Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Duration of immunity (protection from reinfection) following SARS-CoV-2 infection

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About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services —** Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

List of abbreviations used in this report

ACE2	angiotensin-converting enzyme 2
aHR	adjusted hazard ratio
aIRR	adjusted incidence rate ratio
aRR	adjusted RR
BAU/mL	binding antibody units per millilitre
cDNA	complementary DNA
CCI	Charlson Comorbidity Index
CI	confidence interval
CKD	chronic kidney disease
COVID-19	Coronavirus disease 2019
Ct	cycle threshold
ELISA	enzyme-linked immunosorbent assay
ESKD	end stage kidney disease
GSA	geographical statistical area
HCW	healthcare worker
HIQA	Health Information and Quality Authority
HR	hazard ratio
HPSC	Health Protection Surveillance Centre
HSE	Health Service Executive
IgA	immunoglobulin A
IgM	immunoglobulin M
IgG	immunoglobulin G
IgGAM	immunoglobulins G, A, and M
IRR	incidence rate ratios

IQR	interquartile range
IU/ml	international units per milliliter
LTCF	long term care facilities
NAAT	nucleic acid amplification test
Nab	neutralising antibodies
NPHET	National Public Health Emergency Team
NCP	nucleocapsid protein
OR	odds ratio
PCR	polymerase chain reaction
POS	population outcome study design criteria
RADT	rapid antigen detection test
RBD	receptor-binding domain
RNA	ribonucleic acid
RR	relative risk
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	standard deviation
SES	socioeconomic status
SGTF	S-gene target failure
S protein	spike protein
UK	United Kingdom
US	United States
VHA	Veterans Health Administration
WGS	whole genome sequencing
WHO	World Health Organization

Glossary of terms/explanatory notes

Antibody	An antibody is a protein produced by the immune system that binds specifically to a particular substance (its antigen). Each antibody molecule has a unique structure that enables it to bind specifically to its corresponding antigen, but all antibodies have a similar overall structure and are known collectively as immunoglobulins or Igs. Antibodies are produced by plasma cells in response to infection or vaccination, and bind to and may neutralise pathogens (invading microorganisms) or prepare them for uptake and destruction by phagocytes (cells that destroy pathogens). Antibodies to not inhibit the multiplication of viruses within cells.
Cell-mediated immunity (or cellular immunity)	Cell-mediated immunity, or a cell-mediated immune response, describes any adaptive immune response in which antigen-specific T cells have the main role in protection. Once a virus enters a cell, cell-mediated immunity is the only effective immune response.
Cycle threshold (Ct)	In reverse transcriptase PCR, a positive reaction is detected by accumulation of a fluorescent signal. The Ct (cycle threshold) is defined as the number of cycles required for the fluorescent signal to cross the threshold (therefore exceed background level). The lower the Ct level, the greater the amount of target nucleic acid in the sample.
Genome	The genetic material of an organism.
Humoral immunity	Humoral immunity is another term for antibody-mediated immunity and the term 'humoral immune response' refers to the antibody response to a specific antigen.
Immunoglobulins	All antibody molecules belong to a family of proteins called immunoglobulins (Ig). Membrane-bound immunoglobulin serves as the specific antigen receptor on B lymphocytes.
IgG	IgG is the class of immunoglobulin characterised by γ heavy chains. It is the most abundant class of immunoglobulin found in the plasma and is also found in tissues.
Immunity	Immunity is the ability to resist infection.
Neutralising antibodies (NAb)	Neutralising antibodies are antibodies that are capable of preventing viruses from infecting cells. Neutralising antibodies usually bind the pathogen protein, which binds the receptor.
Pathogen	Pathogens are microorganisms that can cause disease when they infect a host.
Receptor-binding domain (RBD)	In the context of SARS-CoV-2, RBD refers to a specific section of the spike protein that binds to a molecule (ACE2 receptor) on the surface of human cells that allows the virus to enter the cell.

Reverse transcriptase–polymerase chain reaction	The reverse transcriptase–polymerase chain reaction (RT-PCR) is used to amplify RNA sequences. The enzyme reverse transcriptase is used to convert an RNA sequence into a cDNA sequence, which is then amplified by PCR.
Seroconversion	Seroconversion timing refers to the first time an individual tests positive for antibodies (based on serial serological samples).
Seropositive	When someone has detectable antibodies against a specific antigen
Seronegative	When someone does not have detectable antibodies against a specific antigen
Titre(s)	The strength of a solution or the concentration of a substance in solution as determined by titration.
Whole genome sequencing (WGS)	Whole-genome sequencing (WGS) is the analysis of the entire genomic DNA sequence of an organisml at a single time, providing the most comprehensive characterisation of the genome.

Version History

Version number	Date	Details
V1.0	13 May 2020	
V2.0	9 June 2020	Updated search with 35 new studies
V3.0	6 August 2020	Updated search with 28 new studies
V4.0	11 November 2020	Refined search with 28 new studies
V5.0	5 March 2021	Refined search with 5 new reinfection studies and scoping review on the long-term duration of immune response following SARS-CoV-2 infection
V6.0	14 April 2021	Updated search with 6 new reinfection studies
V7.0	3 June 2021	Updated search with 11 new reinfection studies and systematic search of immune memory responses following SARS-CoV-2 infection
V7.1	22 June 2021	Minor wording change to final paragraph on page 53, summarising the Bernal et al study published as a preprint on 24 May 2021.
V8.0	8 October 2021	Updated with 46 new studies

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Duration of immunity (protection from reinfection) following SARS-CoV-2 infection

Key points

- Sixty-five observational studies, that investigated the risk of SARS-CoV-2 reinfection, were identified that met the inclusion criteria.
- Nineteen studies exclusively included healthcare workers, seven studies included participants based on their vaccination and/or prior infection status, three studies included staff and or older residents of care homes, three studies included patients with chronic kidney disease (CKD), one study included both healthcare workers and patients with a high risk of exposure to SARS-CoV-2, one study included a broad range of essential workers, and one study included university students. The remaining 30 studies all related to general populations.
- Twenty of the 65 studies were conducted in the US; 12 were conducted in the UK; seven in Italy; three each were conducted in Iran and Switzerland; two each were conducted in France, Germany, Israel, Qatar, Sweden, and Spain; and one study each was conducted in Austria, China, Denmark, Egypt, India, Iraq, Mexico, and South Africa.
- Across all studies, the total number of PCR- or antibody-positive participants at baseline was 1,484,413 (median: 1,350; range: 88 to 378,606).
- The median follow-up of individuals within studies was 165 days (5.5 months) (range of medians: 54-300 days), with a maximum follow-up of ≥365 days (12 months) in 10 studies. The study with the longest maximum follow-up of over 17 months was conducted in Israel.
- Reinfection was a rare event: the median PCR- or antigen-confirmed reinfection rate was 0.6% across studies, ranging from 0% (zero reinfections in nine studies) to 5.9% (which was observed among healthcare workers in a study in the US).
- Confirmation of reinfection by whole genome sequencing (WGS) was conducted in five included studies. The rate of confirmed reinfection was low in each of these studies, ranging from 0.02% to 1.1%.
- All studies reported low relative rates of reinfection comparing prior positive (PCR and or antibody positive) and prior negative groups (no PCR positive and or antibody negative). However, between-study estimates were not directly comparable due to varying definitions for reinfection and different outcome measures. All studies, that separately reported symptomatic and 'all' reinfection

events, reported lower relative rates of symptomatic reinfections. For example, in a large sample of UK health care workers, the relative risk for 'any reinfection' was 0.16 (95% CI: 0.13–0.19), falling to 0.07 (95% CI: 0.06–0.10) for reinfections with COVID-19 symptoms.

- There was limited evidence of waning protection from natural immunity observed across the 11 included studies that examined reinfections over time (within the time frame of these studies). However, one included study found some evidence of reduced (but still high) protection from reinfection against the Delta variant, in the context of longer follow-up (maximum 17 months).
- Studies consistently demonstrated high levels of protection following infection, similar to vaccine-mediated effectiveness. In total, five studies separately reported protective effectiveness in previously infected and vaccinated groups; four of these studies found comparable or greater effectiveness associated with natural immunity; one study found lower effectiveness associated with natural immunity specifically in an older population.
- The risk of reinfection was found to be highest among older adults (≥65 years) in three studies, however no significant difference was found in one study and another study found a very small decreasing risk of reinfection with increasing age. In three studies reporting paediatric data, the risk and/or rates of reinfection were consistently lower in children (<18 years) with two of these studies reporting no cases of reinfection in children. Another study found higher counts of reinfections in the 10-19 age group than in other age categories, however a risk or relative risk was not reported.
- Six included studies assessed the risk of reinfection in subgroups with comorbid or immunocompromising conditions. Five of these studies found that individuals with chronic kidney disease or who were immunocompromised had a higher risk of reinfection, or were at high risk of mortality in the case of reinfection. The sixth study found no significant association between any covariate for comorbidity or an immunocompromising condition and risk of reinfection/breakthrough infection.
- One study directly assessed the relationship between serological antibody levels and reinfection risk among a cohort of dental practitioners in the UK. In this study, the risk of infection was 9.7% in participants who were seronegative at baseline compared to 2.9% in individuals who were seropositive (p=0.001). However, there were no PCR-proven infections among 64 individuals with a baseline anti-SARS-CoV-2 IgG level greater than 147.6 IU/ml (with respect to the WHO international standard NIBSC 20/136).
- Only 12 of the 65 included studies were considered of high methodological quality, with a number of issues identified across studies. Apart from the

inherent biases associated with observational study designs, many studies were downgraded due to poor quality of reporting and for inadequate control of confounders. A recognised limitation of a number of studies was the risk of outcome ascertainment bias. In addition, 15 of the 65 studies are currently published as preprints.

- Importantly, the findings from these observational studies which were largely conducted in the context of stringent public health measures and less transmissible variants, may have limited generalisability to the current context of easing public health measures and a more transmissible Delta variant.
- There is still uncertainty on a range of issues, including the:
  - durability of protective immunity over time
  - protective immunity in paediatric populations
  - the potential for additional protection from vaccination in those with a history of prior infection
  - duration and extent of protective immunity in populations with comorbidities and in those with immunocompromising conditions
  - impact of new variants on protective immunity.
- In conclusion, the evidence suggests that the risk and relative risk of SARS-CoV-2 reinfection is low for over 12 months post-infection. However, there is also some evidence that the duration and or extent of protective immunity following infection may be lower in older adults, in patients with CKD and those with immunocompromising conditions.

Duration of protective immunity following SARS-CoV-2 infection

Background

The Health Information and Quality Authority (HIQA) has developed a series of evidence syntheses to inform advice from HIQA to the National Public Health Emergency Team (NPHET). The advice takes into account expert interpretation of the evidence by HIQA's COVID-19 Expert Advisory Group.

The following specific research question was developed and will form the basis of this evidence summary:

How long does protective immunity (that is, prevention of RT-PCR or antigen-confirmed reinfection) last in individuals who were previously infected with SARS-CoV-2 and subsequently recovered?

This evidence summary is expected to inform a range of policy questions relating to the duration of protective immunity following infection with SARS-CoV-2. Relevant policy questions include the following:

- How long can asymptomatic individuals who have recovered from a prior SARS-CoV-2 infection be:
    - exempted from restriction of movement policies if they become a close contact of a confirmed COVID-19 case?
    - exempted from derogation policies if they become a close contact of a confirmed COVID-19 case?
    - exempted from serial testing, for example serial testing in indoor settings where social distancing is difficult (such as food processing facilities)?
    - exempted from testing prior to scheduled admission to hospital or inter institutional transfer?
    - exempted from travel-related testing requirements?
    - considered at low risk of onward transmission in a household setting?

Seven previous evidence summaries relating to immunity following SARS-CoV-2 infection have been published by HIQA (13 May 2020, 9 June 2020, 6 August 2020, 11 November 2020, 5 March 2021, 14 April 2021 and 3 June 2021). In the 3 June

2021 review, HIQA concluded that SARS-CoV-2 reinfection rates remain low for over ten months following initial infection. Based on a second systematic review of the long-term duration of immune responses, HIQA also found that, while there may be a waning of antibody responses over time, immune memory lasts for up to nine months post-infection. The findings of the immune memory review therefore supported the findings of the reinfection review.

Due to the rapidly evolving evidence base relating to the duration of SARS-CoV-2 immunity, this review updates the evidence base relating to protection from reinfection. The update follows a similar search strategy to previous iterations. The systematic review of immune memory was not updated in the current review.

Methods

A standardised protocol was adhered to and is available on the HIQA website. This evidence summary has been reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement.[1]

The following databases were searched on 5 October 2021, using the search strategies outlined in the protocol:

- Medline (Ebsco)
- Embase (Ovid).

A simplified search strategy using the keywords "SARS-CoV-2" and "reinfection" was used to identify relevant preprints in Europe PMC https://europepmc.org on 5 October 2021. A Google Scholar search was also conducted to identify preprints. This search was restricted to articles published in 2021 and the following sites: Research Square https://www.researchsquare.com/, Authorea https://www.authorea.com, Medrxiv https://www.medrxiv.org**/,** OSF Preprints https://osf.io/preprints/. A Google search was conducted on the 5 October 2021 to identify very recent studies. The first five pages of results were screened.

Forward citation searching of the 19 studies included in version 7 of the review was also conducted.

Table 1 outlines the Population Outcome Study design (POS) criteria for study selection relating to the systematic search for observational cohort studies that report the risk of reinfection over time.

Table 1: Population Outcome Study design (POS) criteria – reinfection review

Population	Individuals (of any age) with evidence of prior SARS-CoV-2 infection, who subsequently recovered.* Evidence of prior infection includes diagnosis by RT-PCR or antigen testing, or evidence of an immune response through antibody detection (seropositivity). Subgroups include healthcare workers, age groups, high risk/very high risk groups,** and vaccinated populations**
Outcomes	**Prevention of reinfection** Primary outcomes: 1. Relative risk of RT-PCR or antigen-confirmed SARS-CoV-2 reinfection,*** comparing populations with evidence of prior infection with populations with no prior evidence of infection, at specified time points

	2. Risk of RT-PCR or antigen-confirmed SARS-CoV-2 reinfection over time 3. Time interval between first and second infections 4. RT-PCR cycle threshold (Ct) results, if reported 5. Whole genome sequencing (WGS) results of reinfected cases comparing first and second infections, if reported 6. Antibody titres in those who are reinfected versus those with no evidence of reinfection, if reported.
Types of studies	**Include:** ▪ Observational studies (prospective or retrospective) **Exclude:** ▪ Cohort studies that included fewer than 100 participants ▪ Case studies ▪ Studies with durations of follow-up of less than 3 months ▪ Animal studies.

*'Recovered' refers to molecular or clinical evidence of viral clearance following initial infection; definitions of recovery in primary studies were used. Common definitions include two consecutive negative respiratory RT-PCR tests 24 hours apart and WHO clinical criteria of viral clearance (27 May 2020).[2] **Definitions used by HSE[3, 4] *** Definitions of reinfection in primary studies were used. A gold-standard confirmation of SARS-CoV-2 reinfection will require confirmation of initial infection and virus detection across two distinct time periods with genetic sequencing data needed to support a conclusion of high probability that reinfection has occurred. Possible SARS-CoV-2 reinfection could be differentiated from persistent viral carriage through a variety of laboratory-based parameters, patient symptomology, and/or epidemiologic links. Common definitions include persons with detected SARS-CoV-2 RNA ≥90 days after the first detection of SARS-CoV-2 RNA, whether or not symptoms were present (US Centers for Disease Control and Prevention, 27 Oct 2020).[5]

Results

The electronic database search resulted in 2,452 records, with an additional 45 records retrieved from other sources (citation searching). Following removal of duplicates, 1,890 reports from electronic databases were screened for relevance. A total of 1,826 records were excluded at title and abstract screening, resulting in 64 reports eligible for full text review. After excluding 38 reports (reasons for exclusion in Appendix 1), this resulted in 26 studies identified from electronic database searching eligible for inclusion. Of the 45 records identified through citation searching, 20 met the inclusion criteria. Therefore, 46 studies were eligible for inclusion in this update.[6-51] Nineteen studies from the previous version of the evidence summary were also included,[52-70] so that 65 studies were included in total (Figure 1).

Nineteen studies exclusively included healthcare workers,[7, 15-17, 20, 22, 24, 25, 34-36, 41, 46, 48, 50, 54, 55, 65, 70] seven studies included participants based on their vaccination and/or prior infection status,[8, 21, 26, 38, 45, 51, 61] three studies included staff and or older residents of care homes,[10, 58, 59] three studies included patients with chronic kidney disease (CKD),[14, 44, 47] one study included both healthcare workers and patients with a high risk of exposure to SARS-CoV-2,[37] one study included a broad range of essential workers,[28] and one study included university students.[32] The remaining 30 studies all related to general populations.[6, 9, 11-13, 18, 19, 23, 27, 29-31, 33, 39, 40, 42, 49, 52, 53, 56, 57, 60, 62-64, 66-69]

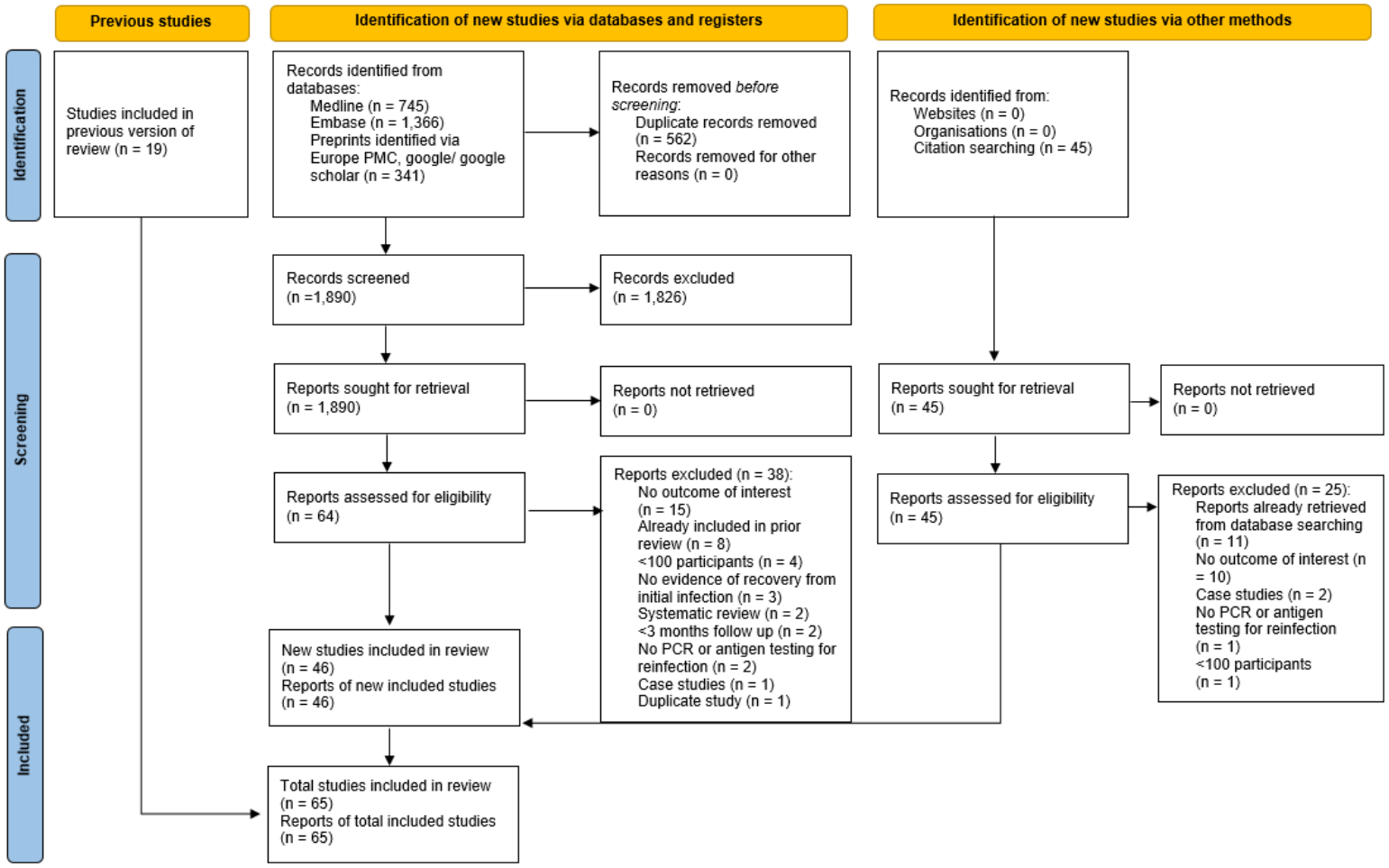
Twenty of the 65 studies were conducted in the US;[10, 12, 14, 18, 26, 27, 32, 34, 37-39, 41, 42, 45, 49, 51, 57, 65, 68, 69] 12 were conducted in the UK;[7, 11, 23, 44, 48, 53-55, 58, 59, 61, 70] seven were conducted in Italy;[15, 19, 31, 35, 40, 50, 62] three each were conducted in Iran[36, 43, 64] and Switzerland;[25, 28, 60] two each were conducted in France,[16, 20] Germany,[22, 46] Israel,[21, 66] Qatar,[8, 52] Sweden,[24, 33] and Spain;[17, 63] and one study each was conducted in Austria,[67] China,[29] Denmark,[56] Egypt,[6] India,[47] Iraq,[9] Mexico,[30] and South Africa.[13]

Fifteen studies are currently published as preprints.[8, 13, 18, 21, 25, 26, 28, 34, 36, 38, 42, 50, 51, 64, 66]

Across studies, the total number of PCR- or antibody-positive participants at baseline was 1,486,413 (median: 1,350; range: 88 to 378,606). The longest duration of follow-up was not stated in all studies, or was provided only as an approximate estimate. When not stated, duration of follow-up was inferred from figures or tables within the study. The median follow-up of individuals within studies was 165 days (5.5 months) (range of medians: 54-300 days), with a maximum follow-up of ≥365 days (12 months) in 10 studies.[16, 17, 19-21, 27, 38, 40, 45, 46] This compares with a median of 135 days (4.5 months) and a maximum of ≥300 days (ten months) follow-up across the 19 studies included in version 7 of this evidence summary. The study with

the longest maximum follow-up duration of over 17 months was conducted by Gazit et al. in Israel.[21] Studies reported a range of primary endpoints (Table 2 and Appendix 2).

Figure 1: PRISMA 2020 flow diagram of study selection



Key: *Record*—The title or abstract (or both) of a report indexed in a database or website (such as a title or abstract for an article indexed in Medline). Records that refer to the same report (such as the same journal article) are "duplicates"; however, records that refer to reports that are merely similar (such as a similar abstract submitted to two different conferences) are considered unique. *Report*—A document (paper or electronic) supplying information about a particular study. It could be a journal article, preprint,

conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report, or any other document providing relevant information. *Study*—An investigation, such as a clinical trial, that includes a defined group of participants and one or more interventions and outcomes. A "study" might have multiple reports. For example, reports could include the protocol, statistical analysis plan, baseline characteristics, results for the primary outcome, results for harms, results for secondary outcomes, and results for additional mediator and moderator analyses.

Table 2: **Summary** of included studies and primary outcome results

First author Country	Participants[a] Follow-up	Author reported primary outcomes	Quality appraisal[l]
General population (n=30)			
Abdelrahman 2021[6] **Egypt**	N=172 **Maximum f/u:** 10 months	**Risk of reinfection:** During the follow-up, six females (3.5%) had laboratory-confirmed COVID-19 re-infection. Their mean age was 35.7 ± 11 years. The mean interval from the complete recovery of the first infection to the onset of the second one was 53 ± 22.2 days with a range from 30 to 90 days. The second infection was milder in severity than the first infection, in 83.3% of cases.	'Poor' quality
Ali 2021[9] **Iraq**	N=829 **Mean f/u:** 5.25 months	**Risk of reinfection:** 3.13% (26 of 829 patient). 25 patients were in the IgG-negative group, and only one patient was IgG-positive. The occurrence of reinfection in the group ranged from 26 to 138 days after recovery from the initial infection. The average Ct value of the first infection in those that were re-infected was 31.47. The average Ct value upon reinfection was 22.88.	'Fair' quality
Abu-Raddad 2021[52] **Qatar**	N=43,044 **Median f/u:** 114 days (3.8 months) **Maximum f/u:** 242 days (8.1 months)	**Risk of reinfection (confirmed by WGS)[b]**: 0.17% (95% CI: 0.10 to 0.30%) **Risk over time:** Incidence rate of reinfection by month of follow-up did not show any evidence of waning of immunity over seven months of follow-up	'Fair' quality
Breathnach 2021[11] **UK**	N=224 (RNA-positive, Antibody negative in first wave) N=2,087 (RNA positive, Antibody positive in first wave) **Minimum f/u:** 4 months **Maximum f/u**: 9 months	**Risk of reinfection:** RNA-positive antibody-negative patients: 2 out of 224 patients reinfected. 0.89% (with ≥90 days between infection events). RNA-positive antibody-positive patients: 18 out of 2,087 patients reinfected. 0.86% (with ≥90 days between infection events). **Relative risk of reinfection**= RNA-positive antibody-negative patients compared to those with no lab evidence of COVID-19 in first wave: 0.20 (95% CI: 0.05 to 0.81). RNA-positive antibody-positive patients compared to RNA-positive antibody negative patients: 1.04 (95% CI: 0.24 to 4.43)	'Fair' quality
Breathnach 2021[53] **UK**	N=10,727 **Median f/u:** N/R **Maximum f/u:** Approx. 11 months (February to December 2020)	**Risk of reinfection:** 0.07% (with ≥90 days between infection events) Of note, there were no reinfections in the first seven months after the peak of the first wave; all eight patients with likely reinfections were diagnosed in December, the last month of the study period; reinfections accounted for 1.69% of all infections in that month[m] **Relative risk of reinfection[c]**= 0.058 (95% CI: 0.029 to 0.116)	'Fair' quality
Caralis 2021[12] **US**	N=600 **Maximum f/u:** Approx. 6 months (12 April 2020 to 21 October 2020)	**Risk of reinfection:** 1.2%, 7 reinfections out of 600. The patients re-tested were COVID-19 PCR positive again an average of 94.9 days (range 62-172 days) after their original presentation and first COVID-19 PCR positive test.	'Poor' quality
Cohen 2021[13] **South Africa**	N=406 **Maximum f/u:** 37 weeks	**Risk of reinfection:** 3% (12/406) experienced a re-infection. Of 12 repeat infection episodes, 6 (50%) were classified as possible and 5 (42%) as probable and 1 (8%) confirmed.	'Good' quality

		Relative risk of reinfection: Documented infection on rRT-PCR or serology prior to the start of the second wave was associated with 84% protection against infection in the second wave (relative risk (RR) 0.16, 95% CI 0.07-0.35. Attack rate in individuals with previous infection (probable and confirmed reinfection) was 3% (6/211) vs 18% (177/978) in individuals without previous infection.	
Finch 2021[18] **US**	N=309 **Maximum f/u:** 6 months	**Rate of reinfection:** 14 possible reinfections out of 309 seropositive individuals (4.5%). **Time to reinfection:** Median time of 66.5 days between initial seropositive test and PCR positive test. **Odds ratio for reinfection:** Adjusted odds ratio of 0.09 (95% CI: 0.005 – 0.48)	'Good' quality
Flacco 2021[19] **Italy**	N=7,173 **Mean f/u**: 201 days (>6 months) **Minimum f/u**: 90 days **Maximum f/u**: 414 days (>12 months)	**Risk of reinfection:** 0.33%, 24 out of 7,173 subjects reinfected. Nine of the re-infected subjects received a first vaccine dose during the follow-up. The mean age and the proportion of subjects with ≥1 comorbidity were substantially higher among those who were reinfected than those who were not (mean age: 54.5 ± 18.4 versus 46.3 ± 21.8 years and 41.7% versus 20.6%, respectively).	'Fair' quality
Graham 2021[23] **UK**	N= 36,509 (out of 1,767,914 users reported a positive swab test at baseline) **Median f/u**: NR **Maximum f/u**: NR	**Risk of reinfection:** 0.7% (95% CI 0.6% to 0.8%), 249 out of 36,509 users reinfected with a period of at least 7 symptom-free days in between positive tests. No change in symptoms or disease duration was found in the context of SARS-CoV-2 Alpha variant. There was no evidence that the frequency of reinfections was higher for the Alpha variant.	'Poor' quality
Hansen 2021[56] **Denmark**	N= 11,068 **Median f/u:** 122 days (4.1 months) **Maximum f/u:** 295 days (9.8 months)	**Main analysis:** **Adjusted rate ratio (aRR) of reinfection**=0.20 (0.16–0.25) This represents 72 reinfections out of 1,346,920 person-days in PCR positive group, compared with 16,819 new infections out of 62,151,056 person-days in PCR negative group. **Additional cohort analysis (that includes all infection periods):** aRR=0.21 (0.18–0.25) By age group: 0-34 years: aRR=0.17 (0.13–0.23); 35–49 years: aRR=0.20 (0.14–0.28); 50–64 years: aRR=0.19 (0.13–0.27); ≥65: years: aRR=0.53 (0.37–0.75)	'Good' quality
Harvey 2021[57] **US**	N=378,606 Median f/u: 54 days (1.8 months) Maximum f/u: 92 days (3.1 months)	Ratio of positive NAAT results (comparing patients who had a positive antibody test at index versus those without)[d]: 2.85 (95% CI: 2.73 to 2.97) at 0-30 days; 0.67 (95% CI: 0.6 to 0.74) at 31-60 days ; 0.29 (95% CI: 0.24 to 0.35) at 60-90 days; 0.10 (95% CI: 0.05 to 0.19) at >90 days	'Poor' quality
Leidi 2021[60] **Switzerland**	N=498 **Mean f/u:** 249 days (8.3 months) **Maximum f/u:** Approx. 10 months	Seropositive group: 5/498 reinfections; incidence: 0.3 per 1,000 person-weeks (considered 'likely' reinfections)[e] Seronegative group: 154/996 infections; incidence: 4.8 per 1,000 person-weeks **Hazard ratio for reinfection**: 0.06, 95% CI 0.02 to 0.14, p<0.001 (with propensity matching)	'Good' quality
Lawandi 2021[27] **US**	N= 131,773 patients received ≥1 positive SARS-CoV-2 PCR result at baseline **Median f/u**: NR **Maximum f/u**: 12 months	**Risk of reinfection:** 0.2%, 235 out of 131,773 suspected reinfection. **Hazard ratio:** hazard ratio for suspected reinfection in women vs men, 1.58 [95% CI: 1.28-1.94]; P < .001.	'Fair' quality

		Patients tend not to be markedly sicker in subsequent episodes. The majority of reinfections required the same level of care as the initial infection. Geographic differences in reinfection rates, stratified by month were not identified	
Manica 2021[62] Italy	N=1,402 **Maximum f/u:** 8 months	Cumulative incidence of symptomatic infections in seropositive group: 0.14% (95%CI: 0.04% to 0.57%) Cumulative incidence of symptomatic infections in seronegative group: 2.60% (95% CI: 2.08% to 3.26%) **Adjusted odds ratio** of developing symptomatic infection: 0.055 (95% CI: 0.014 to 0.220) Note: Investigators used RT-PCR *or* rapid antigen testing to identify reinfection cases.	'Good' quality
Masia 2021[63] Spain	N=146 **Maximum f/u:** 6 months	**Reinfection rate based on whole genome sequencing:** 1 confirmed reinfection out of 146 primary infections (0.68%)	'Good' quality
Mei 2021[29] China	N= 3,677 COVID-19 survivors **Mediam f/u:** 144 days (4.8 months) **Minimum f/u:** 135 days (4.5 months) **Maximum f/u:** 157 days (5.2 months)	**Risk of reinfection:** 1.2%, 45 out of 3,677 reinfected. The median duration between initial hospital discharge and retest positivity was 32.0 days (IQR = 28.0–40.0, range = 9–58). **Antibody titres:** Two of the 45 retest-positive survivors had both IgG and IgM antibodies, 26 were IgG-positive and IgM-negative, two were IgG-negative and IgM-positive, and the remaining 15 were negative for both antibodies. During follow-up, a dramatic reduction in anti-SARS-CoV-2 IgG (88.0%, 95% CI = 84.2–90.4) and IgM (93.2%, 95% CI = 88.5–96.4) antibodies was observed.	'Fair' quality
Murillo-Zamora 2021[30] Mexico	N=99,993 **Mean f/u:** 82.7 days	Risk of reinfection: 0.21%; incidence density was 2.5 reinfections per 100,000 person-days. **Adjusted relative risk of reinfection:** High-risk conditions included the personal history of an immunocompromising condition (RR=1.0038, 95% CI: 1.0011 to 1.0065) or chronic kidney disease (RR=1.0039, 95% CI: 1.0016 to 1.0063). When compared with homemakers, healthcare workers (RR=1.0042, 95% CI: 1.0030 to 1.0055) and other healthcare-related employees (RR=1.0025, 95% CI: 1.0012 to 1.0039) showed an increased reinfection risk.	'Fair' quality
Mohamadreza 2021[64] Iran	N=1,899 **Maximum f/u:** 6 months	Symptomatic reinfection rate: 1.9% (37/1,899)	'Poor' quality
Peghin 2021[31] Italy	N=546 **Median f/u:** 10 months (IQR 6.2–10.4)	**Risk of reinfection:** 1.1% (6 out of 546 patients) All had a previous history of mild COVID-19 (all were healthcare workers) and reinfection occurred a median of 9 months (IQR 8.2–10.2) after the onset of the first episode. Reinfection rates did not differ significantly in seronegative individuals.	'Fair' quality
Peltan 2021[49] US	N=23,176 RT-PCR positive patients **Median f/u:** 85.5 (74–107) days. **Maximum f/u**: 222 days (7.5 months)	**Risk of reinfection:** 10/23,176 (0.04%) – probable or possible recurrence based on virologic data. 114/23,176 (0.49%) – clinical likelihood of recurrence.	'Fair' quality
Perez 2021[66]	N=149,735	**Overall reinfection risk:** 0.1% (at any time between March 2020 and January 2021)	'Fair' quality

