.21262979

Emary KRW, Golubchik T, Aley P, K. , et al. (2021). Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7). SSRN. 3779160. doi: https://doi.org/10.2139/ssrn.3779160

Eyre DW, Taylor D, Purver M, et al. (2021). The impact of SARS-CoV-2 vaccination on Alpha and Delta variant transmission. medRxiv. 2021.09.28.21264260. doi: https://doi.org/10.1101/2021.09.28.21264260

Gazit S, Barak M, Kalkstein N, et al. (2021). BNT162b2 mRNA vaccine effectiveness given confirmed exposure; analysis of household members of COVID-19 patients. medRxiv. 2021.06.29.21259579. doi: https://doi.org/10.1101/2021.06.29.21259579

Harris RJ, Hall JA, Zaidi A, et al. (2021). Impact of vaccination on household transmission of SARS-COV-2 in England. Public Health England. Available at: https://khub.net/documents/135939561/390853656/Impact+of+vaccination+on+house

hold+transmission+of+SARS-COV-2+in+England.pdf/35bf4bb1-6ade-d3eb-a39e-9c9b25a8122a [Accessed 3 Dec 2021].
Hooper L, Clark R, Pearce-Smith N. (2021). Transmission of COVID-19 following COVID-19 vaccination: protocol for a rapid review. PROSPERO. CRD42021257125. doi: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=257125
Ioannou P, Karakonstantis S, Astrinaki E, et al. (2021). Transmission of SARS-CoV-2 variant B.1.1.7 among vaccinated health care workers. Infectious Diseases. 53(11): 876-9. doi: https://doi.org/10.1080/23744235.2021.1945139
Jacobson KB, Pinsky BA, Montez Rath ME, et al. (2021). Post-vaccination SARS-CoV-2 infections and incidence of presumptive B.1.427/B.1.429 variant among healthcare personnel at a northern California academic medical center. Clinical Infectious Diseases. ciab554. doi: https://doi.org/10.1093/cid/ciab554
Jones NK, Rivett L, Seaman S, et al. (2021). Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection. eLife. 10(04): e68808. doi: https://doi.org/10.7554/eLife.68808
Layan M, Gilboa M, Gonen T, et al. (2021). Impact of BNT162b2 vaccination and isolation on SARS-CoV-2 transmission in Israeli households: an observational study. medRxiv. 2021.07.12.21260377. doi: https://doi.org/10.1101/2021.07.12.21260377
Levine-Tiefenbrun M, Yelin I, Katz R, et al. (2021). Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. Nature Medicine. 27: 790-2. doi: https://doi.org/10.1038/s41591-021-01316-7
Lumley SF, Rodger G, Constantinides B, et al. (2021). 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. 2021.03.09.21253218. doi: https://doi.org/10.1101/2021.03.09.21253218
McEllistrem M, J. CC, J. BD, et al. (2021). Single dose of an mRNA Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) vaccine is associated with lower nasopharyngeal viral load among nursing home residents with asymptomatic Coronavirus Disease 2019 (COVID-19). Clinical Infectious Diseases. 73(6): e1365-e7. doi: https://doi.org/10.1093/cid/ciab263
McIntosh L, O'Neill G, Le X. (2021). Systematic review of the efficacy of the COVID-19 vaccine in reducing disease transmission. PROSPERO. CRD42021246054. doi: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=246054
Mostafa HH, Luo CH, Morris CP, et al. (2021). 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. 2021.07.05.21259105. doi: https://doi.org/10.1101/2021.07.05.21259105
Muhsen K, Maimon N, Mizrahi A, et al. (2021). 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. SSRN. 3885633. doi: https://doi.org/10.2139/ssrn.3885633
National Institute of Allergy and Infectious Diseases (NIAID). (2021). A study of SARS CoV-2 infection and potential transmission in individuals immunized with Moderna COVID-19 vaccine. Available at: https://clinicaltrials.gov/show/NCT04811664 [Accessed 9 Dec 2021].
PHE. (2020). Understanding cycle threshold (Ct) in SARS-CoV-2 RT-PCR; a guide for health protection teams. PHE publications gateway number: GW-1651. Public Health England. Available at: https://www.gov.uk/government/publications/cycle-threshold-ct-in-sars-cov-2-rt-pcr [Accessed 3 Dec 2021].

Pouwels KB, Pritchard E, Matthews PC, et al. (2021). Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. medRxiv. 2021.08.18.21262237. doi: https://doi.org/10.1101/2021.08.18.21262237

Pritchard E, Matthews PC, Stoesser N, et al. (2021). Impact of vaccination on SARS-CoV-2 cases in the community: a population-based study using the UK COVID-19 Infection Survey. medRxiv. 2021.04.22.21255913. doi: https://doi.org/10.1101/2021.04.22.21255913

Regev-Yochay G, Amit S, Bergwerk M, et al. (2021). Decreased infectivity following BNT162b2 vaccination: a prospective cohort study in Israel. Lancet Regional Health. Europe. 7: 100150. doi: https://doi.org/10.1016/j.lanepe.2021.100150

Riemersma KK, Grogan BE, Kita-Yarbro A, et al. (2021). Shedding of infectious SARS-CoV-2 despite vaccination when the Delta variant is prevalent - Wisconsin, July 2021. medRxiv. 2021.07.31.21261387. doi: https://doi.org/10.1101/2021.07.31.21261387

Rolando P, Paila YD, Girard B, et al. (2021). Initial analysis of viral dynamics and circulating viral variants during the mRNA-1273 Phase 3 COVE trial. medRxiv. 2021.09.28.21264252. doi: https://doi.org/10.1101/2021.09.28.21264252

Rovida F, Cassaniti I, Paolucci S, et al. (2021). SARS-CoV-2 vaccine breakthrough infections with the Alpha variant are asymptomatic or mildly symptomatic among health care workers. medRxiv. 2021.06.29.21259500. doi: https://doi.org/10.1101/2021.06.29.21259500

Salmon C, Flanagan J, Farkas B, et al. (2021). Transmissibility of COVID-19 among vaccinated individuals: a rapid literature review - Update #2. Available at: https://sporevidencealliance.ca/wp-content/uploads/2021/10/Transmissibility-of-COVID-Vaccinated-Individuals_Final-Report_2021.09.24.pdf [Accessed 3 Dec 2021].