Israel	**Median f/u:** 165 days (5.5 months) **Maximum f/u:** Approx. 325 days[f] (10.8 months)	This represents 154 individuals who had two positive tests at least 100 days apart out of 149,735 individuals with a record of a prior positive PCR test.	
Pilz 2021[67] **Austria**	N=14,840 **Median f/u:** 210 days (7 months) **Maximum f/u:** 300 days (10 months)	**Odds Ratio:** 0.09 (95% CI: 0.07 to 0.13) This represents 40 reinfections out of 14,840 individuals PCR positive in the first wave (0.27%) compared with 253,581 infections out of 8,885,640 (2.85%) in the remaining general population.	'Fair' quality
Qureshi 2021[68] **US**	N=9,119 **Mean** interval between positive tests: 116 days (3.9 months) **Maximum f/u:** N/R; time period applied to dataset: 1 December 2019 to 13 November 2020.	Reinfection rate: 0.7% (95% CI: 0.5%-0.9%), 63/9,119 individuals	'Fair' quality
Ringlander 2021[33] **Sweden**	N=6,014 **Mean f/u:** 7 months	**Risk of reinfection:** 0.02% (1 out of 6,014 patients). Of the 5 patients with cycle threshold values low enough to qualify for whole genome sequencing, 1 was classified as reinfection, 3 as persistent infection and 1 as a technical failure.	'Fair' quality
Slezak 2021[39] **US**	N= 75,149 initial PCR positive at baseline **Median f/u**: NR **Maximum f/u**: 270 days (9 months)	**Cumulative risk of reinfection:** 0.8% (95% CI 0.7 - 1.0%) at 270 days following initial infection. **Hazard ratios:** Adults were significantly more likely to have a suspected reinfection than children (age 18-39: HR 2.71, CI 1.38-5.31, age 40-59: HR 2.22, CI 1.12-4.41, age 60: HR 2.52, CI 1.23-5.17 versus <18 years).	'Fair' quality
Sheehan 2021[69] **US**	N=8,845 **Median f/u:** 138.9 days (4.6 months) **Maximum f/u:** 294.9 days (9.8 months)	Protective effectiveness against any reinfection: 81.8% (95% CI: 76.6% to 85.8%)[g] Protective effectiveness against symptomatic infection: 84.5% (95% CI: 77.9% to 89.1%)	'Fair' quality
Vitale 2021[40] **Italy**	N= 1,579 Positive PCR test at baseline, n=12,968 negative result at baseline and during follow-up; n=528 negative result that converted to positive during follow-up **Median f/u**: 280 days **Maximum f/u**: 314.5 days (10.5 months) for baseline positive PCR participants; 12 months for the study cohort **Minimum f/u**: 7 months for the study cohort	**Risk of reinfection:** 0.31% (95% CI: 0.03% to 0.58%), 5 out of 1,579 reinfected. **Adjusted Relative risk of reinfection**: With those previously infected less likely to become reinfected relative to those with no history of infection. Incidence rate ratio, 0.07 (95% CI: 0.08 to 0.08; log-rank test P < .001) adjusted for age, sex, ethnicity, and the region. **Cumulative risk rate**: during follow-up, hazard ratio between reinfection and infection cohorts is 0.06; 95% CI, 0.05-0.08; log-rank test P < 0.001.	'Good' quality

Yoo 2021[42] **US**	N= 234,866 Positive PCR test at baseline **Median f/u:** NR **Minimum f/u:** 42 days	**Risk of reinfection:** 0.034%; 79 had two positive RT-PCR tests separated by more than six weeks, with a positive IgG test in between out of a cohort size of 234,866. The median number days between a positive IgG test and a subsequent positive RT-PCR test is 21 (IQR 24.5). Comorbid conditions associated with a compromised immune system rank high on the list for patients with potential reinfection.	'Poor' quality
Zare 2021[43] **Iran**	N = 4,039 Positive PCR test at baseline. (N = 8,734 total) **Maximum f/u:** 9 months	**Risk of reinfection:** 0.25% (10 out of 4,039) or 2.5 per thousand (95% CI: 1.2 to 4.5). Four patients over 80 years old with one or more underlying diseases died at the hospital due to COVID-19.The mean age of patients was 64 ± 28 years ranging from 13 to 90. 60% of those reinfected were male. **Time interval:** The mean time interval between the first infection and re-infection was 134.4 ± 64.5 days (range 41–234 days).	'Fair' quality
Health care workers (n=20)			
Abo-Leyah 2021[7] **UK**	N=300 Maximum f/u: 6 months	**Risk of reinfection:** 0.03% (1 of 300 detected by RT-PCR 76 days after having detectable antibodies in their serum) **Relative risk of reinfection:** Hazard ratio 0.15, 95% CI 0.06 to 0.35, p=0.026 over a follow-up period of up to 6 months.	'Fair' quality
Comelli 2021[15] **Italy**	N=160 Median time elapsed between the first positive test in the 1st wave and the first positive test in the 2nd wave was 235 days	**Risk of reinfection:** 1 of 160 (0.6%). 9 of 160 HCWs who tested positive in the 1st wave and who repeated NPS during 2nd wave were positive (5.6%), but 8 of these had a high Ct value.	'Fair' quality
Davido 2021[16] **France**	N=236 **Maximum f/u:** 1 year	**Risk of reinfection:** 0 probable reinfections. 5 suspected reinfections.	'Fair' quality
Dobano 2021[17] **Spain**	N=173 **Maximum f/u:** 12.5 months	**Risk of reinfection:** 2/173 (1.16%) symptomatic reinfection. Two symptomatic reinfection cases were seronegative at baseline, one asymptomatic was seropositive with low antibodies, and one had unknown serostatus. In total, 4 of 173 (2.3%) potential reinfections (three likely reinfections, one suspected).	'Fair' quality
Gallais 2021[20] **France**	N=393 **Maximum f/u:** 13 months	**Risk of reinfection:** One of 393 was reinfected (0.3%) over a nine month course (incidence of 0.40 per 100 person-years).	'Good' quality
Gehring 2021[22] **Germany**	N=98 **Median f/u:** 101 days	**Risk of reinfection:** 0 of 98.	'Fair' quality

Glück 2021[46] Germany	N = 136. **Follow-up:** approx. 12 months.	**Risk of reinfection:** 0 of 136.	'Poor' quality
Hall 2021[71] UK	N=8,278 **Median f/u:** 275 days (9.1 months) (IQR 218–291 days) for the positive cohort and 195 days (6.5 months) (IQR 131–214 days) for the negative cohort. **Maximum f/u:** >11 months	**Incidence density:** 7.6 reinfections per 100,000 person-days in the previous positive cohort compared with 57.3 primary infections per 100,000 person-days in the previous negative cohort **Adjusted incidence rate ratio of reinfection comparing antibody or PCR-positive group with negative group:**[h] ▪ All events (possible and probable reinfections): 0.16 (95% CI: 0.13–0.19) ▪ Symptomatic reinfections only (with COVID-19 symptoms): 0.07 (95% CI: 0.06–0.10) ▪ Asymptomatic reinfections only: 0.48 (95% CI: 0.37–0.63) ▪ Probable reinfections only: 0.002 (95% CI: 0.00–0.01)	'Good' quality
Hanrath 2020[55] UK	N=1,038 **Median f/u:** 173 days (5.8 months) **Maximum f/u:** 229 days (7.6 months)	**Symptomatic reinfection:** A positive PCR test was returned in 0/1,038 (0% [95% CI: 0–0.4) of those with previous infection, compared with 290/10,137 (2.9% [95% CI: 2.6–3.2) of those without (P<0.0001 χ^2 test).	'Fair' quality
Havervall 2021[24] Sweden	N=252 **Maximum f/u:** 12 weeks	**Risk of reinfection:** 3 of 252 (1%), corresponding to 0.13 cases per 100 weeks at risk. **Relative risk of reinfection:** Incident rate ratio was 0.05 (95% CI 0.01-0.18), with a protective effect of 95.2% (95% CI 81.9-99.1%) for HCWs that were seropositive at baseline.	'Fair' quality
Kohler 2021[25] Switzerland	N=144 **Median f/u:** 7.9 months	**Risk of reinfection:** 4.5%, 3 out of 67 seropositive patients who underwent testing tested positive **Relative risk of reinfection:** RR of 0.22 (95%-CI: 0.07 to 0.66, P=0.002) for a positive SARS-CoV-2 test after positive baseline serology.	'Poor' quality
Narrainen[48] 2021 UK	N=115 **Median f/u:** 131 days (approx. 4.4 months). **Minimum f/u:** 99 days (approx. 3.3 months). **Maximum f/u:** 168 days (approx. 5.6 months).	**Risk of reinfection:** One out of 115 (0.87%) individuals previously infected developed infection compared with 104 out of 423 individuals with no evidence of previous infection. **Relative risk of reinfection* (or Odds Ratio):** The attack rate was 0.87% in the 'evidence of previous infection' group compared to 24.59% in the 'no evidence of previous infection' group (odds ratio 0.027, 95% CI 0.004– 0.195, p<0.001).	'Fair' quality
Papasavas 2021[65] US	N=433 **Median f/u:** 5.5 months **Maximum f/u:** 196 days (6.5 months)	0/35 seropositive participants had a subsequent PCR test at least 30 days following the positive antibody test had a positive test 1.3% (29/2173) of seronegative participants had a subsequent positive PCR test	'Fair' quality
Rivelli 2021[34] US	N=2,625 **Median f/u:** 5.6 months	**Risk of reinfection:** 5.94% (156/2,625) experienced reinfection. Incidence rate of COVID-19 reinfection was 0.35 cases per 1,000 person-days.	'Fair' quality

Ronchini[50] 2021 Italy	N=266 infected individuals in the pre-vaccination period (of a total of 1,493 included) **Maximum f/u:** 6 months for pre-vaccination cohort	**Risk of reinfection:** 8/266 (3%) potential reinfections. 7 of the 8 re-infected subjects were IgG+ at the time of enrolment. **Relative risk of reinfection:** Subjects that were IgG+ at the time of enrolment had 66% significantly lower probability of having a positive swab (OR=0.34, 95%CI: 0.14- 0.80, P=0.014).	'Poor' quality
Rovida 2021[35] Italy	N=1,460 **Maximum f/u:** Approx. 6 months	**Absolute and relative risk of reinfection:** 1.78% seropositive subjects (26/1,460) reinfected. Odds ratio: 0.26 (95% CIl: 0.17-0.38).	'Fair' quality
Sabetien 2021[36] Iran	N=5349 **Maximum f/u:** Up to 10 months	**Risk of reinfection:** 97 cases of reinfection from 5,349 previously infected were detected (1.8%). **Adjusted reinfection rates:** The adjusted rate ratio (aRR) of infection was 0.052 (95% CI: 0.043–0.064) among those who previously tested positive compared with those who had previously only tested negative. The estimated protection against repeat infection after a previous SARS-CoV-2 infection was 94.8% (95% CI: 93.6–95.7).	'Poor' quality
Shields 2021[70] UK	N=246 (dental practitioners) Maximum f/u: 6 months	**Adjusted risk ratio** for reinfection: 0.25 (95% CI 0.09 to 0.73) The risk of infection was 9.7% in participants who were seronegative at baseline, compared to 2.9% in individuals who were seropositive (p=0.001) Serological analysis: there were no PCR-proven infections in 64 individuals with a baseline anti-SARS-CoV-2 IgG level greater than 147.6 IU/ml (with respect to the WHO international standard NIBSC 20/136).	'Good' quality
Wilkins 2021[41] US	N=316 **Median f/u:** 216 days	**Risk of reinfection:** 8 of 316 (2.5%) possible reinfections. Possible reinfection rate was 1.27 per 10,000 days at risk (95% CI: 0.55 to 2.51). **Relative risk of reinfection:** Crude incidence rate ratio was 0.30 (95% CI: 0.15 to 0.60) for participants who were seropositive at baseline compared with those who were seronegative at baseline. **Adjusted estimates:** When adjusted for age, sex, race, and occupation, incidence rate ratio was 0.26 (95% CI: 0.13 to 0.53).	'Fair' quality
Schuler 2021[37] US	N=129 **Mean f/u:** 126 days	**Risk of reinfection:** No initially seropositive subjects experienced a subsequent COVID-19 infection during the follow-up.	'Poor' quality
Residents and staff of care homes for older people (n=3)			
Armstrong 2021[10] US	N=6,079 **Maximum f/u:** 9 months	**Risk of reinfection:** 2.6% (156/6,079) of nursing home residents. Median time to repeat positivity of 135 days (range 90– 245 days).	'Fair' quality

Jeffery-Smith 2021[58] UK	N=88 **Mean f/u:** 120 days (4 months) **Maximum f/u:** unclear	**Relative Risk:** 0.04 (95% CI: 0.005–0.27) This represents 1 reinfection out of 88 in seropositive group compared with 22/73 in seronegative group.	'Fair' quality
Krutikov 2021[59] UK	N=634 **Median f/u:** 79 days (2.6 months) **Maximum f/u:** 300 days (10 months)	**Relative adjusted hazard ratios for reinfection:** Residents of care home: aHR=0.15 (0.05-0.44)[i] Staff of care home: aHR=0.39 (0.19-0.82)[i]	'Good' quality
Essential workers (n=1)			
Leidi 2021[28] Switzerland	N=784 **Mean f/u:** 193 days **Maximum f/u:** 269 days	**Risk of reinfection:** 5 of 784 (0.6%) seropositive individuals had a positive SARS-CoV-2 test, with an incidence rate of 0.2 (95% CI 0.1 to 0.6) cases per person-week. **Adjusted estimates:** Seropositive essential workers had a 93% reduction in the hazard (HR of 0.07, 95% CI 0.03 to 0.17) of having a positive test during follow-up compared with seronegative workers.	'Fair' quality
Patients with chronic kidney disease (n=3)			
Banham[44] 2021 UK	N=256 Antibody positive during first wave (March to July 2020) **Maximum f/u**: 305 days (10 months)	**Risk of reinfection:** 10/237 (4.2%) **Relative risk of reinfection:** Risk ratio, 0.37 (95% CI, 0.19 to 0.70) in seropositive group.	'Fair' quality
Cohen 2021[14] US	N=238 antibody positive or with history of infection (N=2,337 participants in total) **Mean f/u:** 2.86 months, since visit 2 (which occurred approx. 3 months after baseline assessment). **Maximum f/u:** approx. 6 months (from baseline assessment)	**Risk of reinfection:** ▪ IgG positive and prior PCR positive = 2.5% ▪ IgG positive and prior PCR negative = 3.4% ▪ IgG positive and/or prior PCR positive = 5.9% **Relative risk** ▪ IgG positive 0.55 (95% CI: 0.32 – 0.95) relative to IgG negative ▪ Prior PCR positive 0.53 (95% CI: 0.24 – 1.19) relative to prior PCR negative- ▪ IgG positive and/or prior PCR positive 0.51 (95% CI: 0.30 – 0.88) relative to IgG negative and prior PCR negative.	'Fair' quality
Kute 2021[47] India	N=1,350 **Median f/u:** 135 days (4.5 months)	**Risk of reinfection:** 13/1,350 (0.96%)	'Poor' quality
University student population (n=1)			
Rennert 2021[32] US	N=2,010 **Minimum f/u:** approx. 2.8 months **Maximum f/u:** approx. 8.5 months	**Risk of reinfection:** 1.6% (33 reinfection cases) or 2.2% (44 reinfections without confirmatory negative test between original infection and reinfection). **Adjusted risk ratio** 0.12 (95% CI: 0.09 to 0.17) relative to the negative group for the autumn 2020.	'Fair' quality

		or 0.16 (95% CI: 0.12 to 0.22) without confirmatory negative test between original infection and reinfection.	
Vaccinated populations with and without previous infection (n=7)			
Abu-Raddad 2021[8] **Qatar**	N=52,039 **Mean f/u:** 3 weeks (mRNA-1273, Moderna) and 6 weeks (BNT162b2, Pfizer-BioNTech). **Maximum f/u:** ~65 days for mRNA-1273, 132 days for BNT162b2	**Risk of reinfection:** Incident rate of reinfection among BNT162b2-vaccinated persons (Pfizer-BioNTech): ▪ 1.66 (95% CI: 1.26-2.18) per 10,000 person-weeks with prior infection (cumulative infection incidence: 0.14% (95% CI: 0.11-0.19%)). ▪ The incidence rate ratio was 0.15 (95% CI: 0.11-0.20) in previously infected individuals versus no prior infection. Incidence rates of reinfection among mRNA-1273-vaccinated persons (Moderna): ▪ 1.55 (95% CI: 0.86-2.80) 10,000 person-weeks with prior infection (cumulative infection incidence: 0.06% (95% CI: 0.03-0.12%)) ▪ The incidence rate ratio was 0.85 (95% CI: 0.34-2.05) in previously infected individuals versus no prior infection. **Absolute reinfection (breakthrough infection) rates** Of the 51,486 BNT162b2 vaccinated individuals (with previous infection) 51 reinfections were observed and of the 24,052 mRNA-1273 vaccinated individuals (with previous infection) 11 reinfections were observed.	'Fair' quality
Cavanaugh[45] 2021 **US**	N = 738 previously infected (246 'case-patients' and 492 'controls') **Maximum f/u**: 16 months **Minimum f/u**: 4 months	**Relative risk of reinfection* (or Odds Ratio):** Kentucky residents with previous infections who were not vaccinated had 2.34 times the odds of reinfection compared with those who were fully vaccinated (OR= 2.34; 95% CI = 1.58–3.47). Partial vaccination was not significantly associated with reinfection (OR = 1.56; 95% CI = 0.81–3.01).	'Fair' quality
Gazit 2021[21] **Israel**	Unvaccinated previously infected: N=62,883 Previously infected and single-dose (Pfizer-BioNTech) vaccinated: N=42,099 Maximum follow up for unvaccinated previously infected = 531 days. Maximum follow up for previously infected and single-dose vaccinated = 225 days	**Risk of reinfection:** 108/46,035 (0.23%) reinfections occurred among those previously infected and unvaccinated. 20/14,029 (0.14%) of the partially vaccinated and previously infected group had a positive RT-PCR test. **Relative risk over time:** After adjusting for comorbidities, a 5.96-fold increased risk (95% CI, 4.85 to 7.33) increased risk for breakthrough infection as opposed to reinfection could be observed (P<0.001) when vaccination or infection occurred at the same time. There was a 7.13-fold (95% CI, 5.51 to 9.21) increased risk for symptomatic breakthrough infection than symptomatic reinfection. **Relative risk of reinfection:** Those previously infected and received a single dose of the vaccine had a significant 0.53-fold (95% CI, 0.3 to 0.92) decreased risk for reinfection vs. those infected without vaccination. **Relative risk of breakthrough infection compared with reinfection:**	'Fair' quality

		After adjusting for comorbidities, a statistically significant 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection as opposed to reinfection was found, when infection occurred at any time. After adjusting for comorbidities, a 27.02-fold risk (95% CI, 12.7 to 57.5) for symptomatic breakthrough infection as opposed to symptomatic reinfection was observed (P<0.001).	
Kojima 2021[26] US	(1) No prior infection and unvaccinated (n=4,313) (2) previous SARS-CoV-2 infection, unvaccinated (n=254) (3) fully vaccinated (either the BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccines) without previous infection (n=739) **Maximum f/u:** 221 days for groups 1 and 2, and 419 days for group 3.	**Risk of reinfection/breakthrough infection:** Group 1 (SARS-CoV-2 naïve (no prior infection) and unvaccinated) had an incidence of 25.9 per 100 person years (95% CI: 22.8-29.3). A total of 254 infections occurred among 4,313 individuals (5.9%). Group 2 (previous SARS-CoV-2 infection and unvaccinated) had an incidence of 0 per 100 person-years (95% CI: 0-5.0). No reinfections occurred (0%). Group 3 (fully vaccinated without previous infection) had an incidence of 1.6 per 100 person-years (95% CI: 0.04-4.2). A total of 4 breakthrough infections occurred among 739 individuals. **Relative risk of reinfection:** The IRR of reinfection among those with previous infection compared to SARS-CoV-2 naïve (no prior infection) was 0 (95% CI: 0-0.19). The IRR of those vaccinated compared to SARS-CoV-2 naïve (no prior infection) was 0.06 (95% CI: 0.02-0.16). The IRR of those vaccinated compared to prior SARS-CoV-2 was not estimable due to zero events in the previously infected group.	'Fair' quality
Lumley 2021[61] UK	N=1,273 **F/u:** 216 days (7.2 months) (13,109 individuals contributed 2,835,260 person-days follow-up) Of the 13,109 HCWs; 8,285 received the Pfizer-BioNTech vaccine (1,407 two doses) and 2,738 received the Oxford-AstraZeneca vaccine (49 two doses). 11 HCWs received another vaccine or could not recall the manufacturer.	▪ Compared to unvaccinated seronegative HCWs, natural immunity provided similar protection against symptomatic infection as two vaccination doses: no HCW who received two vaccine doses had symptomatic infection, and incidence was 98% lower in seropositive HCWs (adjusted incidence rate ratio 0.02 [95%CI <0.01-0.18][j]). ▪ Two vaccine doses or seropositivity reduced the incidence of any PCR-positive result with or without symptoms by 90% (0.10 [0.02-0.38]) and 85% (0.15 [0.08-0.26]), respectively. ▪ Single-dose vaccination reduced the incidence of symptomatic infection by 67% (0.33 [0.21-0.52]) and any PCR-positive result by 64% (0.36 [0.26-0.50]). There was no evidence of differences in immunity induced by prior infection and vaccination for infections with S-gene target failure and the Alpha variant.	'Good' quality
Shrestha 2021[38] US	N=52,238 employees in total; n=2,579 previously infected and n=49,659 not previously infected. n=1,359 of 2,579 (53%) previously infected individuals remained unvaccinated.	**Absolute risk of reinfection:** 0 reinfections occurred in those previously infected (0/2,579; 0%). 2,139 infections occurred in those not previously infected and who remained unvaccinated (2,139/20,804; 10.28%). 15 breakthrough infections occurred in those not previously infected, but fully vaccinated (15/28,855; 0.05%). **Adjusted estimates**	'Fair' quality

	N=20,804 of 49,659 (42%) not previously infected individuals remained unvaccinated. **Median f/u**: 10 months **Maximum f/u**: Up to 1 year for those with previous infection	Lower risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI: 0.015 to 0.061), but not among those previously infected (HR 0.313, 95% CI: 0 to Infinity).	
Young-Xu[51] 2021 **US**	N=5,622 previously infected individuals who remained unvaccinated. (N=47,102 in total; n=9,539 patients with SARS-CoV-2 infection during the first two months of 2021 (matched to n=14,458 and 23,105 patients fully vaccinated, with no previous infection, with Moderna and Pfizer mRNA vaccines, during the same two months)). **Maximum f/u**: 229 days (7.5 months)	**Risk of reinfection:** *Total population:* not vaccinated, 28/5,622 (0.50%); Breaththrough for Moderna, 25/14,458 (0.17%); Breaththrough for Pfizer, 57/23,105 (0.25%). *Age 65+:* not vaccinated, 19/2,480 (0.77%); Breaththrough for Moderna, 16/7,391 (0.22%); Breaththrough for Pfizer, 30/10,789 (0.28%). *Age <65:* not vaccinated, 9/3,142 (0.29%); Breaththrough for Moderna, 9/7,067 (0.13%); Breaththrough for Pfizer, 27/12,316 (0.22%). **Relative risk of reinfection:** HR: 0.34 (95% CI, 0.14-0.78) and 68% HR: 0.32 (95% CI, 0.14-0.70) for Age 65+ with Moderna and Pfizer mRNA vaccines, respectively. For age < 65, the protections offered by vaccines were statistically equivalent to that provided by previous infection. **Adjusted estimates:** Adjusted multivariable Cox model, age<65 who received Moderna and Pfizer vaccines had 65% [HR: 0.35 (95% CI, 0.11-1.13)] and 36% [HR: 0.64 (95% CI, 0.24- 1.69)] lower risk of reinfection, respectively.	'Fair' quality

Key: aHR – adjusted hazard ratio; aOR – adjusted odds ratio; aRR – adjusted rate ratio: CI – confidence interval; f/u – follow-up; IgG - immunoglobulin G; IQR – inter-quartile range; HCW – healthcare worker; NAAT – nucleic acid amplification test; PM – propensity matching; WGS – whole genome sequencing; RR – relative risk; RT-PCR – reverse transcription-polymerase chain reaction; RT-qPCR – real time reverse transcription polymerase chain reaction. Numbers rounded to two decimal points.

[a]In the baseline antibody and or PCR positive group ('seropositive' or prior positive cohort)

[b]Based on cases with WGS confirming the first and second infections were from different viral strains (N=16)

[c]This is the relative risk during second wave (August-December 2020) comparing those previously PCR/antibody positive after first wave (February-July 2020) with PCR/antibody negative after first wave.

[d]NAAT used as proxy; includes all symptomatic reinfections and prolonged viral shedding, comparing patients who had a positive antibody test at index versus those with a negative antibody

[e]Three adjudicators assessed the likelihood of reinfection based on timing, clinical characteristics and Ct values ('likely')

[f]The midpoint of a range of follow-up dates was taken (300-349 days)

[g]Authors report effectiveness with the following calculation: 1-((56/8845)/(4163/141480)

[h]'Possible' reinfection was defined as a participant with two PCR positive samples ≥90days apart with available genomic data, or an antibody positive participant with a new positive PCR at least four weeks after the first antibody positive result. A 'probable' case additionally required supportive quantitative serological data and or supportive viral genomic data from confirmatory samples

[i]Multivariate analysis of risk of PCR positive infection by baseline antibody status, stratified by LTCF and adjusted for sex and age

[j]IRR is the relative incidence of subsequent positive SARS-CoV-2 PCR tests and symptomatic infections comparing antibody-positive and antibody-negative groups at baseline

[k]After adjustment for age, gender, and month of testing or calendar time as a continuous variable.

[l]Based on National Institutes of Health (NIH) quality appraisal criteria

[m] This month (December 2020) coincided with the identification and widespread transmission of the Alpha variant in the UK

Due to heterogeneity in outcome measures and populations, meta-analysis of data was not considered appropriate. The following sections narratively report the findings of included studies by population group (general population, healthcare workers, residents and staff of care homes, essential workers, patients with chronic kidney disease (CKD), university populations, and vaccinated populations).

General population

Thirty studies were identified that investigated reinfection in the general population. Nine studies were conducted in the US;[12, 18, 27, 39, 42, 49, 57, 68, 69] four in Italy;[19, 31, 40, 62] three in the UK;[11, 23, 53] two in Iran,[43, 64] and one each was conducted in Austria,[67] China,[29] Denmark,[56] Egypt,[6] Iraq,[9] Israel,[66] Mexico,[30] Qatar,[52] South Africa,[13] Spain,[63] Sweden,[33] and Switzerland.[60] In addition, three general population studies examined the protection following SARS-CoV-2 infection compared with that offered by COVID-19 vaccination.[8, 21, 45] These studies are discussed as part of the Vaccinated population below.

In the study by Pilz et al.,[67] national SARS-CoV-2 infection data from the Austrian epidemiological reporting system was used to investigate potential reinfection events. The primary outcome was the odds of PCR positivity in individuals who recovered from a confirmed SARS-CoV-2 infection during the first wave (February to 30 April 2020) compared with the odds of first infections in the remainder of the general population during the second wave (from 1 September to 30 November 2020).

In total, 40 possible reinfections were recorded out of 14,840 individuals with a history of prior infection during the first wave (0.27%), compared with 253,581 infections out of 8,885,640 individuals of the remaining general population (2.85%). This translated into an odds ratio of 0.09 (95% CI: 0.07 to 0.13).

Of the 40 possible reinfections, 62.5% were women and the median age was 39.8 years (range: 15.4 to 93.8). There were eight hospitalisations relating to the first infection and five hospitalisations relating to the second infection. Four patients were hospitalised during both infections. One death occurred which was not causally associated with reinfection. Detailed clinical or demographic information was not captured by the dataset. Cycle threshold values were not reported and whole genome sequencing was not performed.

In the study by Hansen et al.,[56] individual-level data were collected on patients who had been tested in 2020 from the Danish Microbiology Database. Infection rates were analysed during the second wave of the COVID-19 epidemic, from 1

September 2020 to 31 December 2020, comparing PCR-positive individuals with PCR-negative individuals during the first wave (March to May 2020). For the main analysis, people who tested positive for the first time between the two waves and those who died before the second wave were excluded. In an alternative cohort analysis, infection rates were compared throughout the year, irrespective of date. Infection rates by age category were reported in this alternative cohort analysis.

During the first wave (prior to June 2020), 533,381 people were tested, of whom 11,727 (2.2%) were PCR positive; 525,339 were eligible for follow-up in the second wave, of whom 11,068 (2.11%) had tested positive during the first wave. Among eligible PCR-positive individuals from the first wave, 72 (0.65%, 95% CI: 0.51 to 0.82%) tested positive again during the second wave compared with 16,819 of 514,271 (3.27%, 95% CI: 3.22 to 3.32%) who tested negative during the first wave. The daily rate of infection during the second wave was 5.35 positive tests per 100,000 people among those who had previously tested positive versus 27.1 per 100,000 people among those who previously tested negative. After adjusting for sex, age group, and test frequency, the adjusted RR (aRR) of reinfection was 0.20 (95% CI: 0.16 to 0.25). Protection against repeat infection was estimated at 80.5% (95% CI: 75.4 to 84.5).

In the alternative cohort analysis, the relative risk was similar (aRR of 0.21, 95% CI: 0.18 to 0.25, estimated protection 78.8%), however there was variation in the aRR by age group:

- 0–34 years: aRR=0.17 95% CI: 0.13–0.23
- 35–49 years: aRR=0.20 95% CI: 0.14–0.28
- 50–64 years: aRR=0.19 95% CI: 0.13–0.27
- ≥65: years: aRR=0.53 95% CI: 0.37–0.75.

Among those aged 65 years and older, the observed protection against repeat infection was substantially lower, at 47.1% (95% CI: 24.7 to 62.8%). There was no difference in estimated protection against repeat infection by sex (male 78.4% versus female 79.1%). There was no evidence of waning protection over time (3–6 months of follow-up: 79.3% protection [95% CI: 74.4 to 83.3] versus ≥7 months of follow-up: 77.7% [95% CI: 70.9 to 82.9]). Clinical information on cases was not captured by the dataset. Cycle threshold values were not reported and whole genome sequencing was not performed.

In the study by Mohamadreza et al.,[64] symptomatic reinfection rates were retrospectively investigated in the three referral hospitals in Iran, six months after the pandemic onset. A total of 32,567 tests were performed involving 1,899 patients. Of these, 37 cases were considered reinfections based on prespecified criteria (two

positive RT-PCR tests at least three months apart, with a negative RT-PCR test between the two positive tests). The mean duration between the discharge and second presentation was 117±61.42 days. The proportions of patients with mild, moderate or severe disease was not significantly different comparing primary and secondary infections. Seven (18.9%) patients were hospitalised during the secondary infection compared with two (5.4%) patients during the primary infection. The clinical, radiological, and laboratory characteristics were not significantly different between the two episodes.

In the preliminary preprint by Perez et al.,[66] reinfection rates within the members of a large healthcare provider (Maccabi Healthcare Services) in Israel were reported. This healthcare provider has more than 2.5 million members (approximately 25% of the population) and is a representative sample of the Israeli population.

A total of 149,735 individuals had a recorded positive PCR test between March 2020 and January 2021. Among them, 154 members had two positive PCR tests at least 100 days apart and were included in this study. The reinfection rate was estimated at approximately 0.1%. In this cohort, 73 individuals (47.4%) had symptoms at both PCR positive events.

In terms of age distribution, reinfections were seen in small numbers across all age groups, with the highest absolute reinfection count observed among individuals aged 10 to 19 years. The first reinfection occurred in July 2020 and reinfection counts peaked in January 2021 (99 members). In terms of the time interval between infection events, 30 individuals had a second positive PCR test more than 200 days following their first positive PCR test. Cycle threshold values were not reported and whole genome sequencing was not performed.

In the study by Manica et al.,[62] IgG serological screening of individuals in five Italian municipalities within the Province of Trento, Italy, was conducted in May 2020. These municipalities were selected as those showing the highest cumulative case incidence in the province during the first COVID-19 wave (ranging between 18.7 and 27.6 per 1,000 individuals).

The serological screening involved 6,074 individuals (median age 50; IQR: 32-63), representing 77.1% of the resident population. Of these, 1,402 (23.1%) were seropositive for IgG. Between 1 June 2020 and 31 January 2021, regular surveillance activities identified 221 new positive SARS-CoV-2 infections (124 symptomatic) among study participants (RT-PCR or rapid antigen positive). The cumulative incidence of identified symptomatic infections over the observation period was 2.67% (95% CI: 2.12% to 3.37%) in the seronegative group and 0.14% (95% CI: 0.04% to 0.58%) in the seropositive group. The odds ratio of being confirmed as a

symptomatic SARS-CoV-2 infection in IgG positive relative to IgG negative participants was 0.054 (95% CI: 0.009 to 0.169), adjusted for age and geographical municipality.

In the study by Flacco et al.[19] all individuals aged ≥ one year in the Italian province of Pescara, diagnosed with SARS-CoV-2 infection (admitted to COVID-19 wards, regardless of symptoms) between March 2020 and May 2021 (n=18,034) were included. The primary outcome was the incidence of a reinfection, defined as a new positive PCR test occurring ≥90 days after complete resolution of the first infection. After an average of 201 days of follow-up (maximum 414 days), a total of 24 reinfections occurring ≥90 days after the resolution of the first 7,173 infections (0.33%) were recorded. Four reinfections required hospitalisation, and one resulted in death. Over half of the reinfections (13/24) detected occurred six to nine months after the resolution of the first infection; no new infection was detected 12 or more months after resolution of the first infection. No reinfections were detected in individuals aged less than 18 years (n=832).

In the study by Vitale et al.[40] the incidence of SARS-CoV-2 primary infection and reinfection was investigated among 15,075 individuals in Lombardy, Italy, who, during the first wave of the pandemic (February to July 2020), underwent diagnostic testing using PCR. Symptomatic and asymptomatic individuals of any age, who were recruited in several screening and contact-tracing programmes, were included in this study. Of the 15,075 individuals who underwent PCR testing at baseline, 12,968 (86%) had a negative result at baseline and during follow up, 528 (3.5%) had a negative result at baseline but subsequently had a positive test and 1,579 (10.5%) had a positive result at baseline. Reinfections were defined as a second PCR positive test at least 90 days after complete resolution of the first infection and with at least two consecutive negative test results between the episodes. Individuals were followed until 28 February 2021 or until a new positive PCR test result. During the follow-up (mean ± SD, 280 ± 41 days) five reinfections (0.31%; 95% CI 0.03% to 0.58%) were confirmed, one of which required hospitalisation. Four of the five reinfections had close connections with health and social care facilities (two worked in hospitals, one underwent transfusions every week, and one resided in a nursing home). The mean ± SD interval between primary infection and reinfection was 230 ± 90 days. The authors concluded that natural immunity appears to confer a protective effect for at least a year, however this study ended prior to the widespread circulation of variants of concern in the region.

In the study by Abu-Raddad et al., 43,044 anti-SARS-CoV-2 nucleocapsid antibody positive participants were followed for a median of 3.8 months (maximum follow-up: 8.1 months) for evidence of reinfection.[52] This retrospective cohort was identified

from a database that covers all serological testing for SARS-CoV-2 conducted in Qatar.

'Suspected cases' of reinfection included all SARS-CoV-2 antibody-positive individuals with at least one PCR positive swab that occurred ≥14 days after the first positive antibody test. These were further classified as showing either 'good' evidence, 'some' evidence, or 'weak/no' evidence of reinfection based on cycle threshold (Ct) and epidemiological criteria. Only 314 individuals had a PCR positive swab ≥14 days after the first-positive antibody test, and qualified for inclusion in the analysis. There were 1,099 swabs (551 positive and 548 negative) collected from these 314 individuals after the first positive antibody test. Investigation of these 314 suspected cases of reinfection yielded 32 cases with good evidence for reinfection (Ct≤30 for reinfection swab), 97 cases with some evidence (Ct>30 for reinfection swab), while evidence was weak for the remaining 185 cases.

Individuals with good or some evidence of reinfection had a median age of 37 years (range: <1 to 72 years) and included 92 men (71.3%). The median interval between the first positive antibody test and the reinfection swab was 52 days (range: 15 to 212 days). The median Ct value of the reinfection swab was 32.9 (range: 13.9 to 38.3). A third of cases were diagnosed based on clinical suspicion (n=34; 26.4%) or individual request (n=9; 7.0%), while the rest (n=86) were identified incidentally either through random PCR-testing campaigns/surveys (n=47; 36.4%), healthcare routine testing (n=18; 14.0%), contact tracing (n=15; 11.6%), or at a port of entry (n=6; 4.7%). At the time of reinfection, eight cases had records in the severity database. One of these was classified as "severe" and two as "moderate", while the other five were classified as "asymptomatic." At time of primary infection, 14 cases had records in the severity database, one of whom was classified as "critical", three as "severe", five as "moderate", two as "mild", and three as "asymptomatic."

Among the 129 cases with good or some evidence for reinfection, 62 had records indicating prior diagnosis of a primary infection. Of these, viral genome sequencing evidence was available for 16 cases. Five of these 16 cases were confirmed as reinfections (confirmation rate: 31.3%). For one pair, there were few changes of allele frequency offering supporting evidence for reinfection. For the four other pairs, there were multiple clear changes of allele frequency indicating strong evidence for reinfection. One of the latter pairs also documented the presence of the D614G mutation (23403bp A>G) at the reinfection swab, a variant that has progressively replaced the original D614 form. For seven additional pairs, while there were one to several changes of allele frequency indicative of a shifting balance of quasi-species, there was no evidence for reinfection. For four pairs, there was strong evidence for *no* reinfection as both genomes were of high quality, yet no differences were

found. Three of these four cases had a Ct<30 for the reinfection swab, indicating persistent active infection.

Applying the confirmation rate obtained through viral genome sequencing, the risk of documented reinfection was 0.17% (95% CI: 0.10 to 0.30%); that is, 31.3% of the suspected 129 reinfections in the cohort of 42,272 anti-SARS-CoV-2 positive participants (followed for 610,832 person-weeks). The incidence rate of documented reinfection was estimated at 0.66 per 10,000 person-weeks (95% CI: 0.56 to 0.78). There was evidence of a decreasing trend in the incidence rate of reinfection with each additional month of follow-up from the first month (incidence rate: 0.97 per 10,000; 52 cases per 167,149 person-weeks) to the sixth month (zero cases per 19,148 person-weeks) (Mantel-Haenszel trend analysis p-value: <0.001). However, these declining rates may be suggestive of persistent shedding of viral RNA early in the convalescent period, rather than true reinfections. There was an increase at ≥7 months, however this was only based on one case of reinfection (per 3,094 person-weeks).

These reinfections were compared to a cohort of 149,923 antibody-negative individuals followed for a median of 17 weeks (range: 0-45.6 weeks). Risk of infection was estimated at 3.09% (95% CI: 2.93-3.27%) and the incidence rate of infection was estimated at 13.69 per 10,000 person-weeks (95% CI: 13.22-14.14). The efficacy of infection against reinfection was estimated at 95.2% (95% CI: 94.1-96.0%).

In the study by Masia et al.,[63] 146 patients admitted to hospital in Spain due to COVID-19 were followed-up at 1, 2 and 6 months for evidence of reinfection. Suspected reinfection cases, based on a minimum interval of 90 days between positive RT-PCR tests, were confirmed using whole genome sequencing.

There were five suspected reinfection cases in total. Median time between infection events was 183 days (range: 167–204). Age ranged from 44 to 73 years. Two patients were symptomatic and readmitted on suspected reinfection, and three patients remained asymptomatic. One patient had a Ct<33, in the other four patients the Cts ranged from 33 to 38.

Genomic sequencing was performed in four individuals with available paired samples. In the three patients with Ct≥33, all were asymptomatic and the same clade 20B was detected. In two of these cases, the clade showed the same hallmark single nucleotide variants. In the third patient, the follow-up sample showed two new mutations, a K374R substitution in the N gene and an A222V substitution in the S gene, probably reflecting adaptive viral changes associated to persistent infection.

Genomic sequencing of the symptomatic patient with a Ct of 18 showed phylogenetically distinct genomic sequences; the first sample was member of the clade 20A, and the most recent sample was member of the clade 20B. Assuming that this is the only confirmed case of reinfection, the reinfection rate was 0.068% (1/146) in this cohort.

In terms of antibody levels, the three patients with asymptomatic recurrence and the symptomatic patient with no sequencing data available showed detectable antibody levels at the time of RT-PCR testing. The patient with symptomatic reinfection had no detectable antibody levels at the time of RT-PCR testing.

In the study by Leidi et al., a seroprevalence survey was conducted based on a representative sample of individuals aged 12 years and older in the canton of Geneva between April and June 2020, immediately after the first pandemic wave.[60] Individuals who developed anti-spike IgG antibodies were matched one-to-two to seronegative controls, using a propensity-score including age, gender, immunodeficiency, body mass index, smoking status and education level.

Among 8,344 seroprevalence survey participants, 498 seropositive individuals were selected and matched with 996 seronegative controls. After a mean follow-up of 35.6 (standard deviation [SD]: 3.2) weeks, 7 out of 498 (1.4%) seropositive participants had a positive SARS-CoV-2 test, of which 5 (1.0%) were classified as likely and two as unlikely reinfections (three adjudicators assessed the likelihood of reinfection based on timing, clinical characteristics and Ct values). This corresponded to an incidence of 0.3 (95% CI 0.1 to 0.7) per 1,000 person-weeks. By contrast, the rate of confirmed SARS-CoV-2 infections was significantly higher in seronegative individuals (15.5%, 154/996) corresponding to an incidence rate of 4.8 (95% CI 4.6 to 6.2) per 1,000 person-weeks, during a similar mean follow-up of 34.7 (SD 3.2) weeks.

Over the study follow-up, seropositive individuals were 94% less likely to have a virologically confirmed SARS-CoV-2 infection, when compared to individuals with no detectable anti-SARS-CoV-2 antibodies at study inclusion (hazard ratio of 0.06, 95% CI 0.02 to 0.14, $p<0.001$).

In the study by Breathnach et al.,[53] reinfection rates recorded at one London laboratory are reported. This laboratory serves four hospitals and a population of 1.3 million. Individuals who had PCR- or antibody-confirmed SARS-CoV-2 infection during the first wave (February to July 2020, with a peak in early April) were identified, and their risk of having a positive SARS-CoV-2 RT-PCR assay in the first five months of the second wave (August to December 2020) was determined. These rates were compared with patients who had a previous negative PCR or antibody

test. Cases where the second positive result was ≤90 days after the first were excluded. The samples included a significant proportion from healthcare workers, who were offered testing for SARS-CoV-2 antibodies in June 2020.

In total, 66,001 patients had a PCR and or serological SARS-CoV-2 assay before the end of July, of whom 10,727 tested positive (PCR and or antibody positive). Of these, eight had a positive PCR assay between 1 August and 30 December 2020, resulting in an absolute reinfection rate of 0.07%. Of 55,274 patients with no laboratory evidence of COVID-19 in the first wave, 713 subsequently had SARS-CoV-2 detected in the second wave (1.29%). The relative risk of SARS-CoV-2 reinfection was reported as 0.06 (95% CI: 0.03 to 0.12). The risk or relative risk over time was not reported.

It is notable that there were no reinfections in this dataset in the first seven months after the peak of the first wave; all eight patients with likely reinfections were diagnosed in December, the last month of the study period, which also coincided with the identification and widespread transmission of the Alpha variant in the UK. That month, reinfections accounted for 1.69% of all infections.

In the ecological study by Graham et al.[23] the association between the regional proportions of infections with the Alpha variant and self-reported rates of reinfection (using a mobile application) in England, Scotland and Wales was examined. Data on possible reinfections (defined as the presence of two self-reported positive tests more than 90 days apart with a minimum of seven days symptom-free before the second positive test) were obtained from longitudinal reports from users of the COVID Symptom Study app who self-reported a positive test (PCR or antigen) for COVID-19 between 28 September and 27 December 2020. During this timeframe the prevalence of the Alpha variant increased significantly in parts of the UK. The correlation between the proportion of Alpha cases and number of reinfections over time, and between the number of positive tests and reinfections was assessed.

Between 28 September and 27 December 2020, 249 possible reinfections were identified in 36,509 app users (0.7%; 95% CI 0.6 to 0.8) who reported a positive swab test before 1 October 2020. There was no evidence that the frequency of reinfections was higher for the Alpha variant than for pre-existing variants. Reinfection occurrences were more positively correlated with the overall regional rise in cases (Spearman correlation 0.56 to 0.69 for the South East of England, London, and the East of England) than with the regional increase in the proportion of infections with the Alpha variant (Spearman correlation 0.38 to 0.56 in the same regions). The authors concluded that based on this evidence, the Alpha variant did not substantially alter the risk of reinfection. However, two major limitations of this study were firstly its reliance on individuals to self-report their test results, and

secondly its ecological nature whereby only correlations between variables could be inferred from the data.

In a US study by Harvey et al.[57] a retrospective database analysis of electronic health records was used to determine the risk of nucleic acid amplification test (NAAT) positivity, a proxy for reinfection, in a cohort of antibody-positive versus antibody-negative individuals. NAAT was used as a proxy for new infections or continued viral shedding.

A total of 3,257,478 unique patients with an index antibody test were identified after excluding 132 patients with discordant antibody tests on the index day. Of these, 2,876,773 (88.3%) had a negative index antibody result (seronegatives), 378,606 (11.6%) had a positive index antibody result (seropositives), and 2,099 (0.1%) had an inconclusive index antibody result (sero-uncertain). The linked data permitted individual longitudinal follow-up for a median of 47 days for the seronegative group (interquartile range (IQR): 8 to 88 days) and a median of 54 days for the seropositive group (IQR: 17 to 92 days).

Among patients with a positive index antibody result, 3,226 (11.3%) had a positive diagnostic NAAT during follow-up that occurred within 30 days of index, decreasing consistently to 2.7% from 31-60 days, 1.1% from 61-90 days, and 0.3% at >90 days. For the seronegative patients, 5,638 (3.9%) showed a positive NAAT result within 30 days. That proportion remained relatively consistent at ~3.0% over all subsequent periods of observation, including at >90 days. The ratio of positive NAAT results among patients who had a positive antibody test at index versus those with a negative antibody test at index declined from 2.85 (95% CI: 2.73 to 2.97) at 0-30 days; to 0.67 (95% CI: 0.6 to 0.74) at 31-60 days; to 0.29 (95% CI: 0.24 to 0.35) at 60-90 days; and to 0.10 (95% CI: 0.05 to 0.19) at >90 days. Cycle threshold values were not reported and whole genome sequencing was not performed. These findings likely indicate persistent viral RNA shedding from the primary infection in the early stages post-infection. While detection of viral RNA at >90 days may reflect prolonged viral shedding, these may constitute reinfection cases.

In the study by Sheehan et al.[69], all 150,325 patients who underwent RT-PCR testing from 12 March 2020 to 30 August 2020 in one multi-hospital health system in Ohio and Florida were investigated. Tests on healthcare workers were excluded. The main outcome was reinfection, defined as RT-PCR positivity ≥90 days after initial testing. Secondary outcomes were symptomatic infection and protective effectiveness of prior infection. Infection rates were determined for distinct periods following the initial test: 4-5 months, 6-7 months and ≥8 months. Protective effectiveness of prior infection was calculated as one minus the ratio of infection rate for positive patients divided by the infection rate for negative patients.

In total, 150,325 (38.9%) patients had tests performed before 30 August 2020, of whom 8,845 (5.9%) tested positive and 141,480 (94.1%) tested negative. After at least 90 days, 1,278 (14.4%) of the positive patients were retested and 63 (4.9%) were reviewed for possible reinfection. One patient had an immediate negative test and was excluded due to a presumed false positive test. Of the 62 reinfections, 31 were symptomatic. Eighteen symptomatic patients were hospitalised within 30 days of the positive test, five with symptoms considered possibly related to COVID-19 (none required intensive care or needed mechanical ventilation).

Of those with negative initial tests, 27.9% (39,487/141,480) were retested and 5,449 (13.8%) were positive. Of these positive tests 2,258 (44.1%) were performed for pre-procedural screening or had an asymptomatic indication. The protective effectiveness of prior infection against reinfection was estimated at 81.8% (95% CI: 76.6 to 85.8), and 84.5% (95% CI: 77.9 to 89.1) against symptomatic reinfection. Protection against reinfection was lowest in months four and five following the initial infection, increasing thereafter up to month eight following the initial infection. Cycle threshold values were not reported and whole genome sequencing was not performed. Of note, while this study included tests performed between 12 March 2020 and 24 February 2021, no disaggregated data are presented by specific time periods or calendar months.

In the study by Qureshi et al.,[68] 9,119 patients with SARS-CoV-2 infection who received serial tests across 62 healthcare facilities in the US were followed between 1 December 2019 and 13 November 2020 for evidence of reinfection. Reinfection was defined as two positive RT-PCR tests separated by an interval of ≥90 days after resolution of first infection (confirmed by two or more consecutive negative RT-PCR tests).

Reinfection was identified in 63 patients (0.7%, 95% CI: 0.5%-0.9%). The mean interval between infections was 116 days. The protective effectiveness of prior infection against reinfection and against symptomatic reinfection was estimated at 81.8% (95% CI: 76.6 to 85.8) and 84.5% (95% CI: 77.9 to 89.1), respectively. Risk of reinfection was greatest just after 90 days and declined thereafter. There were two deaths (3%) associated with reinfection. Intubation/mechanical ventilation was required in two patients (3%) during primary infection, but in none during reinfection. There was a significantly lower rate of pneumonia, heart failure, and acute kidney injury observed with reinfection compared with primary infection among the 63 patients with reinfection.

In the study by Slezak et al.,[39] the burden and severity of suspected reinfection cases was estimated among members of Kaiser Permanente Southern California (KPSC) integrated healthcare organisation in the US. Members of KPSC with PCR-

positive SARS-CoV-2 infection between 1 March and 31 October 2020 were retrospectively reviewed for suspected reinfections (subsequent positive SARS-CoV-2 tests ≥90 days after initial infection), until 31 January 2021. Incidence of suspected reinfection was estimated using the Kaplan–Meier method. Cox proportional hazards models estimated the association between suspected reinfection and demographic and clinical characteristics, hospitalisation, and date of initial infection.

Among 75,149 individuals with a positive PCR test between 1 March and 31 October 2020, a total of 315 had a suspected reinfection, with a cumulative incidence at 270 days of 0.8% (95% CI: 0.7 to 1.0%). Hospitalisation was more common following suspected reinfection 11.4% (36/315) than initial infection 5.4% (4,094/75,149). Suspected reinfection rates were higher in females (1.0%, 95% CI: 0.8–to 1.2% versus 0.7%, 95% CI: 0.5 to 0.9%, p=0.002) and in immunocompromised patients (2.1%, 95% CI: 1.0 to 4.2% versus 0.8%, 95% CI: 0.7 to 1.0%, p=0.004). Suspected reinfection rates were lower in children than adults (0.2%, 95% CI: 0.1 to 0.4% versus 0.9%, 95% CI: 0.7 to 1.0%, p=0.023). Patients hospitalised at initial infection were more likely to have a suspected reinfection (1.2%, 95% CI: 0.6 to 1.7% versus 0.8%, 95% CI: 0.7 to 1.0%, p=0.030), as were those with initial infections later in 2020 (150-day incidence 0.4%, 95% CI: 0.2 to 0.5% September to October versus 0.2%, 95% CI: 0.1 to 0.3% March to May and 0.3%, 95% CI: 0.2 to 0.3% June to August, p=0.008). In an adjusted Cox proportional hazards model, being female (HR 1.44, 95% CI: 1.14 to 1.81), adult (aged 18 to 39, HR 2.71, 95% CI: 1.38 to 5.31, aged 40 to 59 HR 2.22, 95% CI: 1.12 to 4.41, aged ≥60 HR 2.52, 95% CI: 1.23 to 5.17 versus aged <18 years), immunocompromised (HR 2.48, 95% CI: 1.31 to 4.68), hospitalised (HR 1.60, 95% CI: 1.07 to 2.38), and initially infected later in 2020 (HR 2.26, 95% CI: 1.38 to 3.71 September to October versus March to May) were significant independent predictors of suspected reinfection. The authors concluded that while reinfection with SARS-CoV-2 is uncommon, it appears to be more likely in females, adults, immunocompromised individuals and those previously hospitalised due to COVID-19.

In the study by Cohen et al.,[(13)] the burden and transmission of SARS-CoV-2 over the two epidemic waves in South Africa was estimated. Of note the second wave, which occurred between December 2020 and March 2021 was associated with the dominance of the Beta variant of concern. A prospective cohort study was conducted between July 2020 and March 2021 in one rural and one urban community in South Africa. Mid-turbinate nasal swabs were collected twice-weekly from randomly selected, consenting household members irrespective of symptoms and tested for SARS-CoV-2 using PCR. Serum was collected every two months and tested for anti-SARS-CoV-2 antibodies. Possible reinfections were defined as >28 to 90 days

between PCR-positive specimens or between first seropositive specimen and PCR-positive specimen (with no genomic sequence data available); probable reinfection was defined as >90 days between PCR-positive specimens or between first seropositive specimen and PCR-positive specimen (with no genomic sequence data available); and confirmed reinfection was defined as distinct Nextstrain clades on sequencing or variant PCR between PCR-positive specimens meeting the temporal above mentioned criteria for possible or probable reinfections.

Among 1,189 members (follow-up rate 93%), from 71,759 nasal specimens, 834 (1%) were SARS-CoV-2-positive. By PCR detection and serology combined, 34% (406/1,189) of individuals experienced ≥1 SARS-CoV-2 infection episode, and 3% (12/406) experienced any reinfection. Of the 12 repeat infection episodes, six (50%) were classified as possible, five (42%) as probable and one (8%) was confirmed. The authors concluded that infection before the second wave was 84% (95% CI; 65% to 93%) protective against re-infection when the Beta variant predominated in South Africa. This was similar to the degree of protection reported for previously circulating variants, although household transmission increased significantly following the emergence of the Beta variant (OR 3.7, 95% CI 1.6 to 8.4).

In the study by Murillo-Zamora et al.,[30] risk factors associated with symptomatic reinfection were investigated in a nationwide retrospective cohort study in Mexico. All adults (aged 20 years or older) whose index symptomatic laboratory confirmed COVID-19 infection appeared between March and June 2020 and who recovered were included in this retrospective cohort study. Participants were followed until September 2020. The main outcome was symptomatic reinfection of SARS-COV-2 and was defined by the reappearance of symptoms of COVID-19 at 28 days or more after initial laboratory-confirmed illness and a positive PCR result during the second illness. Data from 99,993 participants were analysed for a total follow-up of 8,268,237 person-days. The overall risk of SARS-COV-2 symptomatic reinfection was 0.21% (n = 210) and the incidence density was 2.5 reinfections per 100,000 person-days. The mean elapsed days (± SD) between COVID-19 episodes was 61.0 ± 31.0 days and ranged from 28 to 116 days. Mild subsequent illness was documented in 169 (80.5%) of reinfected participants and the observed fatality rate was 4.3% (n = 9).

In multivariable linear regression analysis (adjusting for sex, age, occupation, primary disease severity and comorbidities, as appropriate), older adults (≥ 50 years) ($RR_{per\ year}$ 0.99997, 95% CI: 0.99814 to 0.99958) and those with severe primary disease were at reduced risk of symptomatic reinfection ($RR_{per\ year}$ =0.9989, 95% CI: 0.9981 to 0.9997). Though importantly these estimated risk reductions were very small. Conversely, healthcare workers ($RR_{per\ year}$ =1.0042, 95% CI:

1.0030 to 1.0055) and patients who had an immunocompromising condition ($RR_{per\ year}$ =1.0038, 95% CI: 1.0011 to 1.0065) or those with chronic kidney disease ($RR_{per\ year}$ =1.0039, 95% CI: 1.0016 to 1.0063) had at greater risk of symptomatic reinfection. An important limitation of this study is that asymptomatic reinfections were not included in the analysis, and this likely resulted in an under-ascertainment of reinfection cases.

Twelve other studies examined the risk of reinfection in general populations.[6, 9, 11, 12, 18, 27, 29, 31, 33, 42, 43, 49] The results of these 12 studies are broadly in agreement with the studies mentioned above, in that the risk of reinfection was found to vary but remained low (ranging from 0.02%[33] to 4.5%)[18] over the duration of the studies (maximum follow-up ranged from five[29] to 12 months).[27] It is likely that differences in the definition used for reinfection, along with regional prevalence of SARS-CoV-2, contributed to the varying reinfection rates reported. For example, in the study by Ringlander et al., whole genome sequencing was required to confirm reinfection (0.02% confirmed reinfection rate reported),[33] whereas in the study by Finch et al., a new positive PCR test more than 30 days after an initial seropositive result was defined as a possible reinfection (4.5% possible reinfection rate reported).[18]

Healthcare workers

Nineteen studies were identified that exclusively included healthcare workers,[7, 15-17, 20, 22, 24, 25, 34-36, 41, 46, 48, 50, 54, 55, 65, 70] and one study included both healthcare workers and general patients.[37] Of these 20 studies, five were conducted in the UK;[7, 48, 54, 55, 70] four in the US;[34, 37, 41, 65] three in Italy;[15, 35, 50] two each in France[16, 20] and Germany,[22, 46] and one each in Iran,[36] Spain,[17] Sweden[24] and Switzerland.[25] In addition, three studies involving healthcare workers examined the protection provided by SARS-CoV-2 infection compared with that offered by COVID-19 vaccination.[55, 61, 70, 71] These three studies are discussed as part of the Vaccinated population below. A further three studies were identified that included both staff and residents of care homes for older people,[26, 38, 61] and these are discussed in the section relating to Residents and staff of care homes for older people studies.

The study by Hall et al.[71] reports interim results after seven months of follow-up from Public Health England's 'SIREN' study. In total, 30,625 hospital staff (including healthcare workers, support staff and administrative staff of NHS hospitals across the UK) were included into the study from 18 June 2020 to 31 December 2020, of which 25,661 participants with linked data on antibody and PCR testing were included in the analysis. Data were extracted from all sources on 5 February 2021, and included data up to 11 January 2021. These results update previously published

interim results,[54] which related to 20,787 hospital staff, followed between 18 June and 9 November 2020.

Overall, 8,278 participants were assigned to the PCR/antibody-positive cohort and 17,383 to the negative cohort. Of the 8,278 participants in the positive cohort, 91.2% were antibody positive at enrolment, 7.0% were antibody negative at enrolment, but had a previous antibody positive result or positive PCR result and 1.8% had a previous PCR positive result, but no linked antibody data. The total follow-up time up to 11 January 2021 was 2,047,113 person-days for the positive cohort and 2,971,436 person-days for the negative cohort. The median length of follow-up per participant was 9.2 months (IQR 7.3-9.7) for the positive cohort and 6.5 months (IQR 4.4-7.1) for the negative cohort.

A median of eight post-enrolment PCR tests (IQR 6–11) and five post-enrolment antibody tests (IQR 3–7) were done. The PCR test density during follow-up was 64 per 1,000 days of participant follow-up in the positive cohort and 70 per 1,000 days of participant follow-up in the negative cohort. During the follow-up period (between 8 December 2020 and 11 January 2021), 13,401 (52.2%) participants were vaccinated, 9,468 in the negative cohort and 3,933 in the positive cohort. Vaccine roll-out accelerated in January 2021. The number of participants who contributed follow-up time to this analysis who had been vaccinated for 21 days or more (the period at which a protective effect from vaccination would be expected) was 833 from the positive cohort, contributing 4,941 days of follow-up, and 2,279 from the negative cohort, contributing 12,839 days of follow-up. In total, 0.4% of the study's person-time of follow-up included participants 21 days or more following vaccination.

PCR positivity for primary infections in the positive cohort peaked in the first week of April, in the negative cohort PCR positivity peaked in the last week of December 2020. By 11 January 2021, 1,859 new infections were detected in the study population: 1,704 primary infections in the negative cohort and 155 reinfections in the positive cohort. Of the primary infections, 1,369 (80.3%) of these cases were symptomatic at infection, 1,126 (66.1%) with typical COVID-19 symptoms, and 243 (14.3%) with other symptoms; 293 (17.2%) were asymptomatic; and 42 (2.5%) did not complete a questionnaire at the time of their symptoms. There were 864 seroconversions in participants without a positive PCR test; these were not included as primary infections in this interim analysis.

There were 155 reinfections identified in the positive cohort, two of which were categorised as probable and 153 as possible. A probable case additionally required "supportive quantitative serological data or supportive viral genomic data from samples available". Of these 155 cases, 78 (50.3%) were symptomatic, 50 (32.3%) with typical COVID-19 symptoms, including both probable cases. At baseline

antibody testing, 127 of the reinfection cases were antibody positive, 18 were antibody negative, but had a previous antibody positive or positive PCR test result, seven had no history of an antibody positive result, but had a previous positive PCR result. There were also three participants who were antibody negative at baseline but due to having had both a primary infection and reinfection during follow-up moved cohort.

The median interval between the primary infection and reinfection episode for the 47 cases with a positive PCR test from their primary episode was 201 days (range 95–297). For the 99 cases who provided a history of COVID-19 symptoms, used as a proxy to estimate the date of their primary infection, the median interval between primary infection and reinfection was 241 days (range 90–345).

The incidence of COVID-19 symptomatic infections was 64.8 cases per 1,000 participants; other symptomatic infections was 14.0 cases per 1,000; asymptomatic cases was 16.9 cases per 1,000, and all new PCR positive infections was 98.0 cases per 1,000 in the negative cohort. The incidence density between June 2020 and January 2021 was 7.6 reinfections per 100,000 person-days of follow-up in the positive cohort and 57.3 new PCR positive infections per 100,000 person-days of follow-up in the negative cohort.

A proportional hazards frailty model using a Poisson distribution was used to estimate incidence rate ratios (IRRs) to compare the incidence rates in the positive and negative cohorts to provide a relative estimate of the protective effect of a previous SARS-CoV-2 infection. The fixed covariates included in the model were age, gender, ethnicity, region, staff group, and index of multiple deprivation. Time varying covariates included in the model were 21 days after COVID-19 vaccination and regional prevalence of the Alpha variant.

Restricting reinfections to probable reinfections only, the adjusted IRR (aIRR) was 0.002 (95% CI 0.00–0.01), after controlling for other risk factors and for a given site. Therefore, participants in the positive cohort had 99.8% lower risk of new infection than did participants in the negative cohort. Restricting infections to those who had COVID-19 symptoms on reinfection, the aIRR was 0.074 (95% CI 0.06–0.10) (93% lower incidence of new infection than participants in the negative cohort). Using the broadest definition of reinfections, including all those who were possible or probable, the aIRR was 0.159 (95% CI 0.13–0.19). Although the results showed that previous infection offered protection against all five categories of reinfection, the lowest protection was provided against asymptomatic reinfection (aIRR 0.48 95% CI 0.37–0.63).

The study authors did not find any evidence that increased prevalence of the Alpha variant adversely affected reinfection rates in the cohort during this follow-up period. Models suggested that the protective effect of previous infection increased when the Alpha variant was dominant (IRR 0.18, 95% CI 0.15–0.23) compared with IRR 0.13 (0.10–0.17).