Salo J, Hägg M, Kortelainen M, et al. (2021). The indirect effect of mRNA-based Covid-19 vaccination on unvaccinated household members. medRxiv. 2021.05.27.21257896. doi: https://doi.org/10.1101/2021.05.27.21257896

Shah ASV, Gribben C, Bishop J, et al. (2021). Effect of vaccination on transmission of SARS-CoV-2. New England Journal of Medicine. 385: 1718-20. doi: https://doi.org/10.1056/NEJMc2106757

Shapiro J, Dean N, Madewell Z, et al. (2021). Efficacy estimates for various COVID-19 vaccines: what we know from the literature and reports. medRxiv. 2021.05.20.21257461. doi: https://doi.org/10.1101/2021.05.20.21257461

Shitrit P, Zuckerman NS, Mor O, et al. (2021). Nosocomial outbreak caused by the SARS-CoV-2 Delta variant in a highly vaccinated population, Israel, July 2021. Euro Surveillance. 26(39): pii=2100822. doi: https://doi.org/10.2807/1560-7917.ES.2021.26.39.2100822

Shrotri M, Krutikov M, Palmer T, et al. (2021). 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. Lancet Infectious Diseases. 21(11): 1529-38. doi: https://doi.org/10.1016/S1473-3099(21)00289-9

Singanayagam A, Hakki S, Dunning J, et al. (2021). Community transmission and viral load kinetics of SARS-CoV-2 Delta (B.1.617.2) variant in vaccinated and unvaccinated individuals. SSRN. 3918287. doi: https://doi.org/10.2139/ssrn.3918287

Thompson MG, Burgess JL, Naleway AL, et al. (2021). Prevention and attenuation of Covid-19 with the BNT162b2 and mRNA-1273 vaccines. New England Journal of Medicine. 385(4): 320-9. doi: https://doi.org/10.1056/NEJMoa2107058

Venice S, Morris M-K, Sotomayor-Gonzalez A, et al. (2021). Predominance of antibody-resistant SARS-CoV-2 variants in vaccine breakthrough cases from the San Francisco Bay Area, California. medRxiv. 2021.08.19.21262139. doi: https://doi.org/10.1101/2021.08.19.21262139

Vignier N, Berot V, Bonnave N, et al. (2021). Breakthrough infections of SARS-CoV-2 Gamma variant in fully vaccinated gold miners, French Guiana, 2021. Emerging Infectious Diseases. 27(10): 2673-6. doi: https://doi.org/10.3201/eid2710.211427

WHO. (2021). WHO Coronavirus (COVID-19) Dashboard. World Health Organization Available at: https://covid19.who.int/ [Accessed 1 Dec 2021].

5. RAPID REVIEW METHODS

5.1 Eligibility criteria

Table 7 details the inclusion and exclusion criteria used to select evidence for this review. Initial scoping searches identified a rapid literature review (Salmon et al. 2021) that included relevant evidence published up to 23 August 2021. We used this as a source of relevant study outcome data up to this date. We also included primary studies published since 23 August 2021 (last date of search 5 October 2021) or older studies that were not included in the review by Salmon et al. (2021).

.

Table 7: Eligibility criteria for included evidence

	Inclusion criteria	Exclusion criteria
Population	People who have received partial or complete COVID-19 vaccination	
Settings	Any setting (we will report on specific transmission setting, where reported)	
Intervention / exposure	SARS-CoV-2 / COVID-19	
Comparison	Unvaccinated people with COVID-19 infection. Non-comparative data were also considered	
Outcome measures	SARS-CoV-2 transmission (including transmission rate, secondary attack rate) Ct values (used as a proxy to signify viral load) Duration of illness	
Study design	We will prioritise systematic reviews where possible, but include observational studies if required.	
Countries	Any	
Language of publication	English	
Publication date		
Publication type	Published and preprint	
Other factors *Any other key points to note*	We will also look for evidence in other respiratory viruses (e.g. influenza), if evidence on SARS-CoV-2 transmission is limited. We will also report symptom status (e.g. pre-symptomatic, asymptomatic, symptomatic, types and severity of symptoms), where reported. We will report on type of vaccination (including partial and complete vaccination status) and variant strains, e.g. variants of concern, if available.	

5.2 Literature search

We searched for evidence on the transmission risk of SARS-CoV-2 from vaccinated people to unvaccinated or vaccinated people.

A systematic literature search for evidence was carried out between 6 and 14 October 2021. Table 8 lists all databases and resources searched. The key concepts included in the searches were COVID-19/SARS-CoV-2 and vaccination and transmission. The searches were limited to English language and had a general animals exclusions filter applied when available. No date limits or study design filters were applied to the searches. Ongoing trials, comment/editorials, and preprints were included in the searches through careful decision-making regarding resource selection. Appendix 1 gives the search strategy used for MEDLINE. Search strategies for other databases are available on request. The eligibility criteria used to select evidence for the appraisal are outlined in Table 8, and in the full protocol in Appendix 2. These criteria were developed with input from the wider Wales COVID-19 Evidence Centre group and consultation with stakeholders.

Table 8: resources list

Database	Segment	Date Searched
Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily	1946 to October 05, 2021	06/10/21
Ovid Embase	1996 to 2021 October 05	06/10/21
Cochrane Library	Issue 10 of 12, October 2021	06/10/21
Cochrane COVID-19 Study Register	-	07/10/21
INAHTA HTA database	-	06/10/21
Love COVID for covid-specific search (Epistemonikos)	-	06/10/21
Clinicaltrials.gov	-	13/10/21
WHO ICTRP [International Clinical Trials Registry Platform]	-	13/10/21
PROSPERO recent/ongoing systematic reviews database	-	14/10/21
NICE Covid-19 evidence	-	08/10/21
NICE Evidence Search [Filters: guidance; commissioning guides, evidence summaries, HTA, systematic reviews]	-	08/10/21
TRIP Pro	-	07/10/21
Google Advanced Search	-	11/10/21

5.3 Data extraction

Three researchers checked eligible studies against the inclusion/exclusion criteria. A single researcher extracted data from relevant evidence sources; a sample of these were checked by a second researcher. Extracted data included details of study characteristics and reported outcomes.

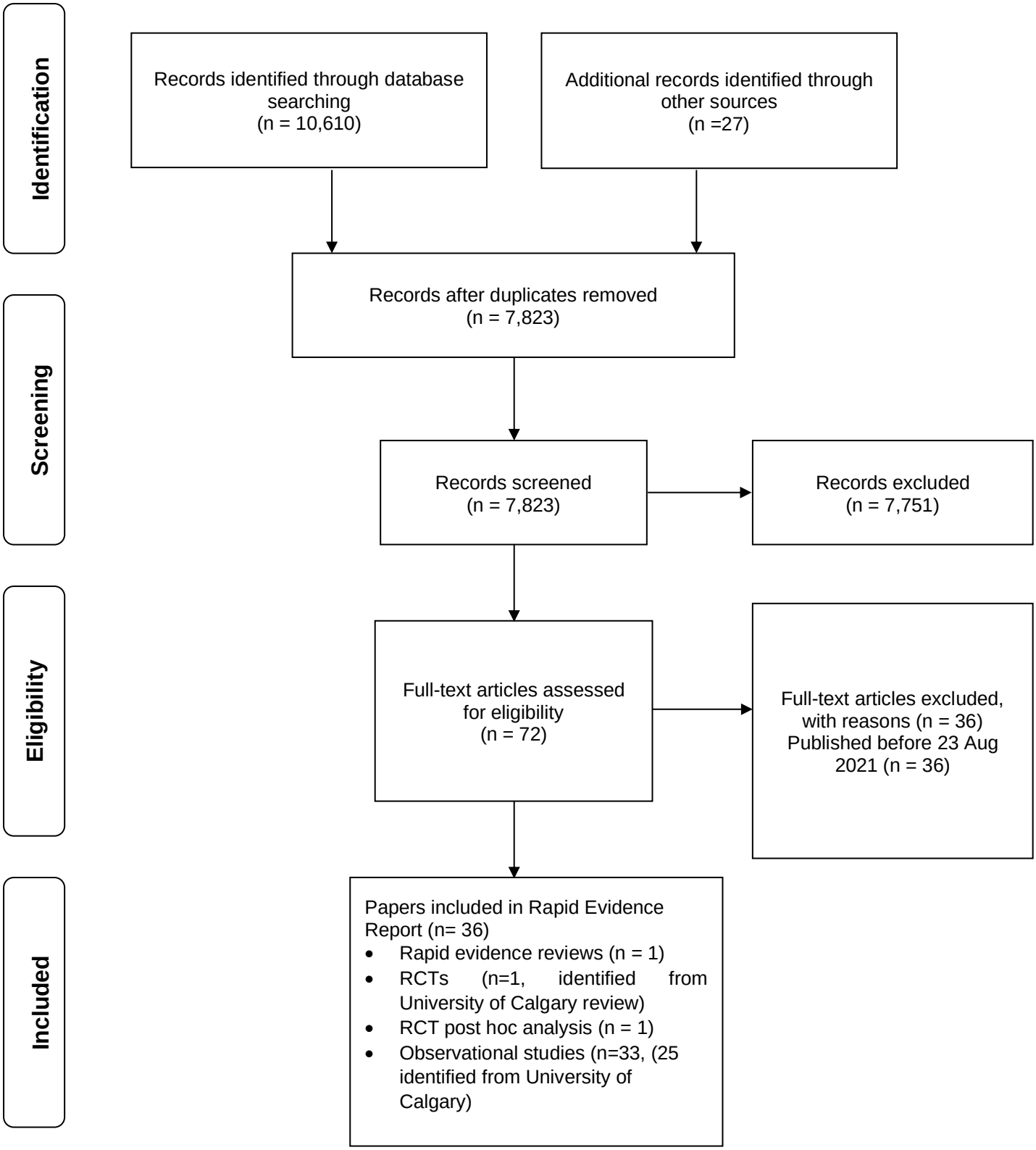
5.4 Quality appraisal

Risk of Bias assessments were undertaken using ROBINS-I for observational studies, Cochrane Risk of Bias tool for RCTs (RoB2) and ROBIS for the University of Calgary review. ROBINS-I assessments were completed independently by two researchers (SB and LE) for each observational study; any difference in scores were reviewed and joint agreement reached. RoB2 and ROBIS were completed independently by a single researcher (SB).

5.5 Synthesis

Evidence was synthesised narratively.

Flow diagram outlining selection of relevant evidence sources



6. EVIDENCE

6.1 Data extraction tables

Table 9: Summary of the University of Calgary (Salmon et al. 2021) rapid literature review

Included Studies	Inclusion criteria	Quality	Observations/notes
Number of included studies: Total: 45 studies Including six RCTs and 39 observational studies **Publication date of included studies:** Up to 23 August 2021 https://sporevidencealliance.ca/key-activities/covid-19-evidence-synthesis/	Review period: up to 23 August 2021 Review purpose: to identify comparative observational studies and randomized controlled trials (RCTs) evaluating the effectiveness or efficacy of COVID-19 vaccination in reducing infection transmission, asymptomatic viral carriage, and other proxies of possible transmission, such as cycle threshold (Ct) values and viral load. Included study designs: RCTs and observational studies (cohort and case studies). Included outcome measures: Ct values, viral load, asymptomatic laboratory confirmed cases by RT-PCR post-vaccination and the number of persons who are infected by someone who has COVID-19 and has had the vaccine (direct transmission)	ROBIS overall score: LOW Each domain: Concerns regarding specification of study eligibility criteria: LOW Concerns regarding methods used to identify and/or select studies: LOW Concerns regarding methods used to collect data and appraise studies: LOW Concerns regarding the synthesis and findings: HIGH	Data on the following outcomes were extracted for this review: Ct values, viral load, the number of persons who are infected by someone who has COVID-19 and has had the vaccine (direct transmission). On the overall risk of bias domain for observational studies, 20 studies were rated as moderate risk of bias, 14 were serious, three were critical, one was low, and one did not have sufficient information.

	Studies evaluating the transmissibility or infectivity of COVID-19 among vaccinated individuals were included.		

Abbreviations: RCTs: Randomised controlled trials, RT-PCR: reverse transcription polymerase chain reaction test, Ct: cycle threshold

Table 10: Summary of included primary studies

Study reference	Study Details	Vaccine Information	Effectiveness Outcomes	Comments
Vignier et al. (2021) **Country:** French Guiana	**Study Design:** Prospective Cohort **Participants** All participants were miners in a gold mine. **Age:** Median age 53.3 **%Female:** 4.72% **Total sample size:** 37 **Date of Recruitment:** May-June 2021 **Overall RoB:** Serious **VOC:** Gamma	**Vaccine:** BNT162b2 **Manufacturer**: Pfizer BioNTech **Number of Doses:** 1 or 2	• Ct values	The Gamma variant COVID-19 outbreak had a high attack rate among persons fully vaccinated with BNT162b2 vaccine. Working conditions of the miners could have contributed to transmission. This is a small, isolated population so generalisability is limited. Ct values were only reported for infected people, no unvaccinated comparators.
Singanayagam et al. (2021) **Country:** UK	**Study Design:** Prospective, longitudinal, cohort study **Participants** All contacts notified within 5 days of index case symptom onset were selected to be contacted within our recruitment capacity. **Age:** NR **Female%:** NR **Total sample size:** Varied **Date of Recruitment:** Sept 2020-Sept 2021 **Overall RoB:** Serious	**Vaccine:** BNT162b2 or ChAdOx1 nCoV-19 or CoronaVac inactivated whole-virion vaccine **Manufacturer:** Pfizer BioNTech or Oxford AstraZeneca or Sinovac **Number of Doses:**1 or 2	• Secondary attack rate of vaccinated people • Viral loads • Ct values	Fully vaccinated individuals with breakthrough infections have peak URT viral load similar to unvaccinated cases and can efficiently transmit infection in household settings, including to fully vaccinated contacts.

	VOC: B.1.617.2 (Delta) and Alpha and Pre-alpha			
Elliott et al. (2021) **Country:** UK	**Study Design:** Retrospective Cohort study **Participants** Participants were sampled from the NHS patient list. **Age**: 18-64 years (Ct values) Female%: NR **Total sample size**: Varied **Date of Recruitment:** May 2021-July 2021 **Overall Rob:** Moderate **VOC**: B.1.617.2 (Delta) and Alpha	**Vaccine:** NR **Manufacturer**: NR **Number of Doses**:1 or 2	• Ct values	
Eyre et al. (2021) **Country:** UK	**Study Design:** Retrospective Cohort study **Participants** Adults > 18 years. Contact with asymptomatic or symptomatic index case (living in the same household or in contact face-to-face, within <1m for ≥1 minute or <2m for ≥15 minutes). PCR testing 1-10 days after index case's PCR. **Age**: median(IQR)[range] index case and contact ages were 34(24-49)[18-102] and 43(29-54)[18-107] years respectively. **Female%:** 57% **Total sample size**: Varied **Date of Recruitment**: Jan 2021-July 2021 **Overall RoB**: Serious **VOC**: B.1.617.2 (Delta) and Alpha	**Vaccine:** BNT162b2 or ChAdOx1 nCoV-19 **Manufacturer:** Pfizer BioNTech or Oxford AstraZeneca **Number of Doses:**1 or 2	• Direct transmission • Viral load • Ct values	Ct values weren't significantly different; transmission was reduced however protection against onward transmission waned within 3 months post-second vaccination.