In the study by Hanrath et al.,[55] symptomatic reinfection in UK healthcare workers during the second wave of the UK pandemic was investigated, comparing those who had evidence of prior SARS-CoV-2 infection from the first wave with those who had no evidence of prior infection. In the first wave (10 March to 6 July 2020), 481/3,338 symptomatic healthcare workers tested positive for SARS-CoV-2 by PCR, while SARS-CoV-2 IgG was detected in 937/11,103 (8.4%). From these, 1,038 healthcare workers were identified with evidence of previous infection (PCR and or antibody positive) and 10,137 without (negative antibody and PCR). The primary endpoint for analysis was symptomatic SARS-CoV-2 infection, defined as a positive PCR for SARS-CoV-2 from a combined nasopharyngeal/oropharyngeal swab taken as part of a symptomatic staff testing programme in the period from 7 July 2020 to 20 November 2020.

During the second time period, 2,243 symptomatic healthcare workers underwent PCR testing; 128 of these had previous confirmed SARS-CoV-2 infection while 2,115 had not. In those previously infected, there was a median of 173 (IQR: 162–229) days from the date of first positive PCR or antibody result to the end of the analysis period. Test positivity rates were 0% (0/128 [95% CI: 0–2.9]) in those with previous infection compared to 13.7% (290/2,115 [95% CI: 12.3–15.2]) in those without ($p<0.0001$, $\chi 2$ test). Considering the population as a whole, a positive PCR test was returned in 0% (0/1,038 [95% CI: 0–0.4%]) of those with previous infection, compared to 2.9% (290/10,137 [95% CI: 2.6–3.2]) of those without ($p<0.0001$, $\chi 2$ test).

Fewer healthcare workers in the previous infection group presented for symptomatic testing in the second period: 128/1,038 (12.3% [95% CI: 10.5–14.5]) compared with 2,115/10,137 (20.8% [95% CI: 20.1–21.6]) in the group without previous infection ($p<0.0001$ $\chi 2$ test). Asymptomatic PCR screening was undertaken on a pilot basis in an additional 481 healthcare workers, 106 with past infection and 375 without. These healthcare workers were distinct from the study population. There were similarly no positive results in the group with previous infection, 0/106 (0% [95% CI: 0–3.5]), compared with 22/375 (5.9% [95% CI: 3.9–8.7], $p=0.011$) positive PCR results in the group without previous infection, consistent with results of symptomatic testing.

In summary, there were no reinfection events in healthcare workers with prior evidence of infection (compared with 2.9% positivity in those without evidence of prior infection). Additionally, in a separate population, there were no asymptomatic reinfections in healthcare workers with evidence of prior infection (compared with 5.9% positivity in those without evidence of prior infection).

In the study by Shields et al.,[70] 1,507 dental care professionals in the UK were recruited in June 2020 and followed longitudinally for six months, which included commencement of vaccination. Baseline seroprevalence of antibodies against SARS-CoV-2 spike glycoprotein was 16.3% in this cohort, compared to estimates in the general population of 6-7%. At six months, 74.1% (n=1,116/1,507) of the cohort returned questionnaires regarding SARS-CoV-2 infections and blood samples were retrieved from 62.6% (n=944/1,507). Overall, 94 PCR-positive SARS-CoV-2 infections were reported by study participants, representing an overall infection risk of 8.4%. The risk of infection was 9.7% in participants who were seronegative at baseline compared with 2.9% in individuals who were seropositive (p=0.001). The emergence of antibodies following infection was associated with a 75% risk reduction for reinfection, with an adjusted risk ratio of 0.25 (95% CI: 0.09 to 0.73, adjusted for age, sex, ethnicity and smoking).

In reference to the first WHO standard for SARS-CoV-2 immunoglobulin (NIBSC 20/136), study authors estimated that the minimum level of anti-SARS-CoV-2 spike glycoprotein IgG antibodies necessary to confer six months protection from infection was 147.6 IU/ml. Using the NIBSC standard 20/162 generated a similar estimate of 195.2 IU/ml.

It is notable that this study coincided with vaccine roll-out. However, as the seropositive cohort was based on samples from June 2020, the relative reinfection rates relate to the effectiveness of natural immunity to prevent reinfection. Vaccine effectiveness rates were not reported. However, the serological responses of individuals receiving a single dose of the Pfizer-BioNTech SARS-CoV-2 were analysed based on prior exposure to the virus, defined by either positive baseline serology, or PCR-confirmed infection during the follow up period. Vaccination on the background of prior exposure to the virus was associated with a more rapid and quantitatively greater total antibody response against the SARS-CoV-2 spike glycoprotein, consistent with the boosting of immunological memory.

In the study by Papasavas et al.,[65] a longitudinal evaluation of the seroprevalence and epidemiology of SARS-CoV-2 specific antibodies on US health care workers was performed, which included RT-PCR testing at follow-up, over a period of approximately six months. The baseline prevalence of SARS-CoV-2 antibody among

6,863 HCWs was 6.3%. The incidence of reinfection in the seropositive group was zero: 0/35 seropositive participants who had a subsequent PCR test at least 30 days following the positive antibody test had a positive test, compared with 1.3% (29/2,173) seronegative participants had a subsequent positive PCR test.

The study by Davido et al.,[16] included 236 previously infected hospital staff members in France. Of these, 71 contracted SARS-CoV-2 in the first wave of the pandemic, from 1 March 2020 to 11 June 2020, and 165 in the second wave of the pandemic, from August 2020 until the end of study, 1 March 2021. Hence, the maximum follow up of the study was one year. Suspected reinfection was defined using one of the following criteria:

- a subsequent positive RT-PCR >45 days after the initial presentation if the second test was accompanied by symptoms or epidemiological exposure
- a subsequent positive RT-PCR >90 days after the initial presentation if the second test was performed among an asymptomatic hospital staff member that was a close contact of a person known to have a laboratory-confirmed COVID-19.

Probable reinfection was defined by clinical context (symptoms, exposure) plus a Ct value <37 and the absence of other diagnoses, which was assessed by an infectious disease specialist and a microbiologist. During the second wave, there were five cases (2.1%) of suspected reinfections. No probable reinfections were detected. Two cases were false positives and three cases were considered to be persistent shedding. Screening for the Alpha variant in France began on 1 January 2021. The study only reported a few hospital staff members infected by the Alpha variant. None of the five suspected reinfections involved the Alpha variant.

The study by Dobaño et al.,[17] assessed the occurrence of reinfections in a prospective cohort study of 173 Spanish primary healthcare workers followed for up to 12.5 months after COVID-19 symptoms onset. Seropositivity to SARS-CoV-2 spike and receptor-binding domain antigens up to 149–270 days was 92.5% (90.2% IgG, 76.3% IgA, 61.0% IgM). Fully vaccinated workers were excluded from the study. In a subset of 64 healthcare workers who had not yet been vaccinated by April 2021, seropositivity was 96.9% (95.3% IgG, 82.8% IgA) up to 322–379 days post symptom onset. Likely reinfection was defined as a positive PCR test >90 days after primary infection. A positive PCR test <90 days from primary infection was considered suspected reinfection. One suspected reinfection and three likely reinfections were detected by passive case detection, two of which displayed symptoms and were among seronegative individuals (five and seven months after the first episode), one in a low antibody responder and one in an individual whose serostatus was unknown. The overall rate of symptomatic reinfection was 2 out of

173 (1.16%). Despite heterogeneity in antibody levels following SARS-CoV-2 infection, most healthcare workers remained seropositive for anti-S antibodies up to 12.5 months after contracting COVID-19.

The study by Gallais et al.,[20] performed a longitudinal assessment of the kinetics of SARS-CoV-2 antibodies, the incidence of reinfection, and sensitivity of infectious SARS-CoV-2 variants to vaccination on healthcare workers from Strasbourg University Hospital in France. A total of 1,496 healthcare workers were included between 6 April and 7 May 2020 and followed for up to 13 months. By the end of the study, 14.6% of the 393 previously infected healthcare workers had been fully vaccinated. A total of 4,290 serial serum samples from 393 convalescent COVID-19 and 916 COVID-19 negative HCWs were tested against the Receptor Binding Domain (RBD) of the spike protein and nucleocapsid protein (N). The sensitivity of infectious SARS-CoV-2 variants before and after vaccination were evaluated between month 11 and month 13 using the S-Fuse live-virus neutralisation assays. Only 1 of the 393 previously infected healthcare workers was reinfected (0.3%) over a nine month period (incidence of 0.40 per 100 person-years).

In the study by Rivelli et al.,[34] the incidence of SARS-CoV-2 reinfection (defined as subsequent SARS-CoV-2 infection ≥ 90 days from prior infection) was estimated among a convenience sample of 2,625 healthcare employees in a large Midwestern healthcare system in the US over a 10-month period (March 2020 to January 2021). Of 2,625 participants who experienced at least one SARS-CoV-2 infection during the 10-month study period, 156 (5.94%) experienced reinfection, a median of 126.5 days (IQR 105.5-171) after initial infection. Of these 156 participants, 42 (26.9%) had COVID-clinical roles, 110 (70.5%) had non-COVID clinical roles, and four (2.6%) had non-clinical roles within the healthcare system. Incidence rate of SARS-CoV-2 reinfection was 0.35 cases per 1,000 person-days, with participants working in COVID-clinical and clinical units experiencing 3.77 and 3.57 times, respectively, greater risk of reinfection relative to those working in non-clinical units. The authors concluded that SARS-CoV-2 reinfection is rare within a 10-month period, but that the risk is elevated among healthcare staff in clinical roles.

A further 12 studies examined the risk of reinfection in healthcare workers.[7, 15, 22, 24, 25, 35, 36, 41, 46, 48, 50] The results of these 12 studies are broadly in agreement with the studies mentioned above, in that the risk of reinfection was found to vary but remained low (ranging from 0%[22, 46] to 4.5%)[25] over the duration of the studies (maximum follow-up ranged from six[35] to 12 months).[24, 46] Both extremes of reinfection rate were found in studies with relatively small sample sizes. For example, only 98 seropositive healthcare workers were included at baseline in the study by Gehring et al. and consequently no reinfections were detected after six months.[22] Conversely, three possible reinfections were detected out of 67

seropositive participants (4.5%) 198 to 220 days after positive baseline serology in the study by Kohler et. al.[25] However, PCR or rapid antigen tests were used for determining reinfections in this study, with the latter potentially contributing some false positive results due to its low positive predictive value in low prevalence settings.[72]

Residents and staff of care homes for older people

Two studies were identified that included both residents and staff at UK care homes.[58, 59] A third study included residents in a nursing home in the US.[10]

In the study by Jeffery-Smith et al.[58], the risk of reinfection according to antibody seropositivity was investigated following outbreaks in two London care homes[58, 73] with high rates of SARS-CoV-2 seropositivity after outbreaks in the first wave of the pandemic. In the first care home, serological investigations in June 2020 identified 50% as seropositive after the first outbreak (18/32 residents; 15/34 staff), and in the second care home, serological investigation in May 2020 identified 50.4% as seropositive (26/52 residents; 33/65 staff).

In total, 88 individuals with evidence of prior infection were investigated for evidence of reinfection (antibody positive N=87; RT-PCR positive N=1). The reinfection rate in this cohort was 1/88 (1.1%), and this reinfection event was observed in a staff member. By comparison, infection risk in the seronegative cohort was 30.1% (22/73, including four people diagnosed by seroconversion). The RR was estimated at 0.038 (95% CI: 0.005 to 0.273). The protection against reinfection after four months in seropositive group was estimated at 96.2% (95% CI: 72.7 to 99.5%).

In terms of whole genome sequencing, the second COVID-19 outbreaks experienced by both care homes were due to SARS-CoV-2 strains that were genetically distinct from their respective first outbreaks (Appendix 2), and fatal cases in residents had identical viral genomes to surviving residents. Ct values were not reported.

In the study by Krutikov et al.[59], staff and residents in 100 long term care facilities (LTCFs) in England were followed between October 2020 and February 2021. In total, 2,111 individuals were included (682 residents and 1,429 staff). The median age of residents was 86 years (IQR: 79-91) and 47 years for staff (IQR range: 34-56). Blood sampling was offered to all participants at three time points separated by 6-8 week intervals in June, August and October 2020. Samples were tested for IgG antibodies to nucleocapsid and spike protein. PCR testing for SARS-CoV-2 was undertaken weekly in staff and monthly in residents. The time-at-risk ('entry time') for participants was 1 October 2020 or 28 days after their first available antibody

test, whichever was later. The primary analysis estimated the adjusted hazard ratio (aHR) of a PCR-positive test by baseline antibody status (Cox regression adjusted for age and gender, and stratified by LTCF). Discrepancies were noted in this study, whereby the results of the Cox regression were reported differently in the abstract and results sections. The findings presented in this review reflect those in the study's results section only.

Baseline IgG antibodies to nucleocapsid were detected in 226 residents (33%) and 408 staff (29%). Staff and residents contributed 3,749 and 1,809 months of follow-up time, respectively. There were 93 PCR-positive tests in seronegative residents (0.054 per month at risk) compared with four in seropositive residents (0.007 per month at risk). There were 111 PCR-positive tests in seronegative staff (0.042 per month at risk) compared with 10 in seropositive staff (0.009 per month at risk). Controlling for the potential confounding effect of individual LTCFs, the relative aHRs for PCR positive infection were 0.15 (95% CI: 0.05 to 0.44) and 0.39 (95% CI: 0.19 to 0.82) comparing seropositive versus seronegative residents and staff, respectively.

Of 12 reinfected participants with data on symptoms, 11 were symptomatic. None of the reinfection cases were admitted to hospital or died as a result of their infection. Ct values were retrieved for 13/14 reinfection samples; the median Ct value for reinfection cases was 36. Antibody titres to spike and nucleocapsid were comparable in PCR-positive and PCR-negative cases. Whole genome sequencing was not performed.

Study authors concluded that the presence of IgG antibodies to nucleocapsid was associated with substantially reduced risk of reinfection in staff and residents for up to 10 months after primary infection, assuming that the earliest infections occurred in March 2020.

The study by Armstrong et al.,[(10)] used a surveillance system for COVID-19 to identify nursing home residents, in Connecticut, US, who tested positive for SARS-CoV-2 by PCR testing ≥90 days after initial positive results. Nursing home testing data over a nine-month period were analysed, from 15 March to 15 December 2020, before nursing home COVID-19 vaccinations began. The study included 6,079 nursing home residents with a previous SARS-CoV-2 infection surviving beyond 90 days of their initial infection. In total, 2.6% (156/6,079) of residents were identified with positive PCR tests occurring ≥90 days after an initial positive test. The median age of the repeat positive cohort was 75 years (range 36–105) and 58% were female. The median time to repeat positivity was 135 days (range 90–245 days). Of the 156 patients who had a repeat positive test, 67% had symptoms at the time of

initial positive test and 35% had symptoms at time of the repeat positive test. Deaths were reported in 12.8% of residents following the repeat positive test. Of the repeat positive tests, 27.5% had Ct values <33, where reported.

Essential workers

One study, conducted in Switzerland, was identified that examined the risk of reinfection in different categories of essential workers (Leidi et al.),[28] which included a total of 10,457 essential workers. Workers were categorised into three pre-defined groups, according to their exposure risk: 3,057 individuals were in occupations likely requiring sustained physical proximity to other individuals (for example, healthcare workers, childcare and social workers), 3,645 were in occupations involving regular brief contact (for example, pharmacists, taxi drivers, grocery workers) and 3,755 workers in other essential occupations (for example, farmers, managers and health researchers). A total of 784 study participants were seropositive at baseline. Participants were recruited from a sero-survey cohort conducted between May and September 2020 in Switzerland. Follow-up occurred until 25 January 2021. The mean follow-up was 6.4 months (193 days) for the seropositive cohort and 6.5 months (195 days) for the seronegative cohort. Maximum follow-up was approximately 269 days (9.8 months). Serological assessment (May to September 2020) took place during low SARS-CoV-2 incidence (<300 weekly cases), but follow-up assessment took place during very high incidence (peaking >6,500 weekly cases in early November). Reinfection was defined as a positive RT-PCR or rapid antigen detection test (RADT) in seropositive individuals; these were clinically investigated by two independent adjudicators and classified as likely or unlikely reinfections.

After follow-up, five (0.6%) seropositive and 830 (8.5%) seronegative individuals had a positive SARS-CoV-2 test, with an incidence rate of 0.2 (95% CI: 0.1 to 0.6) and 3.2 (95% CI: 2.9 to 3.4) cases per person-week, respectively. The adjusted hazard ratio (aHR) of having a virologically-confirmed infection in seropositive compared to seronegative participants was estimated with a Cox proportional hazard model. Covariates included in the model were age, sex, smoking status, obesity and formal educational level. Seropositive essential workers had a 93% reduction in the hazard (aHR of 0.07, 95% CI: 0.03 to 0.17) of having a positive test during follow-up, with no significant differences between-occupational groups.

Patients with chronic kidney disease

Three studies were identified that examined the risk of reinfection with SARS-CoV-2 in patients with chronic kidney disease (CKD).

In the first study, a prospective cohort study was conducted by Cohen et al.[14] among adults with end stage kidney disease (ESKD) treated with in-centre haemodialysis in the US. Exposure was ascribed on the basis of the presence or absence of IgG against SARS-CoV-2 at baseline, and separately, a documented medical history of COVID-19 before study entry. Of the 2,337 consented participants who met the inclusion criteria, 9.5% were anti–SARS-CoV-2 IgG positive at baseline and 3.6% had a history of COVID-19. Outcomes were assessed after an infection-free period of three months. The outcomes were any SARS-CoV-2 infection, detected by protocolised PCR tests at 30 day intervals or during routine clinical surveillance, which entailed screening for symptoms of COVID-19 or known exposure at each clinic visit three times a week. A PCR test was conducted in the event of a positive screen. The maximum follow-up period for the study was approximately six months, which included the infection-free period.

During the follow up, 263 participants had evidence of any SARS-CoV-2 infection, including 141 who had a symptomatic infection. Presence of anti–SARS-CoV-2 IgG (versus its absence) at baseline was associated with lower risk of any SARS-CoV-2 infection (IRR, 0.55; 95% CI, 0.32 to 0.95) or of a symptomatic reinfection, 0.21 (95% CI, 0.07 to 0.67).

In the second study, a retrospective multi-centre cohort study of eight Indian transplant centres was conducted by Kute et Al. to identify kidney transplant recipients who became reinfected with SARS-CoV-2 between April 2020 and May 2021.[47] Of the 1,350 kidney transplant recipients who became infected with SARS-CoV-2, 13 (0.96%) were reinfected a median of 135 days later. The median age of the 13 individuals was 46 years and eight were men. Comorbidities were prevalent among the 13 reinfected individuals, with eight patients deemed to be multimorbid; hypertension (n=11) and diabetes (n=3) were the most common conditions. Clinical severity during the first episode of COVID-19 ranged from asymptomatic in three patients, mild in four patients, and moderate in six patients; whereas during the second episode, one patient was asymptomatic, six patients had mild COVID-19 symptoms, and six patients had severe symptoms. Of note, all six patients with severe COVID-19 symptoms in their second episode died, a median of 10 days after their RT-PCR positive test. The authors concluded that in this population of kidney transplant recipients, who were severely immunocompromised, reinfection with SARS-CoV-2 was associated with high levels of mortality.

In the third study, 990 haemodialysis patients were followed for approximately six months in a single centre in the UK. This study by Banham et al. was conducted between 10 March 2020 and 9 January 2021.[44] Antibodies (combined IgG, IgA, and IgM; IgGAM) against SARS-CoV-2 spike glycoprotein were examined by ELISA in

surplus serum from routine clinical samples taken during the first wave (March to July 2020). Clinical data and SARS-CoV-2 infection status were collated from electronic medical records. Antispike SARS-CoV-2 antibodies were detected in 25.9% (256 out of 990) of patients from the first wave of COVID-19, with 54.7% seroconverting without a history of infection (140 out of 256). During the second wave (October 2020 to January 2021), patients were screened routinely for infection using PCR. In total, 90 PCR positive patients were identified out of 937 haemodialysis patients who were at risk and receiving haemodialysis. Eight of 700 seronegative (11.4%) patients became infected, compared with 10 out of 237 (4.2%) of seropositive patients (risk ratio for reinfection, 0.37; 95% CI: 0.19 to 0.70, p=0.001), with no differences in the proportion of patients who were symptomatic, hospitalised, or who died, according to antibody status. The authors concluded that SARS-CoV-2 antibodies in patients on haemodialysis are well maintained and associated with reduced risk of subsequent SARS-CoV-2 infection, but that the risk of reinfection (4.2%) may still be higher than in other non-immunocompromised populations.

University student population

One study was identified that examined the risk of SARS-CoV-2 reinfection in a university student population.[32]

In the retrospective cohort study by Rennert et al.,[32] the risk of COVID-19 reinfection among all students aged 17–24 years who initially tested positive between 19 August 2020 and 5 October 2020 (Autumn 2020 positive group) was evaluated in a university setting in the US. The outcome assessment period was from 28 December 2020 to 1 May 2021 (Spring 2021 semester). Hence, follow-up ranged from a minimum of 84 days (approximately 2.8 months) to a maximum of 255 days (approximately 8.5 months).

As it may be possible to detect SARS-CoV-2 RNAup to 12 weeks after infection, students who tested positive within 12 weeks of the outcome assessment period were excluded from the analysis. During in-person teaching in Autumn 2020 (21 September–25 November 2020), all students with access to main campus facilities were subject to mandatory surveillance PCR testing using either anterior nasal swabs or saliva samples. Students living in university residences, were subject to two weeks of surveillance-based informative testing followed by repeated weekly testing, while non-residential students were subject to random surveillance testing only. In-person instruction resumed during the Spring 2021 semester (6 January 2021). During this period, all university students and employees who accessed main campus facilities were subjected to mandatory weekly saliva PCR tests (same tests used during the Autumn 2020 semester). In both instances, prior to campus return,

all students and employees were required to provide a COVID-19 test result within 10 days of campus return or a positive serologic antibody test.

Of the 16,101 university students in the study, 2,021 students were previously infected in Autumn 2020, 44 (2.2%) of whom were reinfected during the Spring 2021 semester. This was significantly lower than the 12.1% rate among the 14,080 students who tested negative throughout the Autumn 2020 semester ($p<0.0001$). The relative risk of reinfection, adjusted for covariates (age, gender, testing compliance [measured as percentage of eligible periods tested], and residential status) was 0.16 (95% CI: 0.12 to 0.22) relative to the autumn 2020 negative group. The estimated protection against repeat infection was 84% (95% CI: 78% to 88%). Among those reinfected, the median time to reinfection was 129 days (range: 86 to 231). When reinfections without a confirmatory negative test between original infection and reinfection were excluded, 33 (1.6%) students were reinfected during the Spring 2021 semester. The relative risk of reinfection, adjusted for covariates was 0.12 (95% CI: 0.09 to 0.17) relative to the Autumn 2020 negative group; estimated protection against reinfection was 88% (95% CI: 83% to 91%).

Vaccinated population with and without previous infection

Seven studies were identified that compared the estimated protection from reinfection following infection with SARS-CoV-2 and COVID-19 vaccination.[8, 21, 26, 38, 45, 51, 61] Four studies were conducted in the US;[26, 38, 45, 51] and one each was conducted in the UK,[61] Qatar[8] and Israel.[21]

In the study by Lumley et al., reinfection rates among healthcare workers were reported according to vaccination status and in relation to the Alpha variant.[61] This study updates the 2020 study by the same authors[74] and presents data up to 28 February 2021. In this longitudinal cohort study in Oxfordshire, UK, protection from symptomatic and asymptomatic PCR-confirmed SARS-CoV-2 infection conferred by vaccination (Pfizer-BioNTech BNT162b2 or Oxford-AstraZeneca ChAdOx1 nCOV-19) and prior infection (determined using anti-spike antibody status), was assessed using Poisson regression adjusted for age, sex, temporal changes in incidence and role. Staff members were classified into five groups: a) unvaccinated and consistently seronegative during follow-up; b) unvaccinated and ever seropositive; c) one vaccine dose, always seronegative prior to vaccination; d) two vaccine doses, always seronegative prior to first vaccine dose; e) vaccinated (one or two doses) and ever seropositive prior to first vaccination. Vaccinated groups were considered at-risk of infection >14 days after each vaccine dose. The staff vaccination programme began on 8 December 2020, starting with the Pfizer-BioNTech BNT162b2 vaccine, with the addition of the Oxford-AstraZeneca ChAdOx1 nCoV-19 vaccine from 4

January 2021. Some staff members received the ChAdOx1 nCoV-19 vaccine in clinical trials beginning 23 April 2020 and were included following unblinding.

In total, 13,109 individuals participated; 8,285 received the Pfizer-BioNTech vaccine (1,407 two doses) and 2,738 the Oxford-AstraZeneca vaccine (49 received two doses). Compared to unvaccinated seronegative workers, natural immunity (that is, seropositivity due to prior infection) provided similar protection to two vaccine doses against symptomatic infection: no healthcare worker with two vaccine doses had symptomatic infection, and incidence was 98% lower in seropositive healthcare workers (adjusted incidence rate ratio 0.02 [95% CI: <0.01 to 0.18]). Two vaccine doses or seropositivity reduced the incidence of any PCR-positive result with or without symptoms by 90% (0.10 [0.02-0.38]) and 85% (0.15 [0.08 to 0.26]), respectively. Single-dose vaccination reduced the incidence of symptomatic infection by 67% (0.33 [0.21 to 0.52]) and any PCR-positive result by 64% (0.36 [0.26 to 0.50]).

Viral whole genome sequencing was undertaken to determine infecting lineages from 1 December 2020 onwards. Of these, 343/463 (74%) were successfully sequenced; 193/343 (56%) were the Alpha variant, and an additional 19/463 (4%) were not sequenced, but S-gene positive (that is, unlikely to be the Alpha variant). There was no evidence that the Alpha variant changed the extent of protection from any-PCR positive infection in those who were seropositive (aIRR vs non-Alpha variant =0.40 [95% CI: 0.10 to 1.64; p=0.20]) or following a first vaccine dose (aIRR=1.84 [0.75 to 4.49; p=0.18). Additionally, 17% of S-gene target failure (SGTF) was due to a lineage other than the Alpha variant. No other variants of concern (the Alpha variant with E484K, the Beta variant or the Gamma variant) were identified in participants, in an at-risk period. There was no evidence of differences in immunity induced by prior infection and vaccination for infections with S-gene target failure and the Alpha variant.

Study authors concluded that natural immunity resulting in detectable anti-spike antibodies and two vaccine doses both provide robust protection against SARS-CoV-2 infection, including against the Alpha variant.

In the study by Gazit et al.,[(21)] three cohorts were examined regarding their risk of SARS-CoV-2 infection (breakthrough or reinfection). This retrospective matched-cohort study was conducted in Israel, using the centralised electronic database of Maccabi Healthcare Services (MHS). Reinfection was defined as two positive PCR tests a minimum of 90 days apart. The study population included all MHS members aged 16 or older and were categorised into one of three cohorts:

- Group 1: fully vaccinated (two doses of Pfizer-BioNTech mRNA BNT162b2 vaccine) prior to 28 February 2021 with no previous infection (n=673,676)
- Group 2: documented SARS-CoV-2 infection by 28 February 2021 and remained unvaccinated until the start of the outcome assessment period (1 June 2021) (n=62,883)
- Group 3: documented SARS-CoV-2 infection by 28 February 2021 and received one dose of the Pfizer-BioNTech mRNA BNT162b2 vaccine by 25 May 2021, at least seven days before the start of the outcome assessment period (1 June 2021). (n=42,099). At the time in Israel, only one dose was given to those with documented previous infection.

The outcome assessment period of 1 June to 14 August 2021 occurred when the Delta variant was dominant in Israel. Three multivariate logistic regression models were constructed.

In Model 1, Groups 1 and 2 were matched in a 1:1 ratio (n=16,215 in both groups; mean age 36.1 years) by age, sex, geographical statistical area (GSA) and time of first event (second dose of vaccine or PCR-confirmed infection). To control for the time of first event, these must have occurred between 1 January and 28 February 2021. The aim of this model was to examine the long-term protection when vaccination or infection occurred within the same time period. During the outcome assessment period, 257 cases of SARS-CoV-2 infection were recorded, of which 238 occurred in the vaccinated group (1.58% breakthrough infection rate) and 19 in the previously infected group (0.12% reinfection rate). After adjusting for comorbidities, a statistically significant increased odds of infection (OR 13.06; 95% CI: 8.08 to 21.11) was estimated in the fully vaccinated cohort, though the confidence intervals were very wide. Age ≥60 years was associated with an increased risk of infection, but there was no statistical evidence that any of the assessed comorbidities (obesity, cardiovascular diseases, diabetes, hypertension, chronic kidney disease, cancer and immunocompromising conditions) significantly affected the risk of an infection during the follow-up period.

In Model 2, Groups 1 and 2 were matched in a 1:1 ratio (n=46,035 in both groups mean age 36.1 years) as described above; however, this time individuals were not matched by the time of first event, in order to compare vaccine-induced immunity with natural immunity, regardless of time of infection (PCR data were available since 1 March 2020). Throughout the outcome assessment period, 748 cases of SARS-CoV-2 infection were recorded, 640 of which were in the vaccinated group (1.39% breakthrough infection rate) and 108 in the previously infected group (0.23% reinfection rate). After adjusting for comorbidities, a statistically significant increased odds of infection (OR 5.96; 95% CI: 4.85 to 7.33) was estimated in the fully vaccinated cohort. Apart from socioeconomic status (SES) level and age ≥60 there

was no statistical evidence that any of the assessed comorbidities (obesity, cardiovascular diseases, diabetes, hypertension, chronic kidney disease, cancer and immunocompromising conditions) significantly affected the odds of an infection during the follow-up period. Notably, the reinfection rate was almost twice as high in Model 2 compared with Model 1 (0.23% vs. 0.12%) suggesting a potential waning of natural immunity over time.

In Model 3, Groups 2 and 3 were compared, using "natural immunity" (Group 2) as the baseline group. Groups 2 and 3 were matched in a 1:1 ratio (n=14,029 in both groups; mean age 33.2 years) based on age, sex and GSA. The authors found that those who had been previously infected and received a single vaccine dose had a significantly reduced odds of reinfection (OR 0.53; 95% CI: 0.3 to 0.92), as 20 had a positive PCR test (0.14% reinfection rate), compared to 37 in the previously infected and unvaccinated group (0.26% reinfection rate).

When broken down by age group, the authors found that individuals aged 60 years and older had at least a two-fold increase in the likelihood of reinfection (or breakthrough infection) relative to those aged under 40 years, which was statistically significant across the three constructed models (Model 1; OR, 2.7, 95% CI, 1.68 to 4.34. Model 2; OR, 2.89, 95% CI, 1.68 to 4.99. Model 3; OR, 2.2, 95% CI 1.66 to 2.92).[21] No increase in risk was observed for those aged 40-59 years.

While differences in the likelihood of reinfection (or breakthrough infection) were observed, the overall rates of reinfection and breakthrough infection were low in all three models. An important limitation of this study is that there is a potential for immortal time bias, as time-varying confounding (that is, exposures that change over time, particularly vaccine uptake) may not been appropriately controlled for, given that individuals in Group 2 may have decided to avail of a vaccine after 1 June 2021, yet their outcomes were still attributable to Group 2. Additionally, asymptomatic individuals were not routinely tested for SARS-CoV-2 and this may have underestimated the asymptomatic infection rate.

In direct response to the study by Gazit et al.,[21] a comparable retrospective cohort study was conducted by Young-Xu et al. in a US Veterans population.[51] Part of the study design was matched to that of Gazit et al.,[21] focusing on exposure (that is, infection or vaccination) during January and February 2021 and outcome assessment (that is, reinfection or breakthrough infection) during June, July, and the first half of August 2021. The study population included all Veterans included under the care of Veterans Health Administration (VHA) aged 18 or older. Similar to Model 1 in the study by Gazit et al.,[21] individuals were SARS-CoV-2-naïve (no prior infection) prior to 1 January 2021, and then prior to 1 March 2021 were either fully vaccinated or had a documented, laboratory-confirmed, SARS-CoV-2 infection and were

unvaccinated. The outcome assessment occurred between 1 June and 18 August 2021 when the Delta variant was dominant. However, unlike the study by Gazit et al., matched Cox survival models to compare time to events of interest by type of immunity were constructed. Additionally, each previously infected Veteran was matched with up to four vaccinated individuals (Pfizer-BioNTech or Moderna), based on state and index event dates, race/ethnicity, age groups, sex, rural/urban, Charlson Comorbidity Index (CCI) and Veterans Affairs priority groups (based largely on disabilities).