Venice et al. (2021) **Country:** California	**Study Design:** Prospective Cohort study **Participants** COVID-19 patients seen in hospitals and clinics **Age:** Average age 49 years **Female%:** 54% **Total sample size:** Viral load sample size: 39 **Date of Recruitment**: Feb 2021-Jun 2021 **Overall RoB:** Serious **VOC:** B.1.617.2 (Delta) and Alpha	**Vaccine:** BNT162b2 or mRNA-1273 or viral vector (adenovirus) vaccine **Manufacturer**: Pfizer BioNTech or Moderna or Johnson/Jansen **Number of Doses**:2	• Viral load	No significant difference in viral loads for vaccinated or unvaccinated. Only data for 39 out of 125 vaccine breakthrough cases
Rovida et al. (2021) **Country:** Italy	**Study Design**: Prospective Cohort study **Participants** Healthcare workers that were fully vaccinated from Jan to Mar 21. **Age:** NR **Female%:** NR **Total sample size**: 3720 **Date of Recruitment**: Jan 2021- May 2021 **Overall RoB**: Serious **VOC**: Alpha	**Vaccine**: BNT162b2 **Manufacturer:** Pfizer BioNTech **Number of Doses**:2	• Direct transmission (2 cases) • Virus isolation on cell cultures in 21/33 subjects.	Lack of transmission as only 2/33 close contacts caught the virus (alpha). Doesn't report on age, sex, ethnicity. Previous covid infections reported but not adjusted for. Low viral load in vaccinated however no comparison as cell cultures weren't done in unvaccinated.
Riemersma et al. (2021) **Country:** USA	**Study Design:** Retrospective Cohort study **Participants** Fully vaccinated participants only. All samples tested in a Wisconsin commercial laboratory	**Vaccine:** NR **Manufacturer**: NR **Number of Doses**:2	• CT values >14 following 2nd dose	Pre-print Considered time-varying confounding. Partial vaccination excluded. Vaccination

	Age: NR **Female%:** NR **Total sample size:** 291 **Date of Recruitment:** Jun 2021- Jul 2021 **Overall RoB:** Serious **VOC:** B.1.617.2 (Delta) and Alpha			status unknown excluded. Type of vaccine not known. Not adjusted for age, sex, ethnicity. No difference in Ct values or infectious titers between vaccinated and unvaccinated with Delta variant.
Braeye et al. (2021) **Country:** Belgium	**Study Design:** Retrospective Cohort study **<u>Participants</u>** Any person without a positive test (PCR or Antigen) in the past 90 days. People were excluded if a vaccine was received by either index case or HRC during this 14-day period. **Age:** Average age 33 (SD 19.4) **Female%:** 51.5% **Total sample size**: 301,741 (91% unvaccinated) **Date of Recruitment:** Jan 2021- Jun 2021 **Over RoB:** Serious **VOC**: 80% Alpha	**Vaccine**: BNT162b2 or mRNA-1273 or ChAdOx1 or Ad26.COV2.S **Manufacturer:** Pfizer BioNTech or Moderna or AstraZeneca or Janssen **Number of Doses**:1 or 2	• Vaccine efficacy against onwards transmission	Reports that vaccines reduce transmission of the Alpha variant.
Shitrit et al. (2021) **Country:** Israel	**Study Design:** Prospective Cohort study **<u>Participants</u>** Close contacts of the index cases **Age:** Median age was 55 years (interquartile range (IQR): 36–77.5	**Vaccine:** BNT162b2 **Manufacturer**: Pfizer BioNTech **Number of Doses**:2	• Ct values	Cq values (Ct) only reported for vaccinated cohort, so not comparators. Time from vaccination considered.

	Female%: 43.6% **Total sample size**: 42 **Date of Recruitment:** July 2021 **Overall RoB**: Serious **VOC**: Delta			Patient populations were older and had comorbidities. Previous infections not reported. No statistical analysis made. Findings: high transmissibility among vaccinated. Waning immunity, the shortest interval since vaccine was 5 months.
Rolando et al. (2021) **Country:** USA	**Study Design:** Analysis of an RCT **Participants** Adults 18 or over with no previous covid infections that have been exposed to COVID-19. **Age:** Mean age 49 years (range 18-87 years) **Female%:** 50% **Total sample size:** 799 for viral load **Date of Recruitment:** July 2021 **Overall RoB**: Low **VOC:** Epsilon, Gamma, Zeta	**Vaccine:** mRNA-1273 **Manufacturer:** Moderna **Number of Doses**:2	• Viral load	Reported reduced viral load for vaccinated (Delta variant not included).
Emary et al. (2021) **Country:** UK	**Study Design:** RCT **Participants** Aged 18 and over; high-exposure populations eligible for vaccination under the government National Health Service coronavirus vaccine programme.	**Vaccine**: ChAdOx1 nCoV-19 **Manufacturer**: AstraZeneca Dose: Low or Standard Doses	• Ct Values (weekly swabs processed. The minimum Ct value across the N and ORF1ab genes from each PCR test was computed)	Nasal and throat swabs were sequenced from 256 participants and showed significantly lower viral load as represented by

	Age: NR **Female%:** NR **Total sample size:** 8506 **Date of Recruitment:** October 2020 – January 2021 **Overall RoB**: Low **VOC:** B.1.1.7, Other	**Number of Doses**: 2		minimum PCR Ct value (p<0.0001). Furthermore, vaccinated participants were PCR-positive for a shorter period of time (p<0.0001).
Levine-Tiefenbrun et al. (2021) **Country:** Israel	**Study Design:** Retrospective Cohort **<u>Participants</u>** All positive post-vaccination samples **Age:** NR **Female%:** NR **Total sample size**: Varied **Date of Recruitment:** Dec 2020-Jan 2021 **Overall RoB**: Moderate **VOC:** NR	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer BioNTech **Dose**: NR **Number of Doses**:1	• Ct values	Between 12 and 28 days after the first dose, Ct values were significantly higher for vaccinated people than the controls

Regev-Yochay et al. (2021) **Country:** Israel	**Study Design: Cohort** **Participants** Healthcare workers at Sheba Medical Center (Israel) **Age:** NR **Female%:** NR **Total sample size:** 3578 **Date of Recruitment:** December 2020 – March 2021 **Overall RoB:** Moderate **VOC:** NR	**Vaccine:** BNT162b2 or Moderna **Manufacturers:** Pfizer BioNTech or Moderna **Number of Doses:** 1 or 2	• Ct values	Ct values amongst fully vaccinated healthcare workers were significantly higher than unvaccinated healthcare workers (mean difference 5.09, 95% CI: 2.8-7.4, p<0.001)
Jones et al. (2021) **Country:** UK	**Study Design:** Retrospective Cohort **Participants** Vaccinated and unvaccinated Health Care Workers **Age:** NR **Female%:** NR **Total sample size:** Varied **Date of Recruitment:** January 2021 **Overall RoB:** Moderate **VOC**: B.1.1.7 (Alpha)	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer BioNTech **Number of Doses:**1	• Ct values	Reported a non-significant trend towards increase between unvaccinated (median=20.3) and vaccinated HCWs after 12 days post-vaccination (median=30.3), suggesting that samples from infected vaccinated individuals had lower viral loads
McEllistrem et al. (2021) **Country:** USA	**Study Design:** Retrospective Cohort **Participants** A negative baseline nasopharyngeal reverse transcription polymerase chain reaction test (RT-PCR, Palo Alto VA, CA) for SARS-CoV-2 on 12/2/20.	**Vaccine:** BNT162b2 **Manufacturers:** Pfizer BioNTech **Number of Doses:** 1	• Ct values • Viral load	Median Ct values for unvaccinated residents (12.8, IQR: 12.4-14.9) were significantly lower (p=0.009) than

	Age: NR **Female%:** NR **Total sample size**: 10 **Date of Recruitment:** December 2020–February 2021 **Overall** RoB: Moderate **VOC**: NR			vaccinated residents (19.4, IQR: 18.9-25.5).
Shah et al. (2021) **Country:** UK	**Study Design:** Retrospective Cohort **<u>Participants</u>** Healthcare workers were included if they were employed by the National Health Service (NHS) in Scotland on or before the 1st of March 2020 (the first positive reported case of COVID-19 in Scotland) and still employed by the NHS on the 1st of November 2020; healthcare worker cohort was restricted to the working-age population (18-65 years of age). The household member cohort included all ages but was restricted to households with no more than one healthcare worker (4% of healthcare workers lived in multiple healthcare worker households) **Age:** 44.4 (11.4) **Female%:** 78.7% **Total sample size:** 253,599 **Date of Recruitment:** December 2020 – March 2021 **Overall RoB:** Moderate **VOC:** NR	**Vaccine:** BNT162b2 or ChAdOx1 nCoV-19 **Manufacturers:** Pfizer BioNTech or Oxford AstraZeneca **Number of Doses:** 1	• Transmission to contact	Pre-print Fully vaccinated healthcare workers significantly lowered the risk of infection and hospitalisation for their household members (rate per 100 person-years of 9.40 versus 2.98, HR: 0.46 (95% CI: 0.30-0.70) and 0.51 versus 0.22 per 100 person-years, HR: 0.68 (95% CI: 0.17-2.83), respectively.

Lumley et al. (2021) **Country:** UK	**Study Design**: Longitudinal Cohort **Participants** Only those who participated in asymptomatic screening, symptomatic testing or vaccination from 01-September-2020 onwards were included. All staff working for the hospitals were eligible to participate. **Age:** 39 (IQR:30-50) **Female%:** 74.0% **Total sample size:** 13,109 **Date of Recruitment:** up to February 2021 **Overall RoB:** Moderate **VOC:** B.1.1.7 (Alpha)	**Vaccine:** BNT162b2 or ChAdOx1 nCoV-19 **Manufacturers:** Pfizer BioNTech or Oxford AstraZeneca **Number of Doses:** 1 or 2	• Ct values	Pre-print No significant difference in the median Ct values of vaccinated people compared with unvaccinated.
Pritchard et al. (2021) **Country:** UK	**Study Design:** Prospective Cohort **Participants** This analysis included participants aged 16 years or over (i.e. those who theoretically could have received vaccination), and all visits with positive or negative swab results from 1 December 2020 to 3 April 2021. **Age:** NR **Female%:** NR **Total sample size**: 373,402 **Date of Recruitment:** December 2020-April 2021 **Overall RoB:** Moderate **VOC**: NR	**Vaccine**: BNT162b2 or ChAdOx1 nCoV-19 **Manufacturers**: Pfizer BioNTech or Oxford AstraZeneca **Number of Doses**: 1 or 2	• Ct values	Pre-print Statistically significant increase in the median Ct values of partially or fully vaccinated people ($p<0.001$).

Shrotri et al. (2021) **Country:** UK	**Study Design:** Prospective Cohort **Participants** At least two PCR test results in total, and ≥ 1 PCR result during the analysis period. Residents entered the risk period on 8 December 2020 if they had ≥ 1 valid PCR result on or prior to that date; or, if they had no PCR results before 8 December 2020, on the date of their first negative PCR test. Residents with a positive PCR result ≤ 90 days before 8 December entered the risk period 90 days after their positive test. **Age:** 86 (IQR: 80-91) **Female%:** 69.6% **Total sample size:** 10,412 **Date of Recruitment**: December 2020-March 2021 **Overall RoB**: Moderate **VOC**: NR	**Vaccine**: BNT162b2 or ChAdOx1 nCoV-19 **Manufacturers:** Pfizer BioNTech or Oxford AstraZeneca **Number of Doses:** 1 or 2	• Ct values	Pre-print After 28 days, there was a statistically significant decrease in the mean Ct between vaccinated and unvaccinated persons (mean Ct 26.6 (95% CI: 26-27.1) vs 31·3 (95% CI: 29.6-32.9), p<0·001).
Harris et al. (2021) **Country:** UK	**Study Design:** Prospective Cohort **Participants** Households with an index case occurring between 4 January 2021 to 28 February 2021, with 14 days observable follow up for all contacts; households with a single index case age 16+, and no co-primary cases. **Age:** NR **Female%:** Unvaccinated index case: 47.6%, Index case vaccinated 21+ day before: 38.3%, Index case vaccinated <21 days before: 40.6% **Total sample size:** 1,018,842 **Date of Recruitment**: January-February 2021	**Vaccine**: BNT162b2 or ChAdOx1 nCoV-19 **Manufacturers**: Pfizer BioNTech or Oxford AstraZeneca **Number of Doses:** 1	• Transmission to contact	Pre-print Concluded that there is evidence of reduced transmission to household contacts from index cases who have received one dose of either vaccine (PfBNT or AZ). The authors balanced relevant confounding through a matched case-control design.

	Overall RoB: Moderate **VOC**: NR			
Ioannou et al. (2021) **Country:** Greece	**Study Design:** Prospective cohort **<u>Participants</u>** Vaccinated (with BNT162b2) and non-vaccinated healthcare workers who tested positive for COVID-19 at a single centre in Greece **Age:** 42.3 ±9.9 **Female%:** 74.5% **Total sample size:** 52 **Date of Recruitment**: Jan 2021 – April 2021 **Overall RoB:** Moderate **VOC:** B.1.1.7 (Alpha)	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer **Number of Doses:** 2	• Ct values	In Greek healthcare workers found no statistically significant differences between the median Ct values for those that were vaccinated and unvaccinated
Thompson et al. (2021) **Country:** USA	**Study Design:** Prospective Cohort **<u>Participants</u>** Eligible participants include Arizona residents aged 18–85 years who currently work at least 20 hours per week in an occupation involving regular direct contact (within three feet) with others, assessed at the participant level **Age**: NR **Female%:** 62% **Total sample size**: 3975 **Date of Recruitment:** December 2020 – April 2021 **Overall RoB**: Serious	**Vaccine**: mRNA vaccine **Manufacturer**: Moderna, Pfizer **Number of Doses:** 1 or 2	• Viral load	Lower presence of virus in partially and fully vaccinated people compared with the unvaccinated cohort