This study involved a total of 47,102 US Veterans with a mean (SD) age of 62.8 (14.1) years, 91.3% of whom were male. A total of 9,539 patients with SARS-CoV-2 infection during the first two months of 2021 were matched to 14,458 and 23,105 participants fully vaccinated with Moderna and Pfizer-BioNTech mRNA vaccines, respectively. Between June and August 2021, a total of 110 (0.23%) participants tested positive for COVID-19 with those previously infected without subsequent vaccination having the highest infection rate (that is, 2.7 per 100,000 patient-days). Among those aged 65 or older, those previously infected had the highest infection rate (that is, 4.8 per 100,000 patient-days), followed by those fully vaccinated with Pfizer-BioNTech at 1.5 per 100,000 patient-days, and Moderna at 1.2 per 100,000 patient-days. Estimates based on the matched, adjusted multivariable Cox model showed that between June and August 2021, using previously infected patients as the reference, those who received Moderna and Pfizer-BioNTech vaccines had a 66% [HR: 0.34 (95% CI, 0.14 to 0.78)] and 68% [HR: 0.32 (95% CI, 0.14 to 0.70)] significantly lower hazard of infection, respectively. Focusing on infection during July and August specifically, two months during which the prevalence of Delta variant reached 100% in most of the US, no difference in the risk of infection was observed. However there was substantial uncertainty associated with these estimates (HR 2.45 [95% CI, 0.56 to 20.66] and HR 1.89 [95% CI, 0.49 to 7.28] estimated for Moderna and Pfizer-BioNTech, respectively) as indicated by the wide confidence intervals.

For those younger than 65 years, using matched, adjusted multivariable Cox model no difference in the hazard of infection was observed (Pfizer-BioNTech: HR: 0.64 [95% CI, 0.24 to 1.69]; Moderna vaccines: HR: 0.35 [95% CI, 0.11 to 1.13]) or when restricted to infections in July and August 2021 (Pfizer-BioNTech: HR: 1.59 [95% CI, 0.41 to 6.11]; Moderna vaccines: HR: 1.04 [95% CI, 0.24 to 4.58]).

Overall the risk of reinfection/breakthrough infection was very low with 110 of 47,102 (0.23%) becoming (re)infected with SARS-CoV-2 during the outcome assessment period. The authors surmised that the differing results between the current study and that by Gazit et al. may be due to differences in population (in particular the older age profile in the study by Young-Xu et al.), statistical models or

the availability of an additional vaccine (that is, Moderna). Of note, Gazit et al. did find that older age (≥ 60 years) was significantly associated with higher odds of breakthrough infection or reinfection. The authors also consider the possibility that Israel had reached herd immunity at the time of the study by Gazit et al. and hence differences between vaccinated and unvaccinated individuals may have appeared to be minimal at that time.

In the study by Abu-Raddad et al.,[8] the effect of prior SARS-CoV-2 infection was assessed in Qatar's population, using two national retrospective, matched-cohort studies. Qatar experienced two back-to-back SARS-CoV-2 waves from January to June 2021, which were dominated by the Alpha and then the Beta variants, respectively. The study compared incidence of documented SARS-CoV-2 infection in vaccinated individuals (≥14 days after the second dose) who had or had not experienced a prior PCR-confirmed infection between 21 December 2020 and 6 June 2021. Comparisons were undertaken separately for the BNT162b2 (Pfizer) and mRNA-1273 (Moderna) vaccines with cohorts matched in a 1:1 ratio by sex, five-year age group, nationality, and calendar week of the first vaccine dose, to control for differences in exposure risk and variant exposure.

Incidence rates of infection among BNT162b2-vaccinated persons, with and without prior infection (n=51,486 in both groups), were estimated at 1.66 (95% CI: 1.26 to 2.18) and 11.02 (95% CI: 9.90 to 12.26) per 10,000 person-weeks, respectively; incidence rate ratio: 0.15 (95% CI: 0.11 to 0.20). Incidence rates of infection among mRNA-1273-vaccinated persons, with and without prior infection (n=24,052 in both groups), were estimated at 1.55 (95% CI: 0.86 to 2.80) and 1.83 (95% CI: 1.07 to 3.16) per 10,000 person-weeks, respectively; incidence rate ratio: 0.85 (95% CI: 0.34 to 2.05). The absolute rates of infection and reinfection were low in the study. For those vaccinated with BNT162b2 (Pfizer), the incidence of breakthrough (no previous infection) and reinfection (prior infection) was 0.65% (337/ 51,486) and 0.09% (n=51/51,486), respectively. Similarly, for the mRNA-1273-vaccinated individuals, the incidence of breakthrough and re-infection was 0.05% (13/24,052) and 0.05% (11/24,052), respectively. The maximum follow-up durations were approximately 132 and 65 days for the BNT162b2 and mRNA-1273 cohorts, respectively.

The authors concluded that prior infection enhanced protection of those BNT162b2-vaccinated (Pfizer-BioNTech), but not those mRNA-1273-vaccinated (Moderna). It is important to note the comparator populations without previous infection are different as evidenced by the much lower incidence rate of infection in the Moderna cohort (1.83 per 10,000 person-weeks) versus that of the Pfizer-BioNTech cohort (11.02 per 10,000 person-weeks). These population differences may be due to the

Pfizer-BioNTech vaccination rollout commencing several weeks prior to the Moderna campaign in Qatar and so a greater proportion of higher risk populations may have received the Pfizer-BioNTech vaccine. Additionally, there is substantially longer follow-up with the Pfizer-BioNTech vaccine. Therefore, direct comparisons of vaccine effectiveness between the two cohorts in this study is challenging.

In the study by Shrestha et al.,[38] the cumulative incidence of SARS-CoV-2 infection was examined among 52,238 employees in an American healthcare system. All employees of the Cleveland Clinic Health System working in Ohio on 16 December 2020, the day COVID-19 vaccination was started, were included in this retrospective cohort study. Any individual who tested positive, by PCR, for SARS-CoV-2 at least 42 days earlier was considered previously infected. An individual was considered fully vaccinated 14 days after receipt of the second dose of a SARS-CoV-2 mRNA vaccine (Pfizer-BioNTech or Moderna vaccine). The cumulative incidence of SARS-CoV-2 infection over the next five months, among previously infected subjects who received the vaccine (n=1,220), was compared with those of previously infected subjects who remained unvaccinated (n=1,359), previously uninfected subjects who received the vaccine (n=28,855), and previously uninfected subjects who remained unvaccinated (n=20,804). The study period was from 16 December 2020 until 15 May 2021, with historic PCR results available from 12 March 2020. Reinfection was defined as two positive PCR test results at least 90 days apart.

Of the 2,154 SARS-CoV-2 infections that occurred during the study period, 2,139 (99.3%) occurred among those not previously infected who remained unvaccinated or were waiting to get vaccinated, and 15 (0.7%) occurred among those not previously infected who were fully vaccinated. No episode of reinfection was recorded over the five month duration of the study in the 2,579 previously infected subjects. The cumulative incidence of SARS-CoV-2 infection among previously uninfected subjects who remained unvaccinated, reached a cumulative incidence of approximately 5% by the end of the five month study period. In a Cox proportional hazards regression model, after adjusting for the phase of the epidemic, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (aHR 0.031, 95% CI: 0.015 to 0.061), but not among those previously infected (aHR 0.313, 95% CI: 0 to infinity) because there were no reinfections. This study was not specifically designed to determine the duration of protection afforded by natural immunity. However, for the previously infected subjects, the median duration since prior infection at study onset was 143 days (IQR 76 – 179 days), with no episodes of reinfection over the following five months, suggesting that a history of SARS-CoV-2 infection provides protective immunity for at least 10 months. However, an important limitation of this study is that asymptomatic individuals were not systematically retested after prior infection or

vaccination, and so the number of asymptomatic reinfections or breakthrough infections may have been underestimated.

A US case-control study conducted between May and June 2021 reported a reduced risk of reinfection after COVID-19 vaccination.[45] In this study by Cavanaugh et al., which included Kentucky residents aged 18 years and older infected with SARS-CoV-2 in 2020, the vaccination status of those reinfected during May–June 2021 (that is, the case patients, n=246) was compared with that of residents who were not reinfected (that is, the controls, n=492). Case-patients and controls were matched on a 1:2 ratio based on sex, age (within 3 years), and date of initial positive SARS-CoV-2 test (within 1 week). Case-patients were considered fully vaccinated if a single dose of Janssen (Johnson & Johnson) or a second dose of an mRNA vaccine (Pfizer-BioNTech or Moderna) was received ≥14 days before the reinfection date. For controls, the same definition was applied, using the reinfection date of the matched case-patient. Partial vaccination was defined as receipt of ≥1 dose of vaccine, but either the vaccination series was not completed or the final dose was received <14 days before the case-patient's reinfection date. Conditional logistic regression, was used to compare no vaccination and partial vaccination with full vaccination among case-patients and controls.

In this case-control study, the odds of reinfection was 2.34 (OR, 2.34; 95% CI, 1.58 to 3.47) in those who were unvaccinated compared with those who were fully vaccinated. Partial vaccination was not significantly associated with reinfection (OR, 1.56; 95% CI, 0.81 to 3.01). The authors concluded that among persons with previous SARS-CoV-2 infection, full vaccination provides additional protection against reinfection. A limitation of this study is its relatively small sample size. Additionally determination of reinfection was based on either a NAAT or an antigen test; it is unclear whether a confirmatory test was required after a positive antigen test result.

In the study by Kojima et al.,[26] the relative risk of SARS-CoV-2 infection among individuals who were SARS-CoV-2 naïve (no prior infection), previously infected, or fully vaccinated was assessed in employees of a clinical laboratory in the US, where all employees were screened daily using PCR. Using an electronic laboratory information system, employees were divided into three groups:

- Group 1: no previous infection and unvaccinated (n=4,313)
- Group 2: previous SARS-CoV-2 infection and unvaccinated (n=254)
- Group 3: fully vaccinated, with either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) (n=739) without previous infection.

Fully vaccinated individuals who had a previous infection were excluded. Person-days were measured from the date of employees' first test and truncated at the end

of the observation period (from 8 May to 15 December 2020 for Groups 1 and 2, and up until 1 July 2021 for Group 3). SARS-CoV-2 infection was defined as two positive SARS-CoV-2 PCR tests in a 30-day period. Individuals with fewer than 14 days of follow up were excluded. Incidence estimates and the 95% confidence intervals were calculated using the Poisson Exact equation. The incidence rate ratio (IRR) was used as a measure of association between groups.

During the observation period, 254, 0, and 4 infections were identified among Groups 1, 2, and 3, respectively. Group 1 had an incidence of 25.9 per 100 person years (95% CI: 22.8 to 29.3). Group 2 had an incidence of 0 per 100 person-years (95% CI: 0 to 5.0). Group 3 had an incidence of 1.6 per 100 person-years (95% CI: 0.04 to 4.2). The IRR of reinfection comparing those with previous infection and unvaccinated with those with no previous infection and unvaccinated was 0 (95% CI: 0 to 0.19). The IRR of those fully vaccinated compared with those with no previous infection and unvaccinated was 0.06 (95% CI: 0.02 to 0.16). The IRR of those fully vaccinated compared with prior infection was not estimable due to zero events in the previously infected group. The authors concluded that previous SARS-CoV-2 infection and vaccination for SARS-CoV-2 were both associated with decreased risk for infection or re-infection in a routinely screened workforce, with a lower absolute incidence rate observed in the previously infected cohort. Important limitations of this study are its relatively small sample size, that the populations are drawn from different time periods (before and after mass vaccination) and that confounders were not adequately controlled for, making direct comparisons between groups less meaningful.

Quality of included studies

The National Heart, Lung and Blood Institute (NIH) quality assessment tool was used for appraisal of observational cohort studies.[75] Fifty-three of the 65 included studies (81.5%) were considered of 'good' or 'fair' methodological quality (Appendix 3). Specifically, 12 studies were deemed of 'good' methodological quality,[18, 20, 40, 54, 56, 59-63, 70, 76] 41 studies were deemed 'fair',[7, 8, 10, 11, 14-17, 19, 21, 22, 24, 26-35, 38, 39, 41, 43-45, 48, 49, 51-53, 55, 58, 65-69] and 12 studies were considered of poor methodological quality.[6, 12, 23, 25, 36, 37, 42, 46, 47, 50, 57, 64]

In three of the 12 studies deemed of poor methodological quality, details of the testing methodology employed was not provided by study authors.[6, 46, 64] In another study of poor methodological quality, a proxy measure for outcomes (NAAT positivity) was used.[77] The baseline exposure ('any' antibody) testing and subsequent reinfection events (NAAT positivity) in this study were derived from a database analysis and the specific tests used, and the validity of these tests, cannot

be evaluated. The clinical characteristics of seropositive individuals who subsequently tested positive by NAAT, and the course of disease, could not be determined. The reason for NAAT testing (screening or symptomatic testing) is unknown. Additionally, the follow-up was not considered long enough to adequately capture reinfection events (median 1.8 months). Two other studies relied on self-reporting of PCR or antigen test results,[23, 25] and in another study it is unclear how previous SARS-CoV-2 infection at baseline was confirmed.[37] Two studies did not sufficiently describe how the cohort of patients recovering from COVID-19 was selected, and instead focused on the cases of reinfection.[12, 47] One study included both PCR-confirmed and clinically-confirmed (without testing) COVID-19 cases at baseline, which may have introduced selection bias.[36] Another study compared outcomes from cohorts that were included at distinctly different time periods.[50] Finally, one study retrospectively searched for participants with a specific pattern of testing (PCR positive test followed by an IgG positive test followed by another PCR positive test, with a minimum of 42 days between the two PCR tests) in a large database of 4.2 million test results; participants with any other test result patterns were excluded from the analysis.[42] Given that it is unlikely that antibody testing was routinely done in all participants in this database, focusing exclusively on this specific pattern of testing likely introduced selection bias.

The studies deemed of 'fair' methodological quality were downgraded for a number of reasons, the most common reason being a lack of controlling for confounders. In these studies, potential confounding variables were either not assessed or not measured appropriately, or the statistical analysis was not adequately described (Appendix 3). Additionally, as all studies were observational in nature, they cannot be used to demonstrate causality. Therefore, only associations between prior infection and reinfection risk can be measured. While estimates of the effectiveness of natural immunity to prevent reinfection were reported in a number of studies, such measures cannot be reliably estimated on the basis of these data. Observational studies are prone to bias and confounding. For example, individuals who are aware of their infection status may have altered testing behaviour, introducing potential ascertainment bias. Over half of included studies (37/65) were retrospective in nature. In addition, it was unclear if systematic retesting (that is, serial testing) was undertaken in many of the studies, and the lack of such testing may have resulted in an under-ascertainment of asymptomatic reinfection cases.

Fifteen studies are currently published as preprints,[8, 13, 18, 21, 25, 26, 28, 34, 36, 38, 42, 50, 51, 64, 66] so have not yet been formally peer-reviewed, raising additional concerns about overall quality and the potential for results to change prior to formal publication.

Discussion

Summary of findings

This review identified 65 observational studies that assessed the risk and or relative risk of SARS-CoV-2 reinfection over time, comparing individuals with evidence of prior infection (prior SARS-CoV-2 diagnosis or antibody positivity) with those without. Nineteen studies exclusively included healthcare workers,[7, 15-17, 20, 22, 24, 25, 34-36, 41, 46, 48, 50, 54, 55, 65, 70] seven studies included participants based on vaccination and/or prior infection status,[8, 21, 26, 38, 45, 51, 61] three studies included staff and or older residents of care homes,[10, 58, 59] three studies included patients with chronic kidney disease (CKD),[14, 44, 47] one study included both healthcare workers and patients with a high risk of exposure to SARS-CoV-2,[37] one study included a broad range of essential workers,[28] and one study included university students.[32] The remaining 30 studies were all in general populations.[6, 9, 11-13, 18, 19, 23, 27, 29-31, 33, 39, 40, 42, 49, 52, 53, 56, 57, 60, 62-64, 66-69]

Across studies, the total number of PCR- or antibody-positive participants at baseline was 1,484,413 (median: 1,350; range: 88 to 378,606). The longest duration of follow-up was not stated in all studies, or was provided only as an approximate estimate. When not stated, duration of follow-up was inferred from figures or tables within the study. The median follow-up of individuals within studies was 165 days (5.5 months) (range of medians: 54-300 days), with a maximum follow-up of ≥365 days (12 months) in 10 studies,[16, 17, 19-21, 27, 38, 40, 45, 46] which is an increase from a median of 135 days (4.5 months) and a maximum of ≥300 days (10 months) follow-up within the 19 studies included in version 7 of this evidence summary. The study with the longest maximum follow-up duration of over 17 months was conducted by Gazit et al. in Israel.[21]

Reinfection was a rare event: the median PCR- or antigen-confirmed reinfection rate was 0.6% across studies, ranging from 0% (zero reinfections in nine studies)[16, 22, 26, 37, 38, 46, 55, 57, 65] to 5.9% (which was observed among healthcare workers in a study in the US).[34] By comparison, the infection rate in the seronegative or PCR-negative cohorts across studies was much higher and had a much broader range, reflecting the differing populations and community transmision rates across included studies. Where reported, the median PCR- or antigen-confirmed infection rate was 7.6% across studies, ranging from 1.3% (observed among healthcare workers in a study conducted in the US)[65] to 30.1% (observed among care home residents and staff in a study conducted in the UK).[58]

Apart from the crude risk of reinfection, a range of other primary outcome measures were reported, including odds ratios, relative risks and hazard ratios comparing risk of reinfection in individuals with evidence of prior infection with individuals without. A number of studies controlled for confounding and reported figures adjusted for variables such as age, sex, testing frequency and calendar month, while others did not. Due to heterogeneity in outcome measures and populations, meta-analysis of data was not considered appropriate. However despite the inability to pool data, all studies consistently reported low relative rates of reinfection comparing seropositive and seronegative groups, which remained low for the duration of the studies. In addition, all studies that separately reported symptomatic and 'all' reinfection events consistently reported lower relative rates of symptomatic reinfections. For example, in one large sample of UK healthcare workers, the relative risk for 'any reinfection' was 0.159 (95% CI: 0.13 to 0.19), falling to 0.074 (95% CI: 0.06 to 0.10) for reinfections with COVID-19 symptoms.[71]

Risk of reinfection over time

Where the risk of reinfection over time was reported relative to the initial infection, seven studies reported that the risk appeared to be relatively higher, earlier in the recovery period, compared to the end of the study period.[19, 25, 34, 39, 52, 57, 69] These initially higher rates may be suggestive of persistent shedding of viral RNA as opposed to true cases of reinfection in the initial period following the original infection. One study reported no change in the low risk of reinfection over time.[56] One study observed no reinfections for the first seven months post initial infection, and then all eight reinfections were observed in December 2020.[53] Similarly, another study observed a peak of reinfections in January 2021, six months after the first observed reinfection.[66] Importantly the peaks in reinfections observed in these two studies coincided with the second wave of the pandemic in these countries (UK and Israel),[53, 66] highlighting the potential impact of high prevalence on reinfection rates. Another study found some evidence of reduced (but still high) protection from reinfection against the Delta variant, in the context of longer follow-up (maximum 17 months).[21] However, it is uncertain whether this apparent reduction in immune protection was due to waning natural immunity over time, immune evasion properties of the Delta variant, or residual confounding in the study.

A phylogenetic analysis study published by Townsend et al.[78] aimed to estimate the probabilities and corresponding likely times of reinfection associated with the human-infecting coronaviruses SARS-CoV, MERS-CoV, HCoV-229E, HCoV-OC43, HCoV-NL63, and SARS-CoV-2 with a particular focus on SARS-CoV-2. Using a probabilistic framework, the authors estimated that reinfection by SARS-CoV-2 under endemic conditions would likely occur between three and 63 months (5.1 years) after peak antibody response, with a median of 16 months. This protection was

estimated to be less than half the duration for the endemic coronaviruses currently circulating among humans, and so the authors concluded that reinfection with SARS-CoV-2 will become increasingly common as pandemic disease transitions into endemic disease. There is still significant uncertainty regarding the risk of reinfection over time, but as studies with longer follow-up periods are published, the evidence in this regard may become clearer.

Impact of vaccination and new variants

While the objective of this review was to investigate immune responses following natural immunity, a number of studies coincided with vaccine rollout. The comparative effectiveness of natural versus vaccine-mediated immunity (or combinations of both) is of considerable interest and likely to impact policy going forward.

Seven studies were identified that compared the estimated protection from reinfection following natural immunity and COVID-19 vaccination.[8, 21, 26, 38, 45, 51, 61] Studies consistently demonstrated high levels of protection following natural immunity, similar to vaccine-mediated effectiveness. In total, five studies separately reported protective effectiveness in previously infected and vaccinated groups; four of these studies found comparable or greater effectiveness associated with natural immunity;[21, 26, 38, 61] and one study found lower effectiveness associated with natural immunity, specifically in an older population.[51] Two studies directly compared effectiveness in matched cohorts, with conflicting evidence regarding the relative effectiveness of natural- versus vaccine-induced immunity: one of these studies reported that natural immunity offered stronger protection than vaccines against reinfection,[21] whereas the other study reported the opposite.[51] However, these differences may be explained by the older population in the latter study,[51] where vaccination provided significantly stronger protection than previous infection in those aged 65 years and older, with no statistical difference seen between natural and vaccine-induced immunity in those adults aged less than 65 years. Importantly the absolute rate of reinfection and breakthrough infection was low in all of these studies.

Four of the seven studies considered the potential for vaccination to further reduce the risk of infection in those with a history of prior infection, with evidence from three studies suggesting that vaccination may provide additional protection.dxx An included case-control study found that being unvaccinated in those previously infected with SARS-CoV-2 was associated with an increased likelihood of reinfection versus those previously infected and fully vaccinated.[45] Evidence of additional protection was observed with a single dose of the BNT162b2 (Pfizer-BioNTech) vaccine against the Delta variant,[21] and for those fully vaccinated with BNT162b2

(Pfizer-BioNTech) (but not mRNA-1273 (Moderna)) against the Alpha and Beta variants.[8] In contrast another study found that those previously infected did not benefit further from vaccination, though this study involving a relatively smaller sample size, reported no cases of reinfection and so had little to gain from vaccination.[38] Evidence is still quite limited with regard to the relative effectiveness of natural versus vaccine-induced immunity and the benefit of vaccination in previously infected individuals, and thus should be interpreted with caution.

Additionally, recent studies have coincided with widespread transmission of new variants, namely the Alpha, Beta and Delta variants. Seven included studies examined the impact of variants of concern on the risk of reinfection.[13, 16, 21, 23, 51, 54, 61] No evidence was found that the Alpha or Beta variants were associated with an increased risk of reinfection in five of the seven studies.[13, 16, 23, 54, 61] However, there was some evidence of waning natural immunity against the Delta variant observed in one study (patients followed up for a maximum of 17 months).[21] In this study, the estimated increased protection against (re)infection provided by prior infection relative to vaccination, decreased from OR 13.06 (95% CI, 8.08 to 21.11) to OR 5.96 (95% CI, 4.85 to 7.33), when the timing of the initial infection occurred at any time since March 2020 compared to when the timing matched with vaccination (January to February 2021). It is uncertain whether this apparent reduction in immune protection is due to waning natural immunity over time, immune evasion properties of the Delta variant, or residual confounding in the study; however, reinfections were still very low (0.23% reinfection rate).[21] Similarly, an apparent reduction in the protection offered by vaccinations relative to natural immunity against reinfection was observed in a US study during the periods when the Delta variant accounted for almost 100% of cases;, however the difference was not statistically significant and confidence intervals are very wide (versus natural immunity) (HR 2.45 [95% CI, 0.56 to 20.66] and HR 1.89 [95% CI, 0.49 to 7.28] estimated for Moderna and Pfizer-BioNTech, respectively).[51]

In another study by Public Health England, the effectiveness of vaccines against the Delta variant was assessed.[79] This was a test-negative case control design that estimated the effectiveness of vaccination against symptomatic disease over the period that the Delta variant began circulating, with cases identified based on sequencing and S-gene target status. After two doses of either BNT162b2 or ChAdOx1 COVID-19 vaccine, the authors reported only modest differences in vaccine effectiveness for each of the two vaccines against the Delta variant compared with the dominant Alpha variant. Overall 2-dose vaccine effectiveness was lower for ChAdOx1 than with BNT162b2 (74.5% vs. 93.7% and 67% vs 88% for Alpha and Delta, respectively). Pooled estimates highlight that effectiveness was notably lower after one dose of either vaccine for the Delta variant (30.7%; 95% CI: 25.2 to

35.7%) compared with the Alpha variant (48.7%; 95% CI: 45.5 to 51.7%), with similar results for both vaccines.

Sequencing-confirmed reinfection rates

Confirmation of reinfection by whole genome sequencing was conducted in five included studies.[33, 52, 58, 61, 63] In four of these studies, whole genome sequencing was conducted for paired viral specimens to confirm reinfection, in cases where reinfection was suspected, for example two positive PCR tests greater than 50 days apart.[33] In the fifth study, whole genome sequencing was performed on all PCR-positive samples from 1 December 2020 onwards (the study commenced on 27 March 2020).[61] The rate of confirmed reinfection was low in each of these studies ranging from 0.02%[33] to 1.1%.[58] Confirming reinfection requires detecting the virus at two different time points and using viral genomic data to distinguish reinfection from persistent viral carriage. This process is resource intensive and is hindered by challenges of logistics and capacity, such as storing samples from primary infection and performing viral genome sequencing which can take up to two weeks and requires specialist staff and equipment.[80] These challenges may explain why whole genome sequencing was not performed in the large majority of included studies.

Reinfection risk by age group

Nine studies examined the rates of reinfections across age groups; six studies reported the relative risk of reinfection by age category,[21, 27, 30, 39, 51, 56] while three studies reported descriptive differences,[19, 42, 66] allowing comparisons across groups.

Hansen et al. reported that in individuals aged 65 years or more, the aRR was 0.53 (0.37–0.75), compared with 0.17, 0.20 and 0.19 in individuals aged 0-34 years, 35-49 years and 50-64 years, respectively.[56] While this study reported low rates in the 0-34 years age group, it is notable that disaggregated data specific to the paediatric population (<18 years) were not reported. Two included UK studies that included older residents of care homes reported lower relative risks of reinfection than that reported by Hansen at al. One reported a much lower risk RR 0.038 (95% CI: 0.005 to 0.273),[58] and the only recorded reinfection occurred in a staff member and not an older resident of the care home. The other study reported an adjusted hazard ratio of 0.15 (95% CI: 0.05 to 0.44) in residents.[59]

A large Israeli study by Gazit et al. found that individuals aged 60 years and above had a two-fold increase in the likelihood of reinfection (or breakthrough infection) relative to those aged under 40 years, which was statistically significant across the three constructed models (Model 1; OR, 2.7, 95% CI, 1.68 to 4.34. Model 2; OR,

2.89, 95% CI, 1.68 to 4.99. Model 3; OR, 2.2, 95% CI 1.66 to 2.92).[21] No statistically significant association was found between those aged 40-59 and the risk of reinfection/breakthrough infection. Slezak et al. reported that across all age groups 18 years and above, adults were significantly more likely to be reinfected than children (age 18-39: HR 2.71, 95% CI: 1.38 to 5.31, age 40-59: HR 2.22, 95% CI: 1.12 to 4.41, age ≥60: HR 2.52, 95% CI: 1.23 to 5.17, versus <18 years).[39] The lower protection in the over-65s group may be attributable to immunosenescence; however, little is known about this phenomenon in the context of COVID-19.

However, two included studies reported conflicting findings. Lawandi et al. found no significant difference in the cumulative risk of reinfection between individuals aged less than 65 versus those aged 65 years or older, although a nonsignificant trend of increased risk with older age was observed on longer follow-up.[27] Importantly this study did not include children under the age of 18. Murillo-Zamora et al. reported that increasing age was associated with a reduced risk of reinfection ($RR_{per\ year}$ = 0.99997, 95% CI 0.99814–0.99958), though this study was limited to symptomatic reinfections only, and only included individuals aged 20 years or older.

Separately, Young-Xu et al. compared the protection offered by natural immunity versus vaccine-induced immunity in a large population of US Veterans (n=47,102; mean age 63).[51] The authors found that among those aged 65 years or older, Moderna and Pfizer mRNA vaccines offered stronger protection against infection than previous infection, lowering the risk by an additional 66% [HR: 0.34 (95% CI, 0.14 to 0.78)] and 68% [HR: 0.32 (95% CI, 0.14 to 0.70). However, among adults aged less than 65 years, the protection offered by vaccines were found to be statistically equivalent to that provided by previous infection.

Four studies reported data specific to the paediatric group.[19, 39, 42, 66] Two studies reported no cases of reinfection in children aged under 18 years,[19] or under 15 years.[42] In the study by Slezak et al. reinfection rates were lower in children (<18 years) than adults (≥18 years) (n=9, 0.2%, 95% CI 0.1 to 95% CI 0.7 to 1.0%, p=0.023). As outlined above, across all age groups 18 years and above, adults were significantly more likely to be reinfected than children.[39] Somewhat conflicting findings were reported study by Perez et al., with a higher raw count of reinfections in individuals aged 10 to 19 years than in other age categories; however a risk or relative risk was not reported and there were substantial limitations associated with this preliminary study.[66] Across all four of these studies involving paediatric populations, it is unclear whether systematic retesting was done in asymptomatic individuals, and because children are less likely to experience symptomatic COVID-19,[81] reinfections may have been under-ascertained in this population. Additional

research involving serial testing of children post-recovery from COVID-19 may be required to determine the true risk of reinfection in this population.

Reinfection risk in comorbid or immunocompromised populations

Six included studies assessed the risk of reinfection in comorbid or immunocompromised populations.[14, 21, 30, 39, 44, 47]

Two studies reported an increased risk of reinfection in those with immunocompromising conditions compared to those without.[30, 39] Two studies, both in patients with chronic kidney disease, reported a lower risk of reinfection (in those with a history or prior infection or antibodies to SARS-CoV-2) compared to those with no history of infection, but that this protection may be lower than that observed in a general population.[14, 44] In another study the authors found that in a population of kidney transplant recipients previously infected with SARS-COV-2, reinfection was associated with high levels of mortality (46%).[47]

Conversely, the study by Gazit et al.[21] which aimed to compare natural immunity to vaccine-induced immunity through three different models, found no significant association between any included comorbidity or an immunocompromising condition covariate (obesity (BMI ≥30), cardiovascular diseases, hypertension, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, immunocompromised conditions and cancer) and risk of reinfection/breakthrough infection. The lack of statistical significance may be explained by the enrolment of a general population that was less sick on average.

Given the significant risk of severe COVID-19 outcomes to certain immunocompromised populations,[82] further evidence regarding the duration of immunity following SARS-CoV-2 infection in these populations is necessary to inform vaccination booster/third dose policy.

Reinfection risk by serological antibody levels

One study directly assessed the relationship between serological antibody levels and reinfection risk. In this study, conducted among UK dental practitioners, the risk of infection was 9.7% in participants who were seronegative at baseline, compared to 2.9% in individuals who were seropositive (p=0.001). However, there were no PCR-proven infections among 64 individuals with a baseline anti-SARS-CoV-2 IgG level greater than 147.6 IU/ml (with respect to the WHO international standard NIBSC 20/136). Further research is needed on this subject, and while serological levels that

are protective against PCR-confirmed infection may be found, the serological response that prevents transmission is unknown.

Limitations

In this review, all studies were considered large enough to adequately capture reinfection events in their respective populations. Results across all 65 studies consistently demonstrated a substantially lower risk of reinfection in previously infected individuals without a waning of the protective response within the time frame of existing studies, except in one study which found some possible evidence of waning immunity against the Delta variant.[21] However, despite these strengths, there are a number of limitations associated with this review.

As the studies are observational in nature, the prevention of reinfection cannot be causally confirmed, although longitudinal associations can be estimated. Additional concerns relating to observational studies include the greater potential for bias. Outcome ascertainment bias may have been an issue in a number of studies, as antibody test results, or knowledge of prior PCR-positive infection, may have affected individual behaviour. For instance, individuals with evidence of prior infection may have believed that they possessed immunity to SARS-CoV-2, resulting in a reduction in health-seeking behaviour and testing, particularly if they were asymptomatic. Conversely, these individuals may have increased their engagement in social behaviour, placing them at greater risk for infection. The overall direction of bias (whether over- or under-estimating reinfection) cannot be determined. In addition, studies with low participant uptake rates or high attrition may have introduced selection bias. Furthermore, systematic retesting of individuals was not routinely done in all studies, which may have led to under-ascertainment of asymptomatic reinfection cases in certain studies.