	VOC: B.1.429; B.1.1.7; B.1.427			
Jacobson et al. (2021) **Country:** USA	**Study Design:** Retrospective quality improvement **Participants** Post vaccine SARS CoV-2 cases, defined as HCPs with positive SARS-CoV-2 nucleic acid amplification test after receiving one or more vaccine doses **Age:** 37.5 ±10.6 **Female%:** 69.8% **Total sample size**: 283 **Date of Recruitment:** December 2020 – April 2021 **Overall RoB**: Serious **VOC**: B.1.427/B.1.429	**Vaccine:** BNT162b2 or Moderna **Manufacturer:** Pfizer, Moderna **Number of Doses:** 1 or 2	• Ct values ≤ 14 after first dose • Ct values up to 14 days after 1st or 2nd dose • Ct values over 14 days after 2nd dose	No significant difference in Ct values of vaccinated and unvaccinated people
Bailly et al. (2021) **Country:** France	**Study Design:** Prospective cohort **Participants** Residents and staff from a nursing home unit with a positive COVID case **Age**: Fully vaccinated residents: 87.0 ± 8.2 years **Female%:** Fully vaccinated residents: 64.5% **Total sample size**: 18 **Date of Recruitment**: March 2021 **Overall RoB**: Serious **VOC**: 501Y.V2	**Vaccine**: BNT162b2 **Manufacturer:** Pfizer **Number of Doses:** 2 doses	• Ct values after 2 doses	No difference in median Ct values of the unvaccinated residents
	Study Design: Retrospective	**Vaccine:** BNT162b2 or Moderna	• Transmission to unvaccinated spouse 14 days and	Pre-print

Country: Finland	**Participants** Vaccinated and unvaccinated HCW. An individual was included in this sample if their spouse is a healthcare worker and they had not been vaccinated during the sample period. **Age:** Vaccinated: 47.1 ±13.1 Unvaccinated: 43.8 ±14.5 **Female%:** 86.5% **Total sample size**: 288,138 **Date of Recruitment:** December 2020 – March 2021 **Overall RoB**: Serious **VOC**: NR	**Manufacturer:** Moderna, Pfizer **Number of Doses:** 1 or 2	10 weeks after 1st dose • Transmission to unvaccinated child 3-18 years, 14 days and 10 weeks after 1st dose • Transmission to unvaccinated child 3-12 years, 6 weeks and 10 weeks after 1st dose • Transmission to unvaccinated child 13-18 years, 6 and 10 weeks after 1st dose	Reported the highest reduction in transmission at 10 weeks post first vaccination to unvaccinated spouses, 42.9% (95% CI: 22.3-58.1) and to unvaccinated children between the ages of 3-18years old child, 32.9% (95% CI: 4.1-53.0).
Muhsen et al. (2021) **Country:** Israel	**Study Design:** Prospective cohort **Participants** Adherence to routine screening for SARS-CoV-2 infection by RT-PCR testing. Specifically, they had 12 or more out of the 20 planned screening tests for the period September 2020 through January 2021; 2) working in LCTFs that vaccinated >75% of their employees collectively during three consecutive days; and 3) being RT-PCR negative for SARS-CoV-2 infection by the date of immunization with the second vaccine dose. Unvaccinated HCWs at baseline, who were vaccinated later, were censored upon receiving their first vaccination dose **Age**: 46.2 ±11.8 **Female%:** 79.5%	**Vaccine**: BNT162b2 **Manufacturer:** Pfizer **N umber of Doses**: 2	• Ct values over 14 days after 2nd dose	Pre-print

	Total sample size: 9162 **Date of Recruitment:** December 2020 – January 2021 **Overall RoB:** Moderate **VOC**: NR			
de Gier et al. (2021) **Country:** Netherlands	**Study Design:** Retrospective cohort **<u>Participants</u>** Household members and other close contacts of confirmed cases **Age:** NR **Female%:** NR **Total sample size:** Index cases: 113582; contacts: 253168 **Date of Recruitment:** February 2021 – May 2021 **Overall RoB:** Serious **VOC:** B.1.1.7	**Vaccine**: ChAdOx1-S, BNT162b2, Moderna, Janssen **Manufacturer:** Pfizer, Moderna, AstraZeneca, Janssen **Number of Doses:** 1 or 2	• Transmission to contact over 14 days after 1st dose: any household contact, unvaccinated household contacts, any other close contact, unvaccinated close contacts, AstraZeneca vaccinated household contact, Pfizer vaccinated household contact, Moderna vaccinated household contact • Transmission to contact over 7 days after 2nd dose in: any household contact, unvaccinated household contacts, any other close contact, unvaccinated close contacts, AstraZeneca	Pre-print Fully vaccinated individuals were associated with the reduction of transmission of COVID-19 to any household contact by 71% (95% CI: 63-77), 73% (95% CI: 65-79) to any unvaccinated household contact, 22% (95% CI: -5-43) to any other close contact, and 24% (95% CI: -5-43) to any unvaccinated close contact.

			vaccinated household contact, Pfizer vaccinated household contact, Moderna vaccinated household contact, Janssen vaccinated household contact	
de Souza et al. (2021) **Country:** Brazil	**Study Design:** Observational cohort **Participants** Individuals at least 18 years of age exposed to residents infected with SARS-CoV-2 (from either the convent or LTC facility). Residents and employees from both locations were included in the study **Age:** 73 (IQR 50-83) **Female%:** 96.2% **Total sample size:** 26 **Date of Recruitment**: March 2021 **Overall RoB**: Moderate **VOC**: B.1.1.7	**Vaccine:** ChAdIx01, 1 resident vaxxed with Ad26.COV2.S and CoronaVac, **Manufacturer:** AstraZeneca and SinoVac BioTech **Number of Doses:** 1 or 2	• Viral load in individuals >23 days following 1st dose • Viral load in individuals 5-27 days following 2nd dose	Pre-print
Abu-Raddad et al. (2021) **Country:** Qatar	**Study Design**: Matched Case-control 1:1 ratio **Participants** All records of RT-qPCR in Qatar but only samples of matched cohorts were included in the analysis. Only breakthrough infections in fully vaccinated individuals were included in the analysis. Being fully vaxxed was defined as >14 days after the second dose **Age:** 33-35	**Vaccine:** BNT162b2, Moderna **Manufacturer:** Pfizer-BioNTech, Moderna **Number of Doses**: 2	• Ct value over 14 days following 2nd dose of vaccine	When compared with the matched unvaccinated individuals, median Ct values were statistically significantly higher in the vaccinated cohort ($p<0.001$).