Another challenge with regards to the interpretation of these observational studies is the changes in underlying prevalence of SARS-CoV-2 during successive waves of the pandemic, as this likely impacted on rates of reinfection. Similarly, changes to health policies (for example, public health measures and guidance) during the study period further complicates the interpretation of findings. Importantly, the findings from these observational studies which were largely conducted in the context of stringent public health measures and less transmissible variants, may have limited generalisability to the current context of easing public health measures and a more transmissible Delta variant.

Immortal time bias is another important limitation of many of the included studies, particularly those comparing vaccine- and natural-mediated immunity. 'Immortal time' occurs when participants of a cohort study cannot experience the outcome during some of the follow-up period. When immortal time is misclassified or

excluded during analysis, immortal time bias can lead to a biased association.[83] Among included studies, this may occur as participants need to survive a certain amount of time post-exposure (that is, infection) in order to be at risk of reinfection. Other forms of immortal time bias arise when individuals are assigned to the unexposed group until the end of the study period based on their unvaccinated status at a certain timepoint, but the study does not use time-dependant analyses to reclassify these individuals into the exposed group should they later become vaccinated.[21]

Included studies could not determine whether past seroconversion, or current antibody levels, determine protection from infection, although one study did consider the IgG level at which no reinfections occurred.[70] Furthermore, none could define which characteristics are associated with reinfection. The role of T-cell immunity was not assessed in any study, therefore it is not possible to determine whether protection from reinfection is conferred through the measured antibodies or T-cell immunity.

Only five studies undertook genomic sequencing of reinfected cases.[33, 52, 58, 61, 63] Generally, the effect of not undertaking genomic sequencing, is likely to overestimate the number of reinfections, thereby affirming the conclusion that reinfection is rare. However, as whole genome sequencing was not systematically performed all on PCR positive tests irrespective of the time between tests, it is also possible that some true reinfections may have been missed, as these studies applied a minimum time period between PCR positive tests, or between positive antibody and PCR tests, before undertaking confirmatory sequencing. However, given the speed at which more transmissible variants, such as the Delta variant, can become dominant at a population level, the systematic conduct of whole genome sequencing may not necessarily be required to identify reinfections, as reinfections may be inferred based on intervals between infections using routinely collected surveillance data.

Due to the nature of a number of retrospective database analyses included in this review, many studies could not correlate symptomatic infections with protection against repeat infection or evaluate disease progression comparing first and second infections.

Definitions of reinfection varied among included studies and this limits direct comparisons. Where reported, the most commonly used definition for reinfection (in 24 out of 65 studies), was the requirement for a minimum of 90 days between PCR-positive tests, which is broadly in line with US CDC guidelines.[5] There is currently no universally agreed definition for SARS-CoV-2 reinfection. Of note, a survey of reinfection case definitions used by 13 European Union/European Economic Area (EU/EEA) countries, which was conducted by the European Centre for Disease

Prevention and Control (ECDC) in February 2021, found significant variation in practice across countries, with the minimum interval between episodes ranging from 45 to 90 days.[84] A number of studies employed definitions of reinfection that may have identified a significant number of cases of prolonged shedding of dead viral remnants following the primary infection rather than true reinfection cases. For example, one study used a proxy measure for reinfection (NAAT positivity).[77] Additionally, a number of other studies used time intervals between infection events that are unlikely to rule out persistent shedding, the shortest interval being 28 days in two studies.[13, 30] Studies that required additional supporting evidence, such as additional epidemiological or laboratory evidence (Ct values, serological status) were more likely to rule out persistent shedding. Only studies that employed whole genome sequencing could provide confirmation of true reinfection events, however, as noted, this was only undertaken in five studies.

Five studies determined reinfection cases by either RT-PCR or rapid antigen test, despite antigen testing not being considered the optimal testing methodology for diagnosing SARS-CoV-2 infection. In the study by Manica et al., authors report a sensitivity of >90% and specificity >97% for their rapid antigen test. The results of this study, however, were consistent with other studies that exclusively used RT-PCR to diagnose reinfections (aOR of 0.05 [95% CI, 0.01 to 0.17] comparing seropositive and seronegative groups). Similarly low reinfection rates were reported in the studies by Leidi et al.[28] and Graham et al.[23] However, the reported reinfection rate was higher (4.5%) in the study by Kohler et al. which may be explained by the use of rapid antigen tests contributing some false positive results due to its low positive predictive value in low prevalence settings.[72] Another two studies also used antigen testing in a proportion of cases,[10, 71] however these were subsequently confirmed with RT-PCR. No information is provided in the study by Cavanaugh et al. regarding the use of confirmatory tests for antigen positive cases.[45]

A final limitation is that only 12 of the 65 included studies were considered of 'good' methodological quality,[18, 20, 40, 54, 56, 59-63, 70, 76] and 15 studies are currently published as preprints.[8, 13, 18, 21, 25, 26, 28, 34, 36, 38, 42, 50, 51, 64, 66]

Research in context

Unpublished data gathered by the Health Protection Surveillance Centre (HPSC) in Ireland support the findings of this review. The HPSC provided preliminary data relating to suspected reinfection cases during the period 2 March 2020 to 23 March 2021. Of 232,738 confirmed cases of COVID-19 notified during this time, 514 were potentially reinfections, giving a reinfection rate of approximately 0.2%. This is based on the criteria of ≥84 days interval between notification or specimen dates of

PCR positives. This rate falls within the range of absolute reinfection rates identified in the present review.

The European Centre for Disease Prevention and Control (ECDC) published a rapid risk assessment on 30 September 2021 relating to circulating SARS-CoV-2, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA.[85] This rapid risk assessment estimated the risk posed by the circulation of the Delta variant of SARS-CoV-2 until the end of November 2021, based on modelling scenarios and projected levels of vaccine coverage. The ECDC concluded that the risk of reinfection with the Delta variant remains low, though there is evidence of increased risk relative to the previously circulating Alpha variant. For their modelling, the ECDC considered an optimistic set of assumptions: natural immunity protects 100% against reinfection, there is cross-protection across variants, and there is no waning of natural immunity within one year. The data underpinning these assumptions appear to be derived from a previous version of the reinfection HIQA evidence summary,[86] in conjunction with another study included in the current update.[40] The ECDC acknowledged that these are optimistic assumptions and that there are still many unknowns regarding natural immunity.

Conclusion

The evidence suggests that the risk of SARS-CoV-2 reinfection, and the relative risk compared with individuals without prior evidence of SARS-CoV-2 infection, is low for over 12 months post-infection. While evidence supports the hypothesis that natural immunity and vaccination result in equally robust immune responses, including against new variants of concern, the data are limited. However, there is also some evidence that the duration and or extent of protective immunity following infection may be lower in older adults, in patients with CKD and those with immunocompromising conditions. Importantly, the findings from these observational studies which were largely conducted in the context of stringent public health measures and less transmissible variants, may have limited generalisability to the current context of easing public health measures and a more transmissible Delta variant.

There is still uncertainty on a range of issues, including the:

- durability of protective immunity over time
- protective immunity in paediatric populations
- potential for additional protection from vaccination in those with a history of prior infection
- duration and extent of protective immunity in populations with comorbidities and immunocompromised individuals
- impact of new variants on protective immunity.

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Appendices

Appendix 1: Excluded studies with reasons

Table A1: Excluded studies from previous version of evidence summary (version 7.1)

Study	Title	DOI	Exclusion reason
Abu-Raddad 2020	Two prolonged viremic SARS-CoV-2 infections with conserved viral genome for two months	10.1016/j.meegid.2020.104684	Exclusion reason: Wrong outcomes
Abu-Raddad 2020	Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting	10.1093/cid/ciaa1846	Exclusion reason: Duplicate
Abu-Raddad 2021	Two prolonged viremic SARS-CoV-2 infections with conserved viral genome for two months	10.1016/j.meegid.2020.104684	Exclusion reason: Wrong outcomes
Abu-Raddad 2021	SARS-CoV-2 reinfection in a cohort of 43,000 antibody-positive individuals followed for up to 35 weeks	10.1101/2021.01.15.21249731	Exclusion reason: Duplicate
Abu-Raddad 2021	SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy	10.1016/j.eclinm.2021.100861	Exclusion reason: Already included in prior review
Alhusseini 2021	Persistence of SARS-CoV-2: a new paradigm of COVID-19 management	10.7416/ai.2021.2414	Exclusion reason: Wrong study design
Alturaif 2020	Recurrence of Positive SARS-CoV-2 RNA in a COVID-19 Patient: Two Case Reports from Saudi Arabia	10.21203/rs.3.rs-86920/v1	Exclusion reason: Wrong study design
Alvarez-Moreno 2020	Testing Dilemmas: Post negative, positive SARS-CoV-2 RT-PCR is it a reinfection?	10.1016/j.tmaid.2020.101743	Exclusion reason: Wrong study design
Aran 2020	Prior presumed coronavirus infection reduces COVID-19 risk: A cohort study	10.1016/j.jinf.2020.10.023	Exclusion reason: Wrong outcomes
Ariza 2021	Seroprevalence and seroconversion rates to SARS-CoV-2 in interns, residents, and medical doctors in a University Hospital in Bogota, Colombia	10.22354/IN.V25I3.938	Exclusion reason: <100 patients
Asakura 2021	One Possible Reinfection with SARS-CoV-2 Validated by 205-days Interval of Re-detection in Sapporo City, Japan	10.20944/preprints202104.0439.v1	Exclusion reason: Cohort <100 people
Babiker 2021	The Importance and Challenges of Identifying SARS-CoV-2 Reinfections	10.1128/jcm.02769-20	Exclusion reason: Wrong study design
Bichara 2021	Dynamics of anti-SARS-CoV-2 IgG Antibodies Post-COVID-19 in a Brazilian Amazon Population	10.21203/rs.3.rs-228739/v1	Exclusion reason: Wrong outcomes
Bilich 2021	T cell and antibody kinetics delineate SARS-CoV-2 peptides mediating long-term immune responses in COVID-19 convalescent individuals	10.1126/scitranslmed.abf7517	Exclusion reason: Wrong outcomes

Binnendijk 2021	Serological Evidence for Reinfection with SARS-CoV-2; An Observational Cohort Study	10.2139/ssrn.3800076	Exclusion reason: <100 patients
Binnendijk 2021	Serological Evidence for Reinfection with SARS-CoV-2; An Observational Cohort Study	10.2139/ssrn.3800076	Exclusion reason: Cohort <100 people
Boonyaratanakornkit 2020	Clinical, laboratory, and temporal predictors of neutralizing antibodies to SARS-CoV-2 after COVID-19	10.1101/2020.10.06.20207472	Exclusion reason: Wrong outcomes
Borena 2021	Follow-up study in the ski-resort Ischgl: Antibody and T cell responses to SARS-CoV-2 persisted for up to 8 months after infection and transmission of virus was low even during the second infection wave in Austria	10.1101/2021.02.19.21252089	Exclusion reason: Wrong study design
Brehm 2020	Seroprevalence of SARS-CoV-2 antibodies among hospital workers in a German tertiary care center: A sequential follow-up study	10.1016/j.ijheh.2020.113671	Exclusion reason: Wrong outcomes
Bruni 2020	Persistence of anti-SARS-CoV-2 antibodies in non-hospitalized COVID-19 convalescent healthcare workers	10.3390/jcm9103188	Exclusion reason: Wrong outcomes
Carta 2021	Prospective serological evaluation of anti SARS-CoV-2 IgG and anti S1-RBD antibodies in a community outbreak	10.1515/cclm-2021-0127	Exclusion reason: Wrong outcomes
Cassaniti 2021	Seroprevalence of SARS-CoV-2 in 1922 blood donors from the Lodi Red Zone and adjacent Lodi metropolitan and suburban area	10.1016/j.cmi.2021.01.030	Exclusion reason: Wrong outcomes
Cerutti 2020	Clinical immunity in discharged medical patients with COVID-19	Italian Journal of Medicine 2020;14(SUPPL 2):109 2020; no DOI	Exclusion reason: Follow up < 3 months (individual cases)
Cervia 2020	Systemic and mucosal antibody responses specific to SARS-CoV-2 during mild versus severe COVID-19	10.1016/j.jaci.2020.10.040	Exclusion reason: Wrong outcomes
Chen 2020	Clinical course and risk factors for recurrence of positive SARS-CoV-2 RNA: a retrospective cohort study from Wuhan, China	10.18632/aging.103795	Exclusion reason: Follow up < 3 months (individual cases)
Choi 2020	Low Seroprevalence of SARS-CoV-2 Antibodies during Systematic Antibody Screening and Serum Responses in Patients after COVID-19 in a German Transplant Center	10.3390/jcm9113401	Exclusion reason: Wrong outcomes
Choudhary 2021	SARS-CoV-2 Sequence Characteristics of COVID-19 Persistence and Reinfection	10.1101/2021.03.02.21252750	Exclusion reason: Wrong study design
Corr 2020	Seroprevalence of SARS-CoV-2 antibodies in children of United Kingdom healthcare workers: A prospective multicentre cohort study protocol	10.1136/bmjopen-2020-041661	Exclusion reason: Study protocol only;

Coutinho 2021	Model-based estimation of transmissibility and reinfection of SARS-CoV-2 P.1 variant	10.1101/2021.03.03.21252706	Exclusion reason: Wrong study design
Dan 2021	Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection	10.1126/science.abf4063	Exclusion reason: Wrong outcomes
Dao 2021	Recurrence of SARS-CoV-2 viral RNA in recovered COVID-19 patients: a narrative review	10.1007/s10096-020-04088-z	Exclusion reason: Wrong study design
Deisenhammer 2021	6-month SARS-CoV-2 antibody persistency in a Tyrolian COVID-19 cohort	10.1007/s00508-020-01795-7	Exclusion reason: Wrong outcomes
Deng 2021	Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation	10.1101/2021.03.07.21252647	Exclusion reason: Wrong outcomes
denHartog 2021	Persistence of antibodies to SARS-CoV-2 in relation to symptoms in a nationwide prospective study	10.1093/cid/ciab172	Exclusion reason: Wrong outcomes
Dillner 2021	Antibodies to SARS-CoV-2 and risk of past or future sick leave	10.1038/s41598-021-84356-w	Exclusion reason: Wrong study design
Dillner 2021	High amounts of SARS-CoV-2 precede sickness among asymptomatic healthcare workers	10.1093/infdis/jiab099	Exclusion reason: Wrong outcomes
Fels 2021	Genomic surveillance of SARS-CoV-2 in the Bronx enables clinical and epidemiological inference	10.1101/2021.02.08.21250641	Exclusion reason: Wrong study design
FillMalfertheiner 2020	Immune response to SARS-CoV-2 in healthcare workers following a COVID-19 outbreak: A prospective longitudinal study	10.1016/j.jcv.2020.104575	Exclusion reason: Wrong outcomes
Flieder 2021	Retrospective analysis of 426 donors of a convalescent collective after mild COVID-19	10.1371/journal.pone.0247665	Exclusion reason: Wrong outcomes
Forbes 2021	Persistence of antibody response to SARS-CoV-2 in a cohort of haemodialysis patients with COVID-19	10.1093/ndt/gfab066	Exclusion reason: Wrong outcomes
Galanis 2020	Seroprevalence of SARS-CoV-2 antibodies and associated factors in healthcare workers: a systematic review and meta-analysis	10.1101/2020.10.23.20218289	Exclusion reason: Wrong outcomes
Galiana 2021	Late Reinfection With a Different SARS-CoV-2Â Clade in a Patient With Refractory Arterial Hypertension: a Case Report	10.21203/rs.3.rs-392287/v1	Exclusion reason: Cohort <100 people
Gallichotte 2020	Longitudinal Surveillance for SARS-CoV-2 Among Staff in Six Colorado Long Term Care Facilities: Epidemiologic, Virologic and Sequence Analysis	10.2139/ssrn.3724248	Exclusion reason: Wrong outcomes
Ganz-Lord 2020	Title: Covid-19 symptoms, duration, and prevalence among healthcare workers in the New York metropolitan area	10.1017/ice.2020.1334	Exclusion reason: Wrong outcomes
Girardin 2021	Temporal Analysis of Serial Donations Reveals Decrease in Neutralizing Capacity and Justifies Revised	10.1093/infdis/jiaa803	Exclusion reason: Wrong outcomes

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Hall 2021	Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020	10.1101/2021.01.13.21249642	Exclusion reason: Duplicate
Hanrath 2020	Prior SARS-CoV-2 infection is associated with protection against symptomatic reinfection	10.1016/j.jinf.2020.12.023	Exclusion reason: Duplicate
Hanrath 2021	Prior SARS-CoV-2 infection is associated with protection against symptomatic reinfection	10.1016/j.jinf.2020.12.023	Exclusion reason: Already included in prior review
Hansen 2021	Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study	10.1016/s0140-6736(21)00575-4	Exclusion reason: Already included in prior review
Harvey 2020	Real-world data suggest antibody positivity to SARS-CoV-2 is associated with a decreased risk of future infection	10.1101/2020.12.18.20248336	Exclusion reason: Duplicate
Haymond 2021	Viral Neutralization is Durable in Asymptomatic COVID-19 for at least 60 Days	10.1093/infdis/jiab140	Exclusion reason: Wrong outcomes
He 2021	The unexpected dynamics of COVID-19 in Manaus, Brazil: Herd immunity versus interventions	10.1101/2021.02.18.21251809	Exclusion reason: Wrong study design
Higgins 2021	Longitudinal SARS-CoV-2 antibody study using the Easy Check COVID-19 IgM/IgG lateral flow assay	10.1371/journal.pone.0247797	Exclusion reason: Wrong outcomes
Hollinghurst 2021	COVID-19 Infection Risk amongst 14,104 Vaccinated Care Home Residents: A national observational longitudinal cohort study in Wales, United Kingdom, December 2020 to March 2021	10.1101/2021.03.19.21253940	Exclusion reason: Wrong study design
Jin 2020	Correlation between viral RNA shedding and serum antibodies in individuals with coronavirus disease 2019	10.1016/j.cmi.2020.05.022	Exclusion reason: Wrong outcomes
Kang 2021	Longitudinal Analysis of Human Memory T-Cell Response according to the Severity of Illness up to 8 Months after SARS-CoV-2 Infection	10.1093/infdis/jiab159	Exclusion reason: Wrong outcomes
Karbiener 2021	Longitudinal analysis of SARS-CoV-2 antibodies in 8000 U.S. first-time convalescent plasma donations	10.1111/trf.16291	Exclusion reason: Wrong outcomes
Klein 2021	Case Study: Longitudinal immune profiling of a SARS-CoV-2 reinfection in a solid organ transplant recipient	10.1101/2021.03.24.21253992	Exclusion reason: Wrong study design
Lai 2020	Population-based seroprevalence surveys of anti-SARS-CoV-2 antibody: An up-to-date review	10.1016/j.ijid.2020.10.011	Exclusion reason: Wrong study design

Lampasona 2020	Antibody response to multiple antigens of SARS-CoV-2 in patients with diabetes: an observational cohort study	10.1007/s00125-020-05284-4	Exclusion reason: Wrong outcomes
Laursen 2021	Prevalence of SARS-CoV-2 igg/igm antibodies among danish and swedish falck emergency and non-emergency healthcare workers	10.3390/ijerph18030923	Exclusion reason: Wrong outcomes
Letizia 2021	SARS-CoV-2 Seropositivity and Subsequent Infection Risk in Healthy Young Adults: A Prospective Cohort Study	10.2139/ssrn.3779907	Exclusion reason: Follow-up <3 months
Li 2020	Molecular and serological characterization of SARS-CoV-2 infection among COVID-19 patients	10.1016/j.virol.2020.09.008	Exclusion reason: Wrong outcomes
Ling 2020	Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients	10.1097/cm9.0000000000000774	Exclusion reason: Wrong outcomes
Liu 2021	Clinical characteristics and follow-up analysis of 324 discharged covid-19 patients in shenzhen during the recovery period	10.7150/ijms.50873	Exclusion reason: Follow up < 3 months (individual cases)
Lumley 2020	Antibody Status and Incidence of SARS-CoV-2 Infection in Healthcare Workers	10.1056/NEJMoa2034545	Exclusion reason: Duplicate
Lumley 2020	Antibodies to SARS-CoV-2 are associated with protection against reinfection	10.1101/2020.11.18.20234369	Exclusion reason: Duplicate
Luo 2020	Clinical Characteristics, Risk Factor and Transmission of the COVID-19 Discharged Cases with Positive Retest in Guangzhou, China: A Retrospective Cohort Study	10.2139/ssrn.3732143	Exclusion reason: Follow up < 3 months (individual cases)
Mack 2021	Prevalence of SARS-CoV-2 IgG antibodies in a large prospective cohort study of elite football players in Germany (May-June 2020): implications for a testing protocol in asymptomatic individuals and estimation of the rate of undetected cases	10.1016/j.cmi.2020.11.033	Exclusion reason: Wrong outcomes
Mattiuzzi 2020	Sars-cov-2 recurrent rna positivity after recovering from coronavirus disease 2019 (COVID-19): A meta-analysis	10.23750/abm.v91i3.10303	Exclusion reason: Wrong study design
Muecksch 2021	Longitudinal Serological Analysis and Neutralizing Antibody Levels in Coronavirus Disease 2019 Convalescent Patients	10.1093/infdis/jiaa659	Exclusion reason: Wrong outcomes
Mumoli 2020	Clinical immunity in discharged medical patients with COVID-19	10.1016/j.ijid.2020.07.065	Exclusion reason: Follow up < 3 months (individual cases)
Murillo-Zamora 2020	Predictors of severe symptomatic laboratory-confirmed SARS-COV-2 reinfection	10.1101/2020.10.14.20212720	Exclusion reason: Follow up < 3 months (individual cases)

Nag 2020	A Prospective Study on Rapidly Declining SARS-CoV-2 IgG Antibodies Within One to Three Months of Testing IgG Positive: Can It Lead to Potential Reinfections?	10.7759/cureus.11845	Exclusion reason: Follow up < 3 months (individual cases)
Nielsen 2020	SARS-CoV-2 elicits robust adaptive immune responses regardless of disease severity	10.1101/2020.10.08.331645	Exclusion reason: Wrong outcomes
Noh 2021	Longitudinal assessment of anti-SARS-CoV-2 immune responses for six months based on the clinical severity of COVID-19	10.1093/infdis/jiab124	Exclusion reason: Wrong study design
Ortega 2021	Seven-month kinetics of SARS-CoV-2 antibodies and protective role of pre-existing antibodies to seasonal human coronaviruses on COVID-19	10.1101/2021.02.22.21252150	Exclusion reason: Wrong study design
Osman 2020	Re-positive coronavirus disease 2019 PCR test: could it be a reinfection?	10.1016/j.nmni.2020.100748	Exclusion reason: Wrong study design
Patwardhan 2020	Sustained Positivity and Reinfection With SARS-CoV-2 in Children: Does Quarantine/Isolation Period Need Reconsideration in a Pediatric Population?	10.7759/cureus.12012	Exclusion reason: Follow up < 3 months (individual cases)
Peluso 2021	Long-Term SARS-CoV-2-Specific Immune and Inflammatory Responses Across a Clinically Diverse Cohort of Individuals Recovering from COVID-19	10.1101/2021.02.26.21252308	Exclusion reason: Wrong outcomes
Peluso 2021	SARS-CoV-2 antibody magnitude and detectability are driven by disease severity, timing, and assay	10.1101/2021.03.03.21251639	Exclusion reason: Wrong outcomes
Perez 2021	A 1 to 1000 SARS-CoV-2 reinfection proportion in members of a large healthcare provider in Israel: a preliminary report	10.1101/2021.03.06.21253051	Exclusion reason: Already included in prior review
Pilz 2021	SARS-CoV-2 re-infection risk in Austria	10.1111/eci.13520	Exclusion reason: Already included in prior review
Piri 2021	A systematic review on the recurrence of SARS-CoV-2 virus: frequency, risk factors, and possible explanations	10.1080/23744235.2020.1871066	Exclusion reason: Wrong study design
Piri 2021	A systematic review on the recurrence of SARS-CoV-2 virus: frequency, risk factors, and possible explanations	10.1080/23744235.2020.1871066	Exclusion reason: Wrong study design
Pradenas 2021	Stable neutralizing antibody levels 6 months after mild and severe COVID-19 episodes	10.1016/j.medj.2021.01.005	Exclusion reason: Wrong outcomes
Qin 2021	The seroprevalence and kinetics of IgM and IgG in the progression of COVID-19	10.1186/s12865-021-00404-0	Exclusion reason: Wrong outcomes
Ravichandran 2021	Longitudinal antibody repertoire in "mild" versus "severe" COVID-19 patients reveals immune markers associated with disease severity and resolution	10.1126/sciadv.abf2467	Exclusion reason: Wrong outcomes

Sadr 2021	SARS-CoV-2 Reinfection within the first 3 months of COVID-19 Recovery in A Referral Hospital, Tehran, Iran	10.21203/rs.3.rs-271345/v1	Exclusion reason: Follow up < 3 months (individual cases)
Sakharkar 2021	Prolonged evolution of the human B cell response to SARS-CoV-2 infection	10.1126/sciimmunol.abg6916	Exclusion reason: Wrong outcomes
Salehi 2021	COVID-19 Re-infection or Relapse? A Retrospective Multi Center Cohort Study From Iran	10.21203/rs.3.rs-262191/v1	Exclusion reason: Wrong study design
Salvato 2021	Epidemiological investigation reveals local transmission of SARS-CoV-2 lineage P.1 in Southern Brazil	10.21203/rs.3.rs-280297/v1	Exclusion reason: Wrong outcomes
Sandberg 2021	Longitudinal characterization of humoral and cellular immunity in hospitalized COVID-19 patients reveal immune persistence up to 9 months after infection	10.1101/2021.03.17.435581	Exclusion reason: Wrong study design
Sarapultseva 2021	SARS-CoV-2 Seropositivity among Dental Staff and the Role of Aspirating Systems	10.1177/2380084421993099	Exclusion reason: Wrong outcomes
Self 2020	Decline in SARS-CoV-2 Antibodies After Mild Infection Among Frontline Healthcare Personnel in a Multistate Hospital Network - 12 States, April-August 2020	10.15585/mmwr.mm6947a2	Exclusion reason: Wrong outcomes
Shah 2020	Immunity status of Healthcare Workers post recovery from COVID-19: An online longitudinal panel survey	10.1101/2020.11.27.20239426	Exclusion reason: Wrong outcomes
Sheehan 2021	Reinfection Rates among Patients who Previously Tested Positive for COVID-19: a Retrospective Cohort Study	10.1101/2021.02.14.21251715	Exclusion reason: Already included in prior review
Silva 2021	Early detection of SARS-CoV-2 P.1 variant in Southern Brazil and reinfection of the same patient by P.2	10.21203/rs.3.rs-435535/v2	Exclusion reason: Cohort <100 people
Sokal 2021	Maturation and persistence of the anti-SARS-CoV-2 memory B cell response	10.1016/j.cell.2021.01.050	Exclusion reason: Wrong outcomes
Song 2021	Dynamics of viral load and anti-SARS-CoV-2 antibodies in patients with positive RT-PCR results after recovery from COVID-19	10.3904/kjim.2020.325	Exclusion reason: <100 patients
Talbot 2021	Prevalence of IgM and IgG antibodies to SARS-CoV-2 in healthcare workers at a tertiary care New York hospital during the Spring COVID-19 surge	10.1186/s13741-021-00177-5	Exclusion reason: Wrong outcomes
Trieu 2021	SARS-CoV-2-Specific Neutralizing Antibody Responses in Norwegian Healthcare Workers After the First Wave of COVID-19 Pandemic: A Prospective Cohort Study	10.1093/infdis/jiaa737	Exclusion reason: Wrong outcomes
Tuells 2021	Seroprevalence Study and Cross-Sectional Survey on COVID-19 for a Plan to Reopen the University of Alicante (Spain)	10.3390/ijerph18041908	Exclusion reason: Wrong study design

VanElslande 2021	Longitudinal follow-up of IgG anti-nucleocapsid antibodies in SARS-CoV-2 infected patients up to eight months after infection	10.1016/j.jcv.2021.104765	Exclusion reason: Wrong outcomes
Vibholm 2021	SARS-CoV-2 persistence is associated with antigen-specific CD8 T-cell responses	10.1016/j.ebiom.2021.103230	Exclusion reason: Wrong outcomes
Wang 2020	Ct suggests discharged covid-19 patients who were retested rt-pcr positive again for sars-cov-2 more likely had false negative rt-pcr tests before discharging	10.21037/QIMS-2020-19	Exclusion reason: Wrong study design
Wallace 2020	SIREN protocol: Impact of detectable anti-SARS-CoV-2 on the subsequent incidence of COVID-19 in 100,000 healthcare workers: do antibody positive healthcare workers have less reinfection than antibody negative healthcare workers?	10.1101/2020.12.15.20247981	Exclusion reason: Study protocol only
Wang 2021	COVID-19 reinfection: A Rapid Systematic Review of Case Reports and Case Series	10.1101/2021.03.22.21254081	Exclusion reason: Wrong study design
Wheatley 2021	Evolution of immune responses to SARS-CoV-2 in mild-moderate COVID-19	10.1038/s41467-021-21444-5	Exclusion reason: Wrong outcomes
Wu 2020	A follow-up study shows no new infections caused by patients with repeat positive of COVID-19 in Wuhan	10.1101/2020.11.18.20232892	Exclusion reason: Follow up < 3 months (individual cases)
Wu 2021	A follow-up study shows that recovered patients with re-positive PCR test in Wuhan may not be infectious	10.1186/s12916-021-01954-1	Exclusion reason: Wrong outcomes
Yuan 2020	Recurrence of positive SARS-CoV-2 viral RNA in recovered COVID-19 patients during medical isolation observation	10.1038/s41598-020-68782-w	Exclusion reason: Follow up < 3 months (individual cases)
Zheng 2020	Incidence, clinical course and risk factor for recurrent PCR positivity in discharged COVID-19 patients in Guangzhou, China: A prospective cohort study	10.1371/journal.pntd.0008648	Exclusion reason: Follow up < 3 months (individual cases)
Zheng 2021	Sustainability of SARS-CoV-2 Induced Humoral Immune Responses in COVID-19 Patients from Hospitalization to Convalescence Over Six Months	10.1007/s12250-021-00360-4	Exclusion reason: Wrong outcomes

Table A2: Excluded studies from current version of evidence summary (version 8.0)

Study	Title	DOI	Exclusion reason
Abo-Leyah 2021	The seroprevalence and protective effect of sars-cov-2 antibodies in scottish healthcare workers	10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A1280	Exclusion reason: Duplicate study
Abu-Raddad 2021	Effect of vaccination and of prior infection on infectiousness of vaccine breakthrough infections and reinfections	10.1101/2021.07.28.21261086	Exclusion reason: No outcome of interest
Asakura 2021	One Possible Reinfection with SARS-CoV-2 Validated by 205-days Interval of Re-detection in Sapporo City, Japan	10.20944/preprints202104.0439.v1	Exclusion reason: Case studies
Banerjee 2021	Reinfection after Natural Infection with SARS-CoV-2: A Cohort Study	10.2139/ssrn.3882415	Exclusion reason: No PCR or antigen testing for reinfection
Bongiovanni 2021	Evaluation of the immune response to COVID-19 vaccine mRNA BNT162b2 and correlation with previous COVID-19 infection	10.1016/j.jcv.2021.104962	Exclusion reason: <100 participants
Brouqui 2021	COVID-19 re-infection	10.1111/eci.13537	Exclusion reason: No outcome of interest
Byrne 2021	Quantifying the risk of SARS-CoV-2 reinfection over time	10.1002/rmv.2260	Exclusion reason: systematic review
Capetti 2021	One-year durability of anti-spike IgG to SARS-CoV-2: Preliminary data from the anticrown prospective observational study one year durability of COVID-19 anti-spike IgG	10.1016/j.jinf.2021.05.023	Exclusion reason: No outcome of interest
Cavanaugh 2021	Suspected Recurrent SARS-CoV-2 Infections Among Residents of a Skilled Nursing Facility During a Second COVID-19 Outbreak - Kentucky, July-November 2020	10.15585/mmwr.mm7008a3	Exclusion reason: <100 participants
Chemaitelly 2021	SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy	10.1016/j.eclinm.2021.100861	Exclusion reason: Already included in prior review
Choudhry 2021	Disparities of SARS-CoV-2 Nucleoprotein-Specific IgG in Healthcare Workers in East London, UK	10.3389/fmed.2021.642723	Exclusion reason: No outcome of interest
Cox 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	10.1093/cid/ciab608	Exclusion reason: No evidence of recovery from initial infection
Domènech-Montoliu 2021	Persistence of Anti-SARS-CoV-2 Antibodies Six Months after Infection in an Outbreak with Five Hundred COVID-19 Cases in Borriana (Spain): A Prospective Cohort Study	10.3390/covid1010006	Exclusion reason: No PCR or antigen testing for reinfection

Dong 2021	Retrospective analysis on the clinical characteristics of patients who were reinfected with the Corona Virus in 2019	N/A	Exclusion reason: No evidence of recovery from initial infection
Dulery 2021	High incidence of prolonged covid-19 among patients with lymphoma treated with B-CELL depleting immunotherapy	10.1097/HS9.0000000000000566	Exclusion reason: No outcome of interest
Figueiredo-Campos 2021	Seroprevalence of anti-SARS-CoV-2 antibodies in COVID-19 patients and healthy volunteers up to 6 months post disease onset	10.1002/eji.202048970	Exclusion reason: No outcome of interest
Foulkes 2021	SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN)	10.1016/S0140-6736%2821%2900675-9	Exclusion reason: Already included in prior review
Garvey 2021	Details of SARS-CoV-2 reinfections at a major UK tertiary centre	10.1016/j.jinf.2021.03.004	Exclusion reason: No outcome of interest
Gautret 2021	Does SARS-CoV-2 re-infection depend on virus variant?	10.1016/j.cmi.2021.06.029	Exclusion reason: No outcome of interest
Goldberg 2021	Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel	10.1101/2021.04.20.21255670	Exclusion reason: No outcome of interest
Harvey 2021	Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection	10.1001/jamainternmed.2021.0366	Exclusion reason: Already included in prior review
He 2021	The new SARS-CoV-2 variant and reinfection in the resurgence of COVID-19 outbreaks in Manaus, Brazil	10.1101/2021.03.25.21254281	Exclusion reason: No outcome of interest
He 2021	Reinfection by the SARS-CoV-2 P. 1 variant in blood donors in Manaus, Brazil	10.1101/2021.05.10.21256644	Exclusion reason: No outcome of interest
Iversen 2021	Seroprevalence of SARS-CoV-2 antibodies and reduced risk of reinfection through six months: a Danish observational cohort study of 44,000 healthcare workers	10.1016/j.cmi.2021.09.005	Exclusion reason: No PCR or antigen testing for reinfection
Jon 2021	Incidence of COVID-19 recurrence among large cohort of healthcare employees	10.1016/j.annepidem.2021.04.005	Exclusion reason: No evidence of recovery from initial infection
Kral 2021	Long-lasting immune response to a mild course of PCR-confirmed SARS-CoV-2 infection: A cohort study	10.1016/j.jinf.2021.08.030	Exclusion reason: No outcome of interest
Krutikov 2021	Incidence of SARS-CoV-2 infection according to baseline antibody status in staff and residents of 100 long-term care facilities (VIVALDI): a prospective cohort study	10.1016/S2666-7568(21)00093-3	Exclusion reason: Already included in prior review
Krutikov 2021	Prevalence and duration of detectable SARS-CoV-2 nucleocapsid antibody in staff and residents of long-	10.1101/2021.09.27.21264166	Exclusion reason: No outcome of interest;

	term care facilities over the first year of the pandemic (VIVALDI study):		
Leidi 2021	Risk of reinfection after seroconversion to SARS-CoV-2: A population-based propensity-score matched cohort study	10.1093/cid/ciab495	Exclusion reason: Already included in prior review
Letizia 2021	SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: a prospective cohort study	10.1016/S2213-2600(21)00158-2	Exclusion reason: <3 months follow up
Lingel 2021	Unique autoantibody prevalence in long-term recovered SARS-CoV-2-infected individuals	10.1016/j.jaut.2021.102682	Exclusion reason: No outcome of interest
Mack 2021	SARS-CoV-2 Reinfection: A Case Series from a 12-Month Longitudinal Occupational Cohort	10.1093/cid/ciab738	Exclusion reason: Case studies
Maier 2021	Clinical spectrum of SARS-CoV-2 infection and protection from symptomatic re-infection	10.1093/cid/ciab717	Exclusion reason: No outcome of interest
Masia 2021	Incidence of delayed asymptomatic COVID-19 recurrences in a 6-month longitudinal study	10.1016/j.jinf.2021.03.020	Exclusion reason: Already included in prior review
Mishra 2021	Natural immunity against COVID-19 significantly reduces the risk of reinfection: findings from a cohort of sero-survey participants	10.1101/2021.07.19.21260302	Exclusion reason: No outcome of interest;
Murillo-Zamora 2021	Predictors of severe symptomatic laboratory-confirmed SARS-CoV-2 reinfection	10.1016/j.puhe.2021.01.021	Exclusion reason: <3 months follow up
Nazli 2021	Mortality and reinfection rates of the patients with mild COVID-19 at the sixth month after the infection	10.5578/FLORA.20219806	Exclusion reason: No outcome of interest
Pouwels 2021	Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK	10.1101/2021.08.18.21262237	Exclusion reason: No outcome of interest
Prete 2021	Reinfection by the SARS-CoV-2 P. 1 variant in blood donors in Manaus, Brazil	10.1101/2021.05.10.21256644	Exclusion reason: No outcome of interest
Qureshi 2021	Re-infection with SARS-CoV-2 in Patients Undergoing Serial Laboratory Testing	10.1093/cid/ciab345	Exclusion reason: Already included in prior review
Sánchez-Montalvá 2021	Risk of SARS-CoV-2 Infection in Previously Infected and Non-Infected Cohorts of Health Workers at High Risk of Exposure	10.3390/jcm10091968	Exclusion reason: <100 participants
Sadr 2021	SARS-CoV-2 re-positivity within the first 3 months of COVID-19 recovery; probable re-infection	10.22541/au.162117445.56254867/v1	Exclusion reason: <100 participants
Sandberg 2021	SARS-CoV-2-specific humoral and cellular immunity persists through 9 months irrespective of COVID-19 severity at hospitalisation	10.1002/cti2.1306	Exclusion reason: No outcome of interest

Sharma 2021	Breakthrough infection with SARS-CoV-2 and its predictors among healthcare workers in a medical college and hospital complex in Delhi, India	10.1101/2021.06.07.21258447	Exclusion reason: No outcome of interest
Shastri 2021	Severe SARS-CoV-2 Breakthrough Reinfection With Delta Variant After Recovery From Breakthrough Infection by Alpha Variant in a Fully Vaccinated Health Worker	10.3389/fmed.2021.737007	Exclusion reason: Case studies
Shields 2021	COVID-19: Seroprevalence and Vaccine Responses in UK Dental Care Professionals	10.1177/00220345211020270	Exclusion reason: Already included in prior review
Shrotri 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	10.1016/S1473-3099(21)00289-9	Exclusion reason: No outcome of interest
Simonenko 2021	Covid-19 management in patients after heart transplantation	10.1111/tri.13944	Exclusion reason: <100 participants
Taubel 2021	Longitudinal analysis of COVID-19 infection rates and antibody levels pre-and post-vaccination	10.1007/s00228-021-03164-3	Exclusion reason: No outcome of interest
Tiraboschi 2021	Neutralizing-antibody responses following SARS-CoV-2 infection	Not applied	Exclusion reason: No outcome of interest
Vicenti 2021	Time Course of Neutralizing Antibody in Healthcare Workers with Mild or Asymptomatic COVID-19 Infection	10.1093/ofid/ofab312	Exclusion reason: No outcome of interest
Yadav 2021	Conundrum of re-positive COVID-19 cases: A systematic review of case reports and case series	10.1016/j.mjafi.2021.05.025	Exclusion reason: systematic review
Yalçın 2021	Immunogenicity After Two Doses of Inactivated Virus Vaccine in Healthcare Workers with and without Previous COVID-19 Infection: Prospective Observational Study	10.1002/jmv.27316	Exclusion reason: No outcome of interest

Appendix 2: Data extraction

Table A3: Data extraction from previous version of evidence summary (version 7.1) with updated findings where appropriate

Author DOI Title Country Study design Publication status	Population (number of participants, follow-up duration) Patient demographics	Primary endpoints Test parameters: Serial testing intervals SARS-CoV-2 confirmation Serological confirmation Clinical description	Relative risk of reinfection (or Odds Ratio) Adjusted estimates (for covariates) Absolute (/crude) reinfection events Conclusion/relevance
Abu-Raddad 2021 **10.1016/j.eclinm.2021.100861** **SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy.** Qatar Retrospective cohort study **Published**	N=43,044 anti-SARS-CoV-2 antibody positive persons Median follow-up: 16.3 weeks Maximum duration of follow-up: 34.6 weeks Criteria for cases: ▪ Suspected reinfection: All SARS-CoV-2 antibody-positive persons in Qatar with at least one PCR-positive swab that occurred ≥14 days after the first-positive antibody test. ▪ Good evidence for reinfection: Suspected reinfection cases with a PCR Ct ≤30 for the reinfection swab (suggestive of a recent active infection) and who had not had a PCR-positive swab for 45 days preceding the reinfection swab (to rule out	**Primary endpoint:** Risk of reinfection and efficacy of natural immunity **Risk calculations**: ▪ Risk of reinfection: proportion of cases with good or some evidence for reinfection among all eligible anti-SARS-CoV-2 +ve cases (with an antibody-positive test ≥14 days from end-of-study censoring). ▪ Incidence rate of reinfection: number of cases with good or some evidence for reinfection divided by the number of person-weeks contributed by all anti-SARS-CoV-2 positive cases. ▪ Follow-up person-time: starting 14 days after the first positive antibody test until the reinfection swab, all-cause death, or end-of-study censoring (set on December 31, 2020). ▪ Adjusted estimates for the risk of reinfection and the incidence rate of reinfection derived by applying the confirmation rate obtained from viral genome sequencing analysis.	314 individuals (0.7%) had at least one PCR positive swab ≥14 days after the first-positive antibody test. Of these 314 individuals, 129 (41.1%) had supporting epidemiological (with good or some) evidence for reinfection. ▪ Applying the viral-genome-sequencing confirmation rate, the risk of reinfection was estimated at 0.17% (95% CI: 0.10 to 0.30%). ▪ Incidence rate of reinfection: 0.66 per 10,000 person-weeks (95% CI: 0.56 to 0.78). ▪ Risk over time: Incidence rate of reinfection by month of follow-up did not show any evidence of waning of immunity for over 7 months of follow-up. Seronegative comparison: N=149,923 antibody-negative persons followed for a median of 17.0 weeks (range: 0 to 45.6), risk of infection was estimated at 3.09% (95% CI: 2.93 to 3.27%) and incidence rate of infection was

	persisting PCR positivity due to non-viable virus fragments). ▪ Some evidence for reinfection: Suspected reinfection cases who had not had a PCR-positive swab for 45 days preceding the reinfection swab, but whose Ct value for the reinfection swab was >30. ▪ Weak evidence for reinfection: Suspected reinfection cases who had a PCR-positive swab within the 45 days preceding the reinfection swab. Demographics: The cohort included 8,953 (20.8%) women and 34,091 men (79.2%) of 158 nationalities. Median age was 35 years for women (interquartile range (IQR): 28-45 years) and 38 years for men (IQR: 31-47 years)	**Efficacy (of natural immunity against reinfection):** ▪ SARS-CoV-2 incidence was also assessed in a complement cohort including all those testing SARS-CoV-2 antibody-negative in Qatar, to provide an antibody-negative comparator group and to assess the efficacy of natural immunity against reinfection. ▪ Efficacy=1-(Risk in exposed)/(Risk in unexposed) **Test parameters** RT-qPCR: TaqPath™ COVID-19 Combo Kits (Thermo Fisher Scientific, USA) on ABI 7500 FAST (Thermo Fisher, USA) Serology: Roche Elecsys® Anti-SARS-CoV-2 assay (Roche, Switzerland) [ECLIA] **Viral genome sequencing:** For a subset of investigated reinfection cases with good or some evidence for reinfection (where it was possible to retrieve the first infection PCR+ve swab and the reinfection swab), sequencing was conducted to confirm reinfection	estimated at 13.69 per 10,000 person-weeks (95% CI: 13.22 to 14.14). **Efficacy of natural immunity against reinfection:** 95.2% (95% CI: 94.1% to 96.0%). **Severity:** Of the 8 reinfection cases that received severity classification, only 1 reinfection was severe, 2 were moderate, and 0 were critical or fatal. **Symptomatic/serial testing:** Most reinfections (N=86/129, 66.7%) were diagnosed incidentally through random or routine testing, or through contact tracing. **Whole genome sequencing:** ▪ Of the 16 cases where viral genome sequencing evidence was available, 5 cases were confirmed as reinfections, a confirmation rate of 31.3%. ▪ For 1 pair, there were few changes of allele frequency offering supporting evidence for reinfection. For 4 other pairs, there were multiple clear changes of allele frequency indicating strong evidence for reinfection. 1 of the latter pairs also documented the presence of the D614G mutation (23403bp A>G) at the reinfection swab—a variant that has progressively replaced the original D614 form.
Breathnach 2021 UK DOI: 10.1016/j.jinf.2021.01.005	N=10,727 PCR or antibody positive at baseline Median f/u: NR Maximum f/u: Approx. 11 months (February to December 2020)	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection. **Time interval:** Cases where the second positive result was < / = 90 days after the first were excluded. **Test parameters:**	**Risk of reinfection:** 0.07% (with ≥90 days between infection events) **Relative risk of reinfection:** 0.058 (95% CI: 0.029 to 0.116)

Published	**Analysis period:** Minimum interval between tests: 90 days. Study period: February to December 2020. Those who had evidence of COVID-19 in the first wave of infections in the UK (February to July 2020, with a peak in early April), as shown either by a positive SARS-CoV-2 PCR or a positive antibody test were identified. Their risk of having a positive SARS-CoV-2 PCR assay in the first five months of the second wave (August to December 2020) was compared with patients who had a previous negative PCR or antibody test. **Demographics:** Mean age 50; 60% Female	Antibody samples were tested on either the Roche Elecsys or the Abbot Architect according to manufacturer's guidelines. PCR assays were performed on the Roche 6800 or the Altona Diagnostics Real-Star.	Of note, there were no reinfections in the first seven months after the peak of the first wave; all eight patients with likely reinfections were diagnosed in December, the last month of the study period; reinfections accounted for 1.69% of all infections in that month.
Hanrath 2020 10.1016/j.jinf.2020.12.023 Prior SARS-CoV-2 infection is associated with protection against symptomatic reinfection UK Retrospective cohort study	**Analysis period and time interval:** ▪ Two periods for analysis: 1st wave: 10 March - 6 July 2020; 2nd wave: 7 July - 20 November. ▪ Follow-up: median 5.8 months (173 days, IQR: 162–229 days, between first positive test and end of follow-up period). **Number of participants:**	**Primary endpoint:** symptomatic SARS-CoV-2 infection. **Time interval:** In those previously infected, there was a median of 173 (IQR: 162–229) days from the date of first positive PCR/antibody result to the end of the analysis period. **Test parameters:** ▪ Public Health England (PHE) approved RT-PCR assays containing two SARS-CoV-2 gene targets. ▪ SARS-CoV-2 nucleocapsid IgG antibody testing using the Roche Anti-SARS-CoV-2 IgG assay	**Risk difference:** ▪ During 2nd time period, 2,243 HCWs underwent PCR testing for symptoms. 128 had previous confirmed SARS-CoV-2 infection, while 2,115 had not. ▪ A positive PCR test was returned in 0/1,038 (0% [95% CI: 0 to0.4) of those with previous infection, compared to 290/10,137 (2.9% [95% CI: 2.6 to 3.2) of those without (P<0.0001 $\chi 2$ test). **Symptomatic testing:**

Published	▪ 1st wave: N=1,038 HCWs with prior SARS-CoV-2 infection (PCR and or antibody testing) and N=10,137 HCWs without prior exposure. ▪ Of those with prior exposure: 481/3,338 symptomatic HCWs tested positive for SARS-CoV-2 by PCR, while SARS-CoV-2 IgG was detected in 937/11,103. **Demographics:** Median age: 39.5 (prior infection), 40 (no infection) Female: 82.5% (prior infection), 80.5% (no infection)		▪ Fewer HCWs in the previous infection group presented for symptomatic testing. 128/1,038 (12.3% [95% CI: 10.5 to 14.5]) of those with evidence of prior infection had a test due to symptoms in the second period compared to 2115/10,137 (20.8% [95% CI: 20.1 to 21.6]) in the group without previous infection (P<0.0001 χ2 test). **Asymptomatic screening:** Asymptomatic PCR screening was undertaken on a pilot basis in an additional 481 HCWs, 106 with past infection and 375 without. There were similarly no positive results in the group with previous infection 0/106 (0% [95% CI: 0 to 3.5]), compared to 22/375 (5.9% [95% CI: 3.9 to 8.7], P = 0.011) positive PCR results in the group without previous infection. **Author conclusions:** ▪ There were no symptomatic reinfections in a cohort of healthcare workers
Harvey 2021 **10.1001/jamainternmed.2021.0366** **Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection** US	N=3,257,478 (national sample from EHRs) with an index antibody test. 88.3% (n= 2,876,773) had negative index test; 11.6% (n=378,606) positive and 0.1% (n=2,099) inconclusive (the latter excluded from follow-up) **Demographics:** (negative index test group/positive index test group) Mean age = 47.66/44.34 years; Female 56.7%/54.1%	**Primary endpoints:** index antibody test results and post-index diagnostic NAAT* results, with infection defined as a positive diagnostic test post-index, as measured in 30-day intervals (0-30, 31-60, 61-90, >90 days). **Test:** Antibody test and/or diagnostic nucleic acid amplification test (NAAT). NAAT is considered a proxy representing a new infection or may represent continued viral shedding depending on the context and timing **Cycle threshold:** NR	**Duration of seropositivity in the index positive cohort:** 2.6% (n=9,895) of those with a positive antibody test at index had at least one subsequent antibody test during follow-up. Of these: ▪ 12.4% (n=1,227) tested negative when retested within 0-30 days ▪ 18.4% (n=unclear) testing seronegative when the subsequent antibody test occurred >90 days

Retrospective cohort study Published		**Median follow-up:** ▪ 47 days for the seronegative group (IQR 8 to 88 days) ▪ 54 days for the seropositive group (IQR: 17 to 92 days). 11.0% seropositives and 9.5% seronegatives had >1NAAT during follow-up, (mean of 3.3 NAAT for seropositives and 2.3 seronegatives over the follow-up period) 2.6% of those with a positive antibody test at index had at least one subsequent antibody test during follow-up **Serology:** The commercial laboratories antibody testing included a limited set of high throughput antibody tests with validation against a known standard providing between 98% to 100% agreement with both known antibody-positive and antibody-negative specimens, with a 95% confidence interval of 99-100% agreement. The majority of tests performed during the study period were IgG (>91%). Most COVID-19 signs and symptoms were similar between the seropositive and seronegative groups.	Ratio (CI) of positive NAAT results in those with positive antibody test at index versus those with negative: ▪ 2.85 (2.73 - 2.97) at 0-30 days ▪ 0.67 (0.6 - 0.74) at 31-60 days ▪ 0.29 (0.24 - 0.35) at 61-90 days) ▪ 0.10 (0.05 - 0.19) at >90 days. **Duration of NAAT positivity:** Those seropositive at baseline: ▪ 11.3% (n=3,226) had a positive NAAT 0 to 30 days ▪ 2.7% (n=771) from 31-60 days* ▪ 1.1% (n=314) from 61-90 days* ▪ 0.3% (n=86) at >90 days* *Based on calculation Those seronegative at baseline: ▪ 3.9% (n=5,638) had positive NAAT result 0 to 30 days ▪ ~3.0% had positive NAAT over all subsequent periods of observation, including at >90 days
Hall 2021 UK 10.1016/S0140-6736(21)00675-9 SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in	N=8,278 **Median f/u:** 275 days (9.1 months) (IQR 218–291 days) for the positive cohort and 195 days (6.5 months) (IQR 131–214 days) for the negative cohort. **Maximum f/u:** >11 months **Study period (reinfection f/u):** 18 June 2020 to 31 Dec 2020	▪ Questionnaires on symptoms and exposures were sent electronically at baseline and every 2 weeks. ▪ SARS-CoV-2 antibody testing and Nucleic Acid Amplification Testing (NAAT) with real-time PCR (rtPCR) was done at enrolment and at regular intervals (PCR every 2 weeks, antibody testing every 4 weeks). ▪ Most sites used rtPCR; however, a small number of sites used Loop-mediated isothermal amplification testing or Rapid Testing with rtPCR to confirm positive results.	**Incidence density:** 7.6 reinfections per 100,000 person-days in the positive cohort compared with 57.3 primary infections per 100,000 person-days in the negative cohort **Adjusted incidence rate ratio of reinfection comparing antibody or PCR-positive group with negative group** ▪ All events (possible and probable reinfections): 0.159 (95% CI: 0.13 to 0.19)

England: a large, multicentre, prospective cohort study (SIREN) Prospective cohort Published Health care workers UK	Participants were assigned to the positive cohort if they met one of the following criteria: antibody positive on enrolment or antibody positive from previous clinical laboratory samples, with or without a previous positive PCR test; antibody negative on enrolment with a positive PCR result before enrolment. Participants were assigned to the negative cohort if they had a negative antibody test and no documented previous positive PCR or antibody test.	▪ The B.1.1.7 variant emerged and spread during the study period, and the effect of this variant was included in the analysis by creating a binary variable of when the S-Gene Target Failure (SGTF) PCR, used to identify the B.1.1.7 variant in the laboratory network, accounted for 50% or more of the positive results for each region. The SGTF PCR testing was introduced to specific laboratories in England only, termed Pillar 2 laboratories, which are large hospital laboratories established specifically for the COVID-19 response for the purpose of community testing.	▪ Symptomatic reinfections only (with COVID-19 symptoms): 0.074 (95% CI: 0.06 to 0.10) ▪ Asymptomatic reinfections only: 0.484 (95% CI: 0.37 to 0.63) ▪ Probable reinfections only: 0.002 (95% CI: 0.00 to 0.01) Author conclusions: A previous history of SARS-CoV-2 infection was associated with an 84% lower risk of infection, with median protective effect observed 7 months following primary infection.
Hansen 2021 doi.org/10.1016/S0140-6736(21)00575-4 Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study Denmark Retrospective cohort study Published	N=11,068 PCR positive at baseline were analysed in the main analysis. Two 'surges' were defined (in this report 'wave' is used). During the first wave (before June, 2020), N=533,381 people were tested, of whom 11,727 (2.20%) were PCR positive. N=525,339 were eligible for follow-up in the second wave (1 Sept 31 Dec 2020), of whom 11,068 (2.11%) had tested positive during the first wave. Alternative cohort analysis: 2,432,509 individuals were included in the alternative cohort analysis, with 28,875 (1.19%) individuals contributing exposed	**Primary endpoint:** Main analysis: Rate of infection: the number of individuals with positive PCR tests during the second wave divided by the cumulative number of person-days at risk. The number of days at risk for each individual in the sample was the number of days from Sept 1, 2020, until the first positive test, or Dec 31, 2020, whichever came first. Follow-up time was censored in the event of death. Adjusted rate ratio (RR) and accompanying 95% CI was obtained using Poisson regression, adjusted for sex, age group (0–5, 6–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years), and test frequency (number of PCR tests done on each person in 2020 categorised as 1–2, 3–5, 6–10, and ≥11 tests) to control for potential confounding. Additional cohort analysis: All available data was used to investigate rates of reinfection throughout the epidemic, not just during the second wave. Each individual with a PCR test	Max follow-up was 295 days (9.8 months). **Main analysis:** 72 confirmed new infections during follow-up out of 1,346,920 person-days in those positive in first wave, compared with 16,819 new infections out of 62,151,056 person-days in those negative in first wave. Adjusted rate ratio (aRR) of reinfection=0.195 (95% CI: 0.155 to 0.246) **Additional cohort analysis:** aRR=0.212 (95% CI: 0.179 to 0.251) By age group: 0-34 years: aRR=0.173 (95% CI: 0.131 to 0.229) 35–49 years: aRR=0.199 (95% CI: 0.141 to 0.282) 50–64 years: aRR=0.187 (95% CI: 0.127 to 0.274) ≥65: years: aRR=0.529 (95% CI: 0.372 to 0.753)

	time periods and 2,405,683 (98.90%) contributing unexposed time periods, with 2,049 contributing to both unexposed and exposed time periods. **Mean follow-up**: In primary analysis, 1,346,920 person-days follow-up in positive cohort of 11,068 individuals (approx 4 months) and 62,151,056 person-days of follow-up in negative cohort of 514,271 individuals (approx. 4 months). **Duration of study:** Data between 26 Feb and 31 Dec 2020 were included in analyses. For the analysis of reinfection rate over time, reinfection at 3-6 months follow-up was compared to ≥7 months. **Demographics:** Of those PCR positive in first wave (N=72/11,068): Sex: N=46 women, N26 men Age: N=4 aged 0-19 years, N=15 aged 20-34years, N=20 aged 35-50 years, N=16 aged 50-64 years, N=8 aged 65-79 years, N=9 aged 80+.	result was followed up from the time of their first test, irrespective of the date and whether they had a positive or negative result, until Dec 31, 2020, or a new positive test at least 90 days later. If the initial test was negative, a subsequent positive test within the 90 days changed an individual's status from uninfected to previously infected. Additional cohort analysis was then expanded to include interaction terms with sex and age group (restricted to four age groups [0–34, 35–49, 50–64, ≥65 years] to avoid strata with few events). **Test:** The clinical microbiology laboratories applied a range of CE-marked commercial platforms or in-house assays that were all quality controlled according to clinical microbiology diagnostic standards. The TestCenter Denmark laboratory applied an RT-PCR assay with the E gene on SARS-CoV-2 as the target. Rapid antigen test results were excluded from analysis. **Intervals:** No specific time interval – all PCR tests were analysed. **Cycle threshold:** N/R **Whole Genome Sequencing:** Not performed	

Jeffery-Smith 2021 10.2807/1560-7917.ES.2021.26.5.2100092 Antibodies to SARS-CoV-2 protect against re-infection during outbreaks in care homes, September and October 2020 UK Retrospective cohort Published Eurosurveillance	N=88 with evidence of prior infection (antibody positive N=87; RT-PCR positive N=1) Outbreak in Sept/Oct 2020 was compared to serological evidence of prior infection in May/June 2020. Follow-up was approx. 4 months. Two sites: <u>Care home A</u> N=52 residents (median age 84 years; IQR: 76-89). Serological investigations in June 2020 found 33/66 (50.0%) had SARS-CoV-2 antibodies after the first outbreak (18/32 residents; 15/34 staff). <u>Care home L</u> N=64 residents (median age 85 years; IQR: 78-89). Serological investigation in May 2020 identified 59/117 (50.4%) as seropositive (26/52 residents; 33/65 staff). **Case definitions:** A COVID-19 case was defined as any individual testing positive by RT-PCR for SARS-CoV-2, whether tested as a result of symptoms or through routine care home Screening.	**RT-PCR testing** Nasal swabs were subjected to SARS-CoV-2 RT-PCR at the Public Health England (PHE) national reference Laboratory. **Antibody testing** Serological testing was conducted using in-house native virus lysate (PHE, UK) and receptor binding domain (RBD) EIA assays (PHE, UK), and a commercial nucleocapsid (N) assay (Abbott, Illinois, United States) Seropositivity was determined by reactivity in any assay; > 80% of samples were positive in ≥ 2 assays. Neutralising antibody titres were determined by live virus neutralisation **Whole Genome Sequencing** WGS was attempted on all RT-PCR-positive samples tested at the PHE reference laboratory; completed viral genomes were deposited in GISAID.	Reinfection rate: N=1/88 (1.1%) Infection rate in seronegative cohort: 30.1% (N=22/73, includes 4 people diagnosed by seroconversion) RR=0.038 (95% CI: 0.005 to 0.273; p < 0.0001) Effectiveness: protection against reinfection after 4 months estimated at 96.2% (95% CI: 72.7 to 99.5%) **Whole Genome Sequencing:** • The second COVID-19 outbreaks experienced by both care homes were due to SARS-CoV-2 strains that were genetically distinct from their respective first outbreaks. • In both care homes, fatal cases in residents had identical viral genomes to surviving residents. Care home A: ▪ Virus strains from the earlier outbreak had S gene 614D, whereas the strains in the later outbreak were 24–27 single nucleotide polymorphisms (SNPs) different and contained S gene 614G. In the second outbreak, 9 individuals were infected by an identical strain, which differed by 1–2 SNPs from 3 other COVID-19 cases. ▪ The individual with a probable re-infection (S#) shared a virus sequence from B1.36 lineage and the same UK1350_1.2.1.1 phylotype as the other residents and staff, with 6 SNPs differences from the main cluster, including 3 mixed bases which were all outside the S protein RBD coding region.

	A re-infection was defined as an individual testing SARS-CoV-2 RT-PCR positive while having evidence of previous seropositivity by any assay, or a previous RT-PCR-positive result more than 90 days earlier in an individual without serological analysis (assumed to have seroconverted).		Care home L: ▪ Virus strains from the earlier outbreak arose from several introductions and contained a mixture of 614D and 614G strains, whereas the second outbreak strains were all S gene 614G and differed by 11–18 SNPs from earlier strains. ▪ In both care homes, fatal cases in residents had identical viral genomes to surviving residents.
Krutikov 2021 **10.1016/S2666-7568(21)00093-3** **Incidence of SARS-CoV-2 infection according to baseline antibody status in staff and residents of 100 long-term care facilities (VIVALDI): a prospective cohort study** **UK** **Prospective cohort study** **Published**	N=634 seropositive at baseline. N=2,111 participants included in total, comprising 682 residents and 1429 staff. Baseline antibodies to nucleocapsid were detected in 226 residents (33%) and 408 staff (29%) **Setting** Study followed residents and staff at 100 Long Term Care Facilities (LTCFs) **Duration of study** ▪ Blood samples were collected at baseline (June 2020). Blood sampling was ▪ offered to all participants at 3 time points separated by 6-8 week intervals in June, ▪ Aug and Oct 2020. ▪ PCR testing for SARS-CoV-2 was undertaken	**Primary outcome:** All positive PCR tests after entry time were considered to indicate infection or reinfection. Cox regression was used to estimate hazard ratios (HRs) for baseline antibody positivity. The baseline hazard was defined over calendar time, with participants entering the 'risk set' on their entry date (in most cases 1st October 2020) **Antibody testing** All participants were classified into 2 cohorts (positive and negative) according to their first (baseline) antibody test. Exposure status was based on IgG antibodies to nucleocapsid (Abbott) because this test was available for all participants. Subsequent seroconversion was not considered in our primary analysis due to small numbers of participants in which this occurred **Titres** Quantitative antibody data were available for 11/14 reinfection cases, and 42 control participants who were antibody positive at baseline and remained PCR negative throughout follow-up. There was no	**Infection events by group and antibody status:** Residents: 93 infections out of 456 antibody negative residents, compared with 4 reinfections out of 226 antibody positive residents Rate of PCR positive infection per month at risk: 0.054 seronegative versus 0.007 seropositive Staff: 111 infections out of 1,021 antibody negative residents, compared with 10 reinfections out of 408 antibody positive residents Rate of PCR positive infection per month at risk: 0.042 seronegative versus 0.009 seropositive **RR** Relative adjusted hazard ratios for PCR positive infection comparing seropositive versus seronegative: Residents aHR: 0.15 (95% CI 0.05 to 0.44)*

	weekly in staff and monthly in residents. ▪ Patients were followed between Oct 2020 and Feb 2021 for evidence of infection ▪ Staff and residents contributed 3,749 and 1,809 months of follow-up time respectively (mean 2.6 months per participant) ▪ Maximum f/u: 300 days (10 months), based on an assumption as to when the earliest infections took place. **Demographics** The median age of residents was 86 years (IQR: 79-91) and 47 years in staff (IQR: 34-56).	statistically significant difference in antibody titres to spike and nucleocapsid in individuals who were re-infected and those who remained PCR-negative during follow-up, when considering antibodies at the first testing round (baseline), and at the last antibody testing round stratified by the time gap between the antibody test and the PCR test **Cycle threshold:** Ct values were retrieved for 13/14 reinfection samples. The median Ct value for reinfection cases was 36 (30.1-37.0). 6/7 samples that were analysed using the same PCR assay, and 9/14 samples that were tested using assays that targeted the ORF1ab had Ct values >30	Staff aHR: 0.39 (95% CI: 0.19 to 0.82)* *Multivariate analysis of risk of PCR positive infection by baseline antibody status, stratified by LTCF and adjusted for sex and age **Symptoms:** Of 12 reinfected participants with data on symptoms, 11 were symptomatic. **Titres:** Antibody titres to spike and nucleocapsid were comparable in PCRpositive and PCR-negative cases.
Leidi 2021 10.1093/cid/ciab495 Risk of reinfection after seroconversion to SARS-CoV-2: A population-based propensity-score matched cohort study Switzerland Retrospective matched cohort study	N=498 **Mean f/u:** 249 days (8.3 months) **Maximum f/u:** Approx. 10 months **Duration:** Serological status assessment in April-June 2020 to the end of the second pandemic wave (January 2021). **Demographics**	**Primary endpoint:** newly acquired SARS-CoV-2 infections in seropositive individuals from a population-based sample as compared to seronegative controls. **Antibody testing:** Seropositivity was defined by the detection of anti-S1 domain of spike protein IgG antibodies using a two-step sequential strategy. Antibodies were first detected by a commercially available ELISA (Euroimmun, Lübeck, Germany #EI 2606-9601 G). All potentially indeterminate (IgG ratio for detection ≥0.5) and positive results were confirmed by a recombinant immunofluorescence assay (rIFA), as this technique was considered the	**Seropositive group:** 5/498 reinfections; incidence: 0.3 per 1,000 person-weeks ('likely' reinfections) **Seronegative group:** 154/996 infections; incidence: 4.8 per 1,000 person-weeks **Hazard ratio for reinfection**: 0.06, 95% CI: 0.02 to 0.14, p<0.001 (PM matching)

Published	Among 8,344 serosurvey participants, 498 seropositive individuals were selected and matched with 996 seronegative controls. Age range: 12 to 74 years old	reference method in the laboratory of virology of Geneva University Hospitals (WHO Swiss reference lab) at the time the seroprevalence survey took place. **Reinfection definition:** Two independent adjudicators with experience in clinical management of SARS-CoV-2 infected patients evaluated suspected cases via hospital electronic health records or phone interview with participants. Adjudication was based on clinical judgement and criteria included, when available, reason for testing, subject's illness history (including date of symptom onset) and the value and temporal evolution in RT-PCR cycle threshold (Ct). The purpose of this investigation was to differentiate clinical reinfections from protracted RNA detection. Cases of suspected reinfections were classified as likely or unlikely. Conflicts were solved by a third person.	
Lumley 2021 UK **10.1093/cid/ciab608** **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** **Prospective cohort study**	N=1,273 **F/u:** 216 days (7.2 months) (13,109 individuals contributed 2,835,260 person-days follow-up) Of the 13,109 HCWs participated; 8,285 received the Pfizer-BioNTech vaccine (1407 two doses) and 2,738 the Oxford-AstraZeneca vaccine (49 two doses). 11 HCWs received another vaccine or could not recall the manufacturer. Staff members were classified into five groups: 1. unvaccinated and consistently seronegative during follow-up	▪ Antibody status was determined using an anti-trimeric spike IgG ELISA ▪ SARS-CoV-2 infection diagnosed with RT-PCR ▪ B.1.1.7 variant: PCR-positive results from symptomatic community testing were recorded; from November 2020, Oxford University Hospitals used the Thermo Fisher TaqPath PCR assay as their first-line diagnostic assay, which includes orf1ab, S and N gene targets. As such SGTF indicative of theB.1.1.7 variant could be identified, i.e. orf1ab-positive/N-positive only. Oxford Nanopore sequencing was undertaken of all stored PCR-positive primary samples from 1 December 2020 onwards to identify the infecting lineage.	▪ Compared to unvaccinated seronegative HCWs, natural immunity and two vaccination doses provided similar protection against symptomatic infection: no HCW with two vaccines doses had symptomatic infection, and incidence was 98% lower in seropositive HCWs (adjusted incidence rate ratio 0.02 [95% CI: <0.01 to 0.18]). ▪ Two vaccine doses or seropositivity reduced the incidence of any PCR-positive result with or without symptoms by 90% (0.10 [95% CI: 0.02 to 0.38]) and 85% (0.15 [95% CI: 0.08 to 0.26]) respectively. ▪ Single-dose vaccination reduced the incidence of symptomatic infection by 67% (0.33 [95% CI: 0.21 to 0.52]) and any PCR-positive result by 64% (0.36 [95% CI: 0.26 to 0.50]).

Published Health care workers	2. unvaccinated and ever seropositive 3. vaccinated one dose, always seronegative prior to vaccination 4. vaccinated two doses, always seronegative prior to first vaccination 5. vaccinated (one or two doses and ever seropositive prior to first vaccination. The latter group were combined as relatively few staff were previously seropositive and received two vaccine doses. Vaccinated groups were considered at-risk of infection >14 days after each vaccine dose.		There was no evidence of differences in immunity induced by natural immunity and vaccination for infections with S-gene target failure and B.1.1.7.
Manica 2021 **10.1093/cid/ciab556** **Risk of Symptomatic Infection During a Second Coronavirus Disease 2019 Wave in Severe Acute Respiratory Syndrome Coronavirus 2–Seropositive Individuals** **Cohort study** **Published** **Italy**	N=1,402 **Maximum f/u:** 8 months Overall seroscreening population: 6,074. This represented five Italian municipalities within the Autonomous Province of Trento, Italy, where an IgG serological screening aimed at covering the entire adult resident population was conducted between 5 May and 15 May 2020.	**Serological tests:** performed using Abbott SARS-CoV-2 IgG chemiluminescent assays and analyzed on the Abbott Architect i2000SR automated analyzer **Reinfection cases:** Positive cases were ascertained by using either RealTime SARS-CoV-2 assay on naso-oropharyngeal swabs (detectability per ml of UTM buffer 250 copies) or rapid antigenic test (sensitivity >90%, specificity >97%). Out of 221 confirmed cases, 124 were symptomatic. **Symptomatic infections:** Defined as positive participants having fever and either cough or at least two of the following symptoms: widespread myalgia, headache, dyspnoea, pharyngodynia, diarrhea, nausea/vomiting, anosmia/ageusia, asthenia.	Cumulative incidence of symptomatic infections in seropositive group: 0.14% (95% CI: 0.04% to 0.57%) Cumulative incidence of symptomatic infections in seronegative group: 2.60% (95% CI: 2.08% to 3.26%) **Adjusted odds ratio** of developing symptomatic infection: 0.055 (95% CI: 0.014 to 0.220) Four cases were identified among participants who tested positive to IgG in May 2020; two of them were symptomatic. Both these cases were males ascertained in December 2020, who requested to be tested after symptoms onset. The older patient (88 years) was admitted to a hospital but did not require mechanical ventilation or admission to an intensive care unit. The younger patient (52 years)

			was a mild case who was isolated and treated at home.
Masia 2021 10.1016/j.jinf.2021.03.020 Incidence of delayed asymptomatic COVID-19 recurrences in a 6-month longitudinal study Published Spain	N=146 **Maximum f/u:** 6 months Median age was 64 years, 88 (60.3%) were male, and 72.6% had coexisting comorbid diseases.	**Primary endpoint:** Reinfection rate **Serology:** IgG antibody plasma levels against the SARS-CoV-2 internal nucleocapsid protein (N-IgG) and the spike protein (S-IgG) (Anti-SARS-CoV-2 IgG ELISA, Euroimmun, Lubeck, Germany) **Reinfection:** SARS-CoV-2 RNA was detected by RT-PCR (AllplexTM 2019-nCoV Assay, Seegene, Seoul, Korea) which targeted the E, RdRP, and N genes. **WGS:** Genome sequencing of SARS-CoV-2 was performed on nasopharyngeal samples following ARTIC amplicon sequencing protocol for MinIon version V3- Phylogenetic analysis was done using webserver Nextstrain (https://nextstrain.org/), with the SARS-CoV-2 database Nextclade (https://clades.nextstrain.org/).	**Reinfection rate based on whole genome sequencing:** 1 confirmed reinfection out of 146 primary infections (0.68%) Overall, 5 patients with positive RT-PCR occurring more than 90 days since first COVID-19 diagnosis were identified. Median (range) time from diagnosis to new detection of SARS-CoV-2 RNA was 183 (167–204) days. Cases included 3 men, with ages ranging from 44 to 73 years, and 3 of them had subjacent comorbidity. Two patients were readmitted to hospital at re-positivity, and 3 patients remained asymptomatic. Only one patient had a Ct<33, and in the other four patients the Cts ranged from 33 to 38. Genomic sequencing was performed in 4 individuals with available paired samples. In the three patients with Ct≥33, all of them asymptomatic, the same clade 20B was detected. In two of them, the clade showed the same hallmark single nucleotide variants. In the third patient, the follow-up sample showed two new mutations, a K374R substitution in the N gene and an A222V substitution in the S gene, probably reflecting adaptive viral changes associated to persistent infection. Genomic sequencing of the symptomatic patient with a Ct of 18 showed phylogenetically distinct genomic sequences; the first sample was member of the clade 20A, and the most recent sample was member of the clade 20B. The 3 patients with asymptomatic recurrence and

			the symptomatic patient with no sequencing data showed detectable antibody levels at the time of SARS-CoV-2 RNA re-positivity, ranging from 3.01 to 6.01 S/CO for S-IgG and 2.6 to 2.46 S/CO for N-IgG. The patient with symptomatic reinfection had no detectable antibody levels at the time of re-positivity.
Mohamadreza 2021 10.21203/rs.3.rs-262191/v1 COVID-19 Re-infection or Relapse? A Retrospective Multi Center Cohort Study From Iran Preprint Retrospective cohort study Iran	N=1,899 **Maximum f/u:** 6 months **Demographic/clinical criteria:** The majority of patients were male and nurses. The mean age was 37.54 ±15.16 years old. Weakness, myalgia, and fever were the most clinical presentation symptoms in both episodes. Chest Computed Tomography scan showed pneumonia in 56.8% of cases and 43.2% of cases in the first and second episodes respectively Mean duration between discharge and second presentation was 117±61.42 days.	Details of testing methodology not reported.	Symptomatic reinfection rate: 1.9% (37/1,899) Phylogenic sequencing of SARS-CoV-2 and viral culture was not possible.
Papasavas 2021 10.1016/j.jhin.2021.04.021 Seroprevalence of SARS-CoV-2 antibodies, associated epidemiological factors	N=433 Median f/u: 5.5 months Maximum f/u: 196 days (6.5 months) The average age of participants was 43.2 ± 12.9 years (median 43, range 18-81). Of the 6,811	Participants completed a questionnaire on REDCap Three blood draws were completed (initial visit; 2-4 weeks after initial visit; 3-6 months after initial visit)	0/35 seropositive participants who had a subsequent PCR test at least 30 days following the positive antibody test had a positive test 1.3% (29/2,173) seronegative participants had a subsequent positive PCR test

and antibody kinetics among healthcare workers in Connecticut Healthcare workers Published US	participants who reported gender, there were 5,387 females (79.1%). Based on initial testing, 433 (6.3%; 95% CI: 5.7%-6.9%) participants were seropositive (out of a total of 8,663 HCWs provided electronic consent and 6,863 (23% of the entire employee population) provided an initial sample)	Anti-SARS-CoV-2 IgG Antibody Detection: Abbott Architect i2000 platform. Seropositivity was defined as IgG Index (Signal/Cutoff (S/C)) ≥1.4. SARS-CoV-2 diagnosis: RT-PCR testing	
Perez 2021 DOI: 10.1101/2021.03.06.21253051 A 1 to 1000 SARS-CoV-2 reinfection proportion in members of a large healthcare provider in Israel: a preliminary report Retrospective cohort study Pre-print	N=149,735 with history of prior infection Database covered all members in a healthcare provider (Maccabi Healthcare Services) with 2.5 million members (25% of population) Individuals were evaluated for reinfection if they had 2 positive PCR tests at least 100 days apart from 16 Mar 2020 to 27 Jan 2021. **Median f/u:** 165 days (5.5 months) **Maximum f/u:** Approx. 325 days (10.8 months)	The primary outcome was the rate of reinfection (2 positive PCR tests at least 100 days apart) Mean age (SD): 31.5 (19.5); male: 94 (61%) Mean interval between infection events: 165.7 days (SD: 57.6); Range between first and second positive PCR: 100 to >300 days. 11 (7.1%) hospitalised on 1st infection, 4 (2.6%) on 2nd; death 1 (0.6%) on 2nd The age distribution suggests higher count of reinfection among younger individuals. Of 154 with a second PCR positive test, 73 reported symptoms (47.4%) at both tests. **Cycle threshold:** N/R **Whole Genome Sequencing:** Not performed	Of 149,735 individuals with a record of positive PCR test (Mar 2020 to Jan 2021), 154 had 2 positive tests at least 100 days apart (0.1% proportion of reinfection). The reinfection counts were numerically higher in Jan 2021 compared with previous months. The reinfection counts were numerically higher in the 10-19 years age group compared with other age groups.
Pilz 2021 DOI: 10.1111/eci.13520	N=14,840 with history of prior infection at baseline These 14,840 represent recovered patients from the first wave and were compared with 8,885,640 of	Primary outcome was the odds of SARS-CoV-2 reinfections of COVID-19 survivors of the first wave (Feb to Apr 30 2020) versus odds of first infections during the second wave (Sept 1 to Nov 30 2020).	40 possible reinfections were recorded in 14,840 individuals with history of prior infection from the first wave (0.27%), compared with 253,581 infections in 8,885,640 (2.85%) in the remaining general population.

SARS-CoV-2 re-infection risk in Austria Austria Retrospective observational study Published	all the remaining general population from Austrian Epidemiological Reporting System. Of those with tentative reinfections, 62.5% were women; median age (IQR) = 39.8 (25.9 to 54.5). **Median f/u:** 210 days (7 months) **Maximum f/u:** 300 days (10 months)	Mean (SD) time from first to tentative reinfection was 212±25days (4, 12 and 24 reinfections documented in Sept, Oct and Nov, respectively) Range 148 to 251 days One 72-year old woman died following tentative reinfection – she was not hospitalised and cause of death was not causally attributed to COVID-19. Hospitalisation status was coded yes (n=8), no (n=31), unknown (n=1) for first infection and yes (n=5), no (n=27), unknown (n=8) for reinfection (4 were hospitalised during first infections and reinfection) **Cycle threshold:** N/R **Whole Genome Sequencing:** Not performed	OR was estimated at 0.09 (95% CI: 0.07 to 0.13)
Qureshi 2021 Re-infection with SARS-CoV-2 in Patients Undergoing Serial Laboratory Testing 10.1093/cid/ciab345 Retrospective Published US	N=9,119 **Mean** interval between positive tests: 116 days (3.9 months) **Maximum f/u:** N/R; time period applied to dataset: 1 December 2019 to 13 November 2020.	Data were obtained from the Cerner de-identified Coronavirus Disease 2019 (COVID-19) dataset. The methodological aspects of the dataset are available in other publications. Patients with a positive laboratory test for SARS-CoV-2 were identified based on Logical Observation Identifiers Names and Codes; these codes denote detection of SAR-CoV-2 ribonucleic acid in respiratory (nasopharyngeal swabs, bronchoalveolar lavage, sputum) and other specimens or detection of SARS-CoV-2 N gene or RdRp gene in respiratory secretions, all by nucleic acid amplification with probe detection.	Reinfection rate: 63/9,119; 0.7% (95% CI: 0.5% to 0.9%) The mean period (±standard deviation [SD]) between two positive tests was 116 ± 21 days. A logistic regression analysis identified that asthma (odds ratio [OR] 1.9, 95% CI: 1.1 to 3.2) and nicotine dependence/tobacco use (OR 2.7, 95% CI 1.6 to 4.5) were associated with re-infection. There was a significantly lower rate of pneumonia, heart failure, and acute kidney injury observed with re-infection compared with primary infection among the 63 patients with reinfection. There were two deaths (3.2%) associated with reinfection.

Sheehan 2021 **10.1093/cid/ciab234** **Reinfection Rates Among Patients Who Previously Tested Positive for Coronavirus Disease 2019: A Retrospective Cohort Study** US **Retrospective cohort study** **Published**	N=8,845 with history of prior infection at baseline All 150,325 patients who were tested for COVID-19 via PCR from Mar 12 2020 to Aug 30 2020 from one multi-hospital healthcare system were included. Of these, 8,845 (5.9%) tested positive and of these, 1278 (14.4%) were re-tested after 90 days. These were compared with N=39487 with no prior evidence of reinfection who were re-tested after 90 days. **Median follow up:** 138.9 days (4.6 months) **Maximum follow up:** 294.9 days (9.8 months)	Main outcome was risk of reinfection, defined as a positive PCR test ≥90 days after initial testing. Secondary outcomes were symptomatic infection and protective effectiveness of prior infection. Patients with a negative status who tested positive within 90 days of their initial test were excluded. Infection rates were determined for distinct periods following initial test: 4-5 months; 6-7 months and ≥8 months. Of 62 possible reinfections, 31 were symptomatic (shortness of breath being the most common symptom; no patient lost the sense of smell). 18 were hospitalised within 30 days of the positive test, 5 with symptoms considered related to COVID-19. Of those 5, none required ICU or mechanical ventilation. **Cycle threshold:** N/R **Whole Genome Sequencing:** Not performed	**Risk of reinfection** N=1,278 (14.4%) of the positive patients were retested after 90 days and 62 had possible reinfections. Of those, N=31 (50%) were symptomatic. Of those with negative initial tests, 27.9% (39,487/141,480) were retested and 5,449 (13.8%) were positive **Protective effectiveness** Protective effectiveness of prior infection was 81.8% (95%CI 76.6% to 85.8%)* and against symptomatic infection was 84.5% (95%CI 77.9% to 89.1%). *Effectiveness = 1-((62/8845)/(5449/141480)) **Risk of reinfection over time** ▪ Risk of reinfection was greatest just after 90 days and declined thereafter. ▪ Consequently, effectiveness was lowest in months 4-5 and increased for up to 8 months after infection. Many reinfections occurred close to 90 days after initial infection and average time to reinfection was 138.9±46.3 days (range 90.2 to 294.4 days) Protective effectiveness was lowest in months 4-5 and increased for up to 8 months after infection.
Shields 2021 **10.1177/0022034521102027** **COVID-19: Seroprevalence and**	N=246 (dental practitioners) Maximum f/u: 6 months Baseline seroprevalence was 16.3% in overall cohort of 1,507 individuals	**Serological analysis:** A 'commercially available, CE marked' IgGAM ELISA was used that measures the total antibody response (IgG, IgA and IgM simultaneously) against the spike glycoprotein	**Adjusted risk ratio** for reinfection: 0.25 (95% CI: 0.09 to 0.73)

Vaccine Responses in UK Dental Care Professionals **Published** Healthcare workers **UK**		(Product code: MK654, The Binding Site (TBS), Birmingham) **Reinfection:** RT-PCR was used NIBSC and WHO standards: NIBSC 20/136, the first World Health Organization International Standard for anti-SARS-CoV-2 immunoglobulin and NIBSC 20/162 were employed.	The risk of infection was 9.7% in participants who were seronegative at baseline, compared to 2.9% in individuals who were seropositive (p=0.001) Reinfections only occurred in the absence of specific, detectable anti-spike IgG response Serological analysis: there were no PCR-proven infections in 64 individuals with a baseline anti-SARS-CoV-2 IgG level greater than 147.6 IU/ml (with respect to the WHO international standard NIBSC 20/136). Only 5.3% of the cohort developed an IgG response that exceeded this threshold following the first wave of the UK pandemic. Authors suggest that natural immunity alone is unlikely to generate meaningful, durable herd immunity. Notes on vaccination: ▪ It is notable that 53.9% (n=509/944) had received at least one dose of a SARS-CoV-2 vaccine (Oxford/AstraZeneca, n=20; Pfizer-BioNTech, n= 484; Unknown, n=5) during follow up. Estimates on reinfection risk, however, relate to baseline antibody status prior to vaccination. ▪ Of those vaccinated with a single dose of the Pfizer-BioNTech SARS-CoV-2 were analysed based on prior exposure to the virus - defined by either positive baseline serology, or PCR-proven infection during the follow up period, vaccination on the background of prior exposure to the virus was associated with a more rapid and quantitatively greater total antibody response against the SARS-CoV-2

			spike glycoprotein, consistent with the boosting of immunological memory.

Key: aHR – adjusted hazard ratio; aOR – adjusted odds ratio (adjusted for week group); CI – confidence interval; Ct – cycle threshold value; f/u – follow-up; NAAT – nucleic acid amplification test; RT-qPCR – real time reverse transcription polymerase chain reaction; WGS – whole genome sequencing

Table A4: Data extraction from current version of evidence summary (version 8.0)

Author DOI Title Country Study design Publication status	Population (number of participants, follow-up duration) Patient demographics	Primary endpoints Test parameters: Serial testing intervals SARS-CoV-2 confirmation Serological confirmation Clinical description	Relative risk of reinfection (or Odds Ratio) Adjusted estimates (for covariates) Absolute (/crude) reinfection events Conclusion/relevance
Abdelrahman 2021 DOI: 10.1002/jmv.27156 Persistence of symptoms after improvement of acute COVID19 infection, a longitudinal study Egypt Prospective cohort study Published	COVID-19 positive cases, N = 172 Follow-up: via mobile phone every 2 months for 8 to 10 months. **Definition of reinfection:** N/R **Analysis period:** Tested positive for SARS-CoV-2 during the period from 15 May 2020 to 25 July 2020 and were followed up until March 2021. **Demographics:** Mean age 41.8, 59 male, 113 female. Smoking: ▪ 87.8% non-smokers Comorbid diseases: ▪ diabetes mellitus 13.9% ▪ hypertension 21.5% ▪ chronic obstructive lung diseases 5.8%	**Primary endpoint:** laboratory confirmed COVID-19 re-infection (assessed via phone interview at follow-up periods).	**Absolute (/crude) reinfection events:** During the follow-up, six females (3.5%) had laboratory confirmed COVID-19 re-infection. Their mean age was 35.7 ± 11 years. The mean interval from the complete recovery of the first infection to the onset of the second one was 53 ± 22.2 days with a range from 30 to 90 days. The second infection was milder in severity than the first infection, in 83.33% of cases. **Conclusion/relevance** Re-infection with SARS-CoV-2 can occur after recovery.

	▪ chronic renal failure 2.3% ▪ ischemic heart disease 7% ▪ others 5.8%. **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		
Abo-Leyah 2021 DOI: https://doi.org/10.1183/23120541.00080-2021 The protective effect of SARS-CoV-2 antibodies in Scottish healthcare workers Scotland, UK Prospective observational study Published	**Population** N = 300 (HCWs antibody positive at baseline from a total of 2,063 in a cohort of HCWs (1,763 seronegative at baseline)). Median follow up: NR. Time from the first positive antibody test to the end of the follow-up period was 188 days. Maximum follow up: 6 months. **Definition of re-infection** NR. The single reinfection was detected by RT-PCR 76 days after having detectable antibodies in their serum. **Analysis period:** Recruitment between 28 May 2020 and the 2 September 2020. Followed up until the 2 December 2020 (unless symptomatic for COVID-19 at time of enrolment or had tested positive in the preceding 14 days). Follow up time given as 3 months (time from first antibody test to the	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection. **Test parameters:** *SARS-CoV-2 confirmation:* PCR assays were performed at regional and national laboratories (no details given). *Serological confirmation:* Antibody samples were tested by Siemens SARS-CoV-2 total antibody assay, performed on the Siemens Atellica 1300 platform (found to have 95–100% sensitivity when validated against other commercial antibody platforms). *Clinical description:* Symptomatic at reinfection.	**Risk of reinfection:** 0.03% (1 of 300 detected by RT-PCR 76 days after having detectable antibodies in their serum). **Relative risk of reinfection:** Hazard ratio 0.15, 95% CI 0.06 to 0.35, p=0.026 over a follow-up period of up to 6 months. **Conclusion/relevance** The presence of antibodies was associated with an 85% reduced risk of re-infection with SARS-CoV-2.

	end of the follow-up period was 188 days). **Demographics:** Mean age NR; 76.7% Female* (*Calculated from Table 1 – not reported in paper). Proportion fully vaccinated: N/A **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR (Seroprevalence nationally 4.5%, and seroprevalence of 14.5% in the cohort of 300 HCW)		
Abu-Raddad 2021 Qatar DOI: 10.1101/2021.07.25.21261093 Protection afforded by the BNT162b2 and mRNA-1273 COVID-19 vaccines in fully vaccinated cohorts with and without prior infection.	**Population:** *BNT162b2 (Pfizer-BioNTech):* N=503,969 fully vaccinated individuals with no prior PCR-confirmed infection. Of whom 51,486 were matched (by 5-year age group, sex, nationality and week of first vaccine dose) to prior-infection counterparts. N=52,039 fully vaccinated individuals with prior PCR-confirmed infection. Of whom 51,486 were matched (by 5-year age group, sex, nationality and week of first vaccine dose) to no prior infection counterparts.	**Primary endpoint:** Documented SARS-CoV-2 infection in the national cohort of individuals who completed ≥14 days after the second BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccine dose, in those with and without previous infection. **SARS-CoV-2 confirmation:** Nasopharyngeal and/or oropharyngeal swabs (Huachenyang Technology, China) were collected for PCR testing and placed in Universal Transport Medium (UTM). Aliquots of UTM were: a) extracted on a QIAsymphony platform (QIAGEN, USA) and tested with real-time reverse transcription PCR (RT-qPCR) using TaqPath™ COVID-19 Combo Kits (100% sensitivity and specificity; Thermo Fisher	**Relative risk of reinfection** Incidence rates of infection among BNT162b2-vaccinated persons (Pfizer-BioNTech): ▪ 1.66 (95% CI: 1.26 to 2.18) per 10,000 person-weeks with prior infection (cumulative infection incidence: 0.14% (95% CI: 0.11 to 0.19%)) ▪ 11.02 (95% CI: 9.90 to 12.26) per 10,000 person-weeks without prior infection (cumulative infection incidence: 0.93% (95% CI: 0.83 to 1.04%)) ▪ The incidence rate ratio was 0.15 (95% CI: 0.11 to 0.20). Incidence rates of infection among mRNA-1273-vaccinated persons (Moderna):

Two separate retrospective matched cohort studies. Pre-print	Total follow-up time among BNT162b2-vaccinated persons, with and without prior infection, was 308,086.0 and 305,891.9 person-weeks, respectively. (Approx. 6 weeks per person) *mRNA-1273 (Moderna)* N=222,398 fully vaccinated individuals with no prior PCR-confirmed infection. Of whom 24,052 were matched (by 5-year age group, sex, nationality and week of first vaccine dose) to prior-infection counterparts. N=24,290 fully vaccinated individuals with prior PCR-confirmed infection. Of whom 24,052 were matched (by 5-year age group, sex, nationality and week of first vaccine dose) to no prior infection counterparts. Total follow-up time among mRNA-1273-vaccinated persons, with and without prior infection, was 70,729.9 and 70,872 person-weeks, respectively (Approx. 3 weeks per person). Mean follow-up: 3 weeks (mRNA-1273) and 6 weeks (BNT162b2-) starting from 14 days after the second vaccine dose, until endpoint or end of trial.	Scientific, USA) on an ABI 7500 FAST (ThermoFisher, USA); or b) extracted using a custom protocol on a Hamilton Microlab STAR (Hamilton, USA) and tested using AccuPower SARS-CoV-2 Real-Time RT-PCR Kits (100% sensitivity and specificity; Bioneer, Korea) on an ABI 7500 FAST; or c) loaded directly into a Roche cobas® 6800 system and assayed with a cobas® SARS-CoV-2 Test (95% sensitivity, 100% specificity; Roche, Switzerland). The first assay targets the viral S, N, and ORF1ab regions. The second targets the viral RdRp and E-gene regions, and the third targets the ORF1ab and E-gene regions. **Serological confirmation:** Antibodies against SARS-CoV-2 in serological samples were detected using a Roche Elecsys® Anti-SARS-CoV-2 assay (99.5% sensitivity, 99.8% specificity; Roche, Switzerland), an electrochemiluminescence immunoassay that uses a recombinant protein representing the nucleocapsid (N) antigen for antibody binding. Results were interpreted according to the manufacturer's instructions (reactive: optical density (proxy for antibody titre) cut off index ≥1.0 vs. non-reactive: optical density cut off index <1.0. **Additional testing:** Whole genome sequencing, sangar sequencing and other variant screening methods were used in Qatar at this time for broad surveillance purposes, but were	▪ 1.55 (95% CI: 0.86 to 2.80) 10,000 person-weeks with prior infection (cumulative infection incidence: 0.06% (95% CI: 0.03 to 0.12%)) ▪ 1.83 (95% CI: 1.07 to 3.16) per 10,000 person-weeks without prior infection (cumulative infection incidence: 0.08% (95% CI: 0.04 to 0.15%)) ▪ The incidence rate ratio was 0.85 (95% CI: 0.34 to 2.05). **Absolute reinfection (breakthrough infection) rates** Of 51,486 BNT162b2 vaccinated individuals (without previous infection) in matched cohort, 337 had a breakthrough infection. Of the 51,486 BNT162b2 vaccinated individuals (with previous infection) 51 reinfections were observed. of the 24,052 mRNA-1273-vaccinated individuals (without previous infection) in matched cohort, 13 had a breakthrough infection. Of the 24,052 mRNA-1273 vaccinated individuals (with previous infection) 11 reinfections were observed. **Conclusion:** The results demonstrate low infection incidence among those vaccinated with BNT162b2 or mRNA-1273, but among those vaccinated with BNT162b2, protection against infection was further enhanced and infection incidence was further reduced by prior infection (85% or 6.6 fold reduction in incidence rate). In contrast, those vaccinated with mRNA-1273 were as well protected as those who received the vaccine after a prior infection. These

	Maximum follow-up: 132 days for BNT162b2; ~65 days for mRNA-1273 **Analysis:** *Study period:* 21 December 2020 – 6 June 2021 Every individual that met the inclusion criteria in the national database, that is being vaccinated with BNT162b2 or mRNA1273 and completing ≥14 days after the second vaccine dose, for each of these cohort studies, was classified based on infection status (with or without PCR-positive swab before the start of the study). Individuals were matched based on infection status on a 1:1 ratio by sex, 5-year age group, nationality (>75 nationality groups), and calendar week of first vaccine dose to control for differences in exposure risk and variant exposure. Only matched samples were included in the analysis. **Patient demographics:** Median age (IQR) — years *BNT162b2 (prior infection),* 39 (32-48) *BNT162b2 (no prior infection),* 39 (32-48) *mRNA-1273 (prior infection),* 40 (33-47)	not done specifically on each of the specimens in the included study.	findings may have implications for the potential need of a booster vaccination.

	mRNA-1273 (no prior infection), 40 (33-47). Sex, Male – n (%) *BNT162b2 (prior infection),* 36,970 (71.8) *BNT162b2 (no prior infection),* 36,970 (71.8) *mRNA-1273 (prior infection),* 18,697 (77.7) *mRNA-1273 (no prior infection),* 18,697 (77.7) **Definition of reinfection**: RT-PCR confirmed infection at least 14 days after second dose of vaccine administered, with the primary infection occurring prior to the administration of the first dose. **Predominant variant in circulation:** Alpha (B.1.1.7) and Beta (B.1.351). The weekly rounds of viral genome sequencing from 1 January to 19 May 2021 identified Beta (n=623; 50.9%), Alpha (n=193; 15.8%), Delta (n=43; 3.5%), and wild-type/undetermined variants (n=366; 29.9%) in 1,225 randomly collected, PCR positive specimens. The weekly rounds of multiplex RT-qPCR variant screening from 23		

	March to 10 May 10 2021 identified Beta-like (n=2,605; 66.4%), Alpha-like (n=970; 24.7%), and "other" variants (n=349; 8.9%) in 3,924 randomly collected PCR-positive specimen. **Incidence of SARS-CoV-2:** NR		
Ali 2021 DOI: https://doi.org/10.1016/j.nmni.2021.100926 SARS-CoV-2 reinfection in patients negative for immunoglobulin G following recovery from COVID-19 Iraq Prospective cohort study Published	N = 829 (patients admitted to hospital) Mean follow up: 5.25 months (last week of May until the middle of October 2020). **Definition of reinfection:** Symptomatic persons with the second positive RT-PCR test were considered as re-infected patients. **Demographics:** NR **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR	**Primary endpoint:** RT-PCR-confirmed SARS-CoV-2 reinfection with symptoms. **Test parameters:** PowerChek SARS-CoV-2 Real-time PCR Kit (Kogenebiotech, Seoul, Korea