	Female%: 14.90%-21.100% **Total sample size**: 120-842 **Date of Recruitment:** February 2020 – July 2021 **Overall RoB**: Moderate **VOC:** B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta)			
Duerr et al. (2021) **Country:** USA	**Study Design:** Case-control **<u>Participants</u>** Cases included individuals who tested positive by real-time RT-PCR for SARS-CoV-2 RNA regardless of Ct, any time after 14 days of inoculation with the second dose of Pfizer-BioNTech/Moderna or with single dose Janssen. Control group consisted of full-genome sequenced SARS-CoV-2 positive cases, had Ct<30, and were collected in the same time period as the breakthrough infections **Age:** NR **Female%:** NR **Total sample size:** 1147 **Date of Recruitment:** February 2021 – April 2021 **Overall RoB:** Critical **VOC:** B.1.1.7 (Alpha), B.1.526 (Iota), P1, and others	**Vaccine:** BNT162b2, Moderna, or Janssen **Manufacturer:** Pfizer-BioNTech, Moderna, Johnson & Johnson **Number of Doses**: 1 or 2	• Ct values over 14 days following 1st or 2nd dose in breakthrough infections	
Layan et al. (2021)	**Study Design:** Case-control (Observational) **<u>Participants</u>**	**Vaccine:** BNT162b2 **Manufacturer:** Pfizer-BioNTech	• Transmission to contact >7 days following 2nd dose	Pre-print COVID-19 status of healthcare workers

Country: Israel	HCWs employed by Sheba Medical Center with a SARS-CoV-2 case **Age:** 32±16 **Female%:** 58% **Total sample size:** 215-687 **Date of Recruitment:** December 2020 – April 2021 **Overall RoB**: Serious **VOC:** Alpha	**Number of Doses:** 2	• Infected contacts >7 days following 2nd dose	was confirmed through RT-qPCR, while the status of household members was self-reported.
Mostafa et al. (2021) **Country:** USA	**Study Design:** Retrospective cohort (Observational) **Participants** Specimens of SARS-CoV-2 positive patients who had received two doses of either Pfizer-BioNTech (BNT162b2) or Moderna (Moderna) vaccines; specimens of a control unvaccinated cohort from a matched time frame **Age:** 51 (IQR NR) **Female%:** 63.3% **Total sample size:** NR **Date of Recruitment**: January 2021 – May 2021 **Overall RoB**: Serious **VOC:** P.1, B.1.1.7, B.1.351, B.1.526, and B.1.526.1	**Vaccine**: BNT162b2 or ChAdOx1 nCOV-19 **Manufacturer:** Pfizer-BioNTech, Moderna **Number of Doses**: 2	• Ct values 2-100 days following 2nd dose	Pre-print Non-significant differences in median Ct values for the vaccinated
Gazit et al. (2021) **Country:** Israel	**Study Design:** Observational cohort **Participants** A household was defined as having two adults. Only households with two adults were included	**Vaccine:** BNT162b2 **Manufacturer**: Pfizer-BioNTech	• Transmission to contact 0-7 days following 1st dose	Pre-print Reduced infection transmission of the wild-type strain by

	Age: index case: unvaccinated, 56 ±15, recently vaccinated once, 63±12, fully vaccinated 68±9 additional case: unvaccinated, 56 ±15, recently vaccinated once, 63±12, fully vaccinated, 67±9 **Female%:** 50% **Total sample size**: 3627 **Date of Recruitment:** December 2020 – March 2021 **Overall RoB**: Serious **VOC**: NR	**Number of Doses:** 1 and 2	• Transmission to contact >7 days following 2nd dose	80.0% (95% CI: 73.0-85.1) compared to those who were unvaccinated.
Pouwels et al. (2021) **Country:** UK	Study Design: Prospective Cohort Observational **<u>Participants</u>** Participants aged 18 years or over (i.e., those who were eligible for vaccination), and all visits with positive or negative swab results from 1 December 2020 to 1 August 2021. **Age:** 28-57 **Female%:** 53.6-55.8% **Total sample size:** 10,853 **Date of Recruitment**: December 2020 – May 2021 **Overall RoB:** Serious **VOC:** Delta	**Vaccine:** BNT162b2, ChAdOx1, or Moderna **Manufacturer:** Pfizer-BioNTech, Moderna **Number of Doses:** 1 or 2	• Ct values 0 to 20 days following 1st dose • Ct values >21 days following 1st dose, or 0-13 days following 2nd dose • Ct values >14 days following 2nd dose	Pre-print Significantly higher Ct values (median=31.71) for individuals vaccinated with a single dose compared with seronegative unvaccinated individuals (median=28.7; p=0.02)
Salo et al. (2021) **Country:** Finland	Study Design: Retrospective **<u>Participants</u>** Vaccinated and unvaccinated HCW. An individual was included in this sample if their spouse is a healthcare	**Vaccine:** BNT162b2 or Moderna **Manufacturer**: Moderna, Pfizer	• Transmission to unvaccinated spouse 14 days and 10 weeks after 1st dose	Pre-print Highest reduction in transmission to unvaccinated

	worker and they had not been vaccinated during the sample period. **Age:** Vaccinated: 47.1 ±13.1 Unvaccinated: 43.8 ±14.5 **Female%:** 86.5% **Total sample size:** 288,138 **Date of Recruitment**: December 2020 – March 2021 **Overall RoB:** Serious **VOC:** NR	**Number of Doses:** 1 or 2	• Transmission to unvaccinated child 3-18 years, 14 days and 10 weeks after 1st dose • Transmission to unvaccinated child 3-12 years, 6 weeks and 10 weeks after 1st dose • Transmission to unvaccinated child 13-18 years, 6 and 10 weeks after 1st dose	spouses (42.9% [95% CI: 22.3 to 58.1]) and to unvaccinated children between the ages of 3 and18 years old, 32.9% (95% CI: 4.1 to 53.0).
Baltas et al. (2021) **Country:** UK	**Study Design**: Case-control **<u>Participants</u>** All SARS CoV-2 first positive cases recruited into the COG-UK-HOCI study between the 30th of September 2020 and 15th of March 2021 **Age:** median 79, IQR 65 – 86 **Female%:** 42.9% **Total sample size:** 511 **Date of Recruitment:** September 2020 – March 2021 **Overall RoB**: Serious **VOC:** B.1.1.7, B.1.525	**Vaccine:** BNT162b2 or ChAdOx1 nCOV-19 **Manufacturer**: Pfizer-BioNTech, Moderna **Number of Doses:** 1	• Ct values <14 and >14 following 1st dose	No significant difference in the median Ct values of vaccinated people compared with unvaccinated.

Abbreviations: RoB: Risk of Bias, Ct: Cycle threshold, HCWs: healthcare workers, VOC: Variant of concern, RCTs: Randomised controlled trials, RT-PCR: reverse transcription polymerase chain reaction test

7. ADDITIONAL INFORMATION

7.1 Conflicts of interest

The review team declare no conflicts of interest.

7.2 Acknowledgements

We thank Simon Rolfe and Catherine Moore for their advice and input as expert stakeholders for this review. We thank the authors of related evidence reviews conducted by University of Calgary and UK Health Security Agency for providing us with early access to their reports and/or to unpublished data, and for their cooperation and advice on methods.

7. ABOUT THE WALES COVID-19 EVIDENCE CENTRE (WCEC)

The WCEC integrates with worldwide efforts to synthesise and mobilise knowledge from research.

We operate with a core team as part of Health and Care Research Wales, are hosted in the Wales Centre for Primary and Emergency Care Research (PRIME), and are led by Professor Adrian Edwards of Cardiff University.

The core team of the centre works closely with collaborating partners in Health Technology Wales, Wales Centre for Evidence-Based Care, Specialist Unit for Review Evidence centre, SAIL Databank, Bangor Institute for Health & Medical Research/ Health and Care Economics Cymru, and the Public Health Wales Observatory.

Together we aim to provide around 50 reviews per year, answering the priority questions for policy and practice in Wales as we meet the demands of the pandemic and its impacts.

Director:
Professor Adrian Edwards

Contact Email:
WC19EC@cardiff.ac.uk

Website:
https://healthandcareresearchwales.org/about-research-community/wales-covid-19-evidence-centre

8. APPENDICES

Appendix 1. Medline Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to October 05, 2021>		
Vaccination		
1	exp Vaccination/	93087
2	Immunization/	52169
3	Vaccines/	23540
4	(vaccinat* or vaccine* or immuni* or innoculat*).tw,kw.	573682
5	COVID-19 Vaccines/	5505
6	(vaccinat* or vaccine* or immuni* or innoculat*).ti.	256544
7	(vaccinat* or vaccine* or immuni* or innoculat*).ab. /freq=2	252392
8	(vaccinat* or vaccine* or immuni* or innoculat*).kw.	49338
9	(active adj2 immunotherap*).tw,kw.	1712
10	(immune adj2 manipulat*).tw,kw.	918
11	or/1-4,9-10	605391
12	or/5-10	378531
Transmission		
13	exp Disease Transmission, Infectious/	75906
14	exp *Disease Transmission, Infectious/	44050
15	transmi*.tw,kw.	560823
16	COVID-19/tm [Transmission]	3878
17	transmi*.ti.	101247
18	transmi*.ab. /freq=2	139302
19	transmi*.kw.	8909
20	(attack* adj2 rate*).tw,kw.	5122
21	(communit* adj2 (spread* or circulat*)).tw,kw.	644
22	((virus or viral) adj2 (spread* or circulat*)).tw,kw.	10079
23	person-to-person.tw,kw.	3702
24	or/13,15,20-23	615916
25	or/14,16-23	249957
26	11 and 25	18532
Vaccination and transmission		
27	12 and 24	23111
28	26 or 27	30393
29	limit 28 to covid-19	2356
Additional terms		
30	((breakthrough* or break-through*) adj3 infect*).tw,kw.	990
31	limit 30 to covid-19	85
32	((susceptible* or vulnerable*) adj3 contact*).tw,kw.	421
33	limit 32 to covid-19	30
34	Viral Load/	36501
35	((viral or virus) adj load*).tw,kw.	37185
36	(duration* adj3 infecti*).tw,kw.	4393
37	or/34-36	59555
38	(16 or 24) and 37	8383
39	limit 38 to covid-19	686
Set combinations		
40	29 or 31 or 33 or 39	3025
41	exp animals/ not exp humans/	4894614
42	40 not 41	2964
43	limit 42 to english language	2907

Appendix 2. Review protocol

1. Background/context

SARS-CoV-2 infection can present as either symptomatic (COVID-19) or asymptomatic (no symptoms). In asymptomatic cases, people may not be aware that they are infected, but transmission can still occur. Various settings currently undertake regular testing for asymptomatic infection, such as schools, care homes and prior to hospital admission.

Many COVID-19 vaccines have been evaluated for their efficacy and effectiveness in reducing SARS-CoV-2 infection and for reducing the risk of symptomatic COVID-19 disease. However, breakthrough infections can still occur, and the effectiveness of COVID-19 vaccines against transmission from infected vaccinated people to either vaccinated or unvaccinated contacts is unclear. Better understanding of transmission risks in vaccinated populations would be useful to inform the need for continued routine asymptomatic testing.

2. Rapid Question(s)

What is the transmission risk of SARS-CoV-2 from vaccinated people?

3. Eligibility criteria

Table: Eligibility Criteria

	Inclusion criteria	Exclusion criteria
Population	People who have received partial or complete COVID-19 vaccination	
Settings	Any setting (we will report on specific transmission setting, where reported)	
Intervention / exposure	SARS-CoV-2 / COVID-19	
Comparison	Unvaccinated people with COVID-19 infection	
Outcome measures	SARS-CoV-2 transmission (including transmission rate, secondary attack rate) Ct values (used as a proxy to signify viral load) Duration of illness	
Study design	We will prioritise systematic reviews where possible, but include observational studies if required.	
Countries	Any	
Language of publication	English	
Publication date		
Publication type	Published and preprint	
Other factors *Any other key points to note*	We will also look for evidence in other respiratory viruses (e.g. influenza), if evidence on SARS-CoV-2 transmission is limited. We will also report symptom status (e.g. pre-symptomatic, asymptomatic, symptomatic, types and severity of symptoms), where reported.	

	Inclusion criteria	Exclusion criteria
	We will report on type of vaccination (including partial and complete vaccination status) and variant strains, e.g. variants of concern, if available.	

4. Incorporating data from existing reviews

The Rapid Evidence Summary identified systematic reviews assessing transmission in vaccinated populations. These will be used to extract relevant primary evidence for this rapid review.

5. Literature search

5.1 Evidence sources

The following sources will be searched:

Bibliographic databases:

- Medline
- Embase
- Cochrane Library
- Cochrane Covid-19 Study Register
- INAHTA HTA
- Epistemonikos [Love COVID for COVID specific search]

Additional sources:

- Trip Pro
- NICE COVID-19 evidence
- NICE Evidence Search
- Google advanced search

Ongoing studies:

- Clinicaltrials.gov
- WHO ICTRP [International Clinical Trials Registry Platform]
- PROSPERO database

5.2 Search Strategy

There are 3 concepts to this search: COVID-19, transmission, & vaccination. Both the transmission and vaccination concepts retrieve large numbers of hits, so we have explored ways to reduce the hits retrieved without losing relevant records.

1. Full search – where we search freely for the vaccination & transmission concepts both using controlled vocabulary and free-text searching
2. Two-pronged search – where the vaccination & transmission searches are focused in turn:
    a. focused vaccination + full transmission search
    b. full vaccination + focused transmission search

    Searches a & b are then combined using OR.
3. Focused search – where both the vaccination and transmission concepts are focused and the concept of infectivity is added into the transmission concepts to retrieve papers that are potentially missed due to the focusing.

When focusing the search the relevant terms must appear in the title/keywords or occur at least twice in the abstract.

We have also developed a strategy covering other respiratory diseases, transmission & vaccination. Our intention is to follow whichever approach is used for the COVID-19 search. The results from the COVID-19 search will be removed from the other respiratory diseases results prior to download.

The respiratory diseases that have been include are:

- influenza
- severe acute respiratory syndrome / SARS
- respiratory syncytial virus
- middle east respiratory syndrome / MERS
- parainfluenza

Following the meeting between HTW and WC19EC Core Team on Tuesday 5th October it was agreed that the search would proceed as follows:

- Option 2 with no study design search filters or date limits
- The list of resources given above is a stream-lined version of the original list and agreed in the meeting
- The other respiratory diseases search will not be carried out at this time. It may be required at a later date.

5.3 Reference management

References will be saved, de-duplicated, screened and stored with multiple EndNote reference libraries:

1. COVID-19 & vaccination & transmission
2. Other respiratory diseases & vaccination & transmission (as and when required)

6. Study selection process

References will be screened for eligibility using the criteria above. All references identified by the literature searches will be screened by title. Potentially relevant titles will then be scrutinised

7. Data extraction

Data extraction will be based on the outlined eligibility criteria. We will extract details/characteristics on study country, study design, number of participants, relevant outcomes (see eligibility criteria), study settings, vaccination status (of the infected cases and the contacts), virus strains, symptom status.

8. Assessment of methodological quality

Assessment of methodological quality is dependent upon the type of evidence identified.

9. Synthesis

We will undertake quantitative synthesis of the evidence based on the selection criteria outlined above. Where possible, we group reporting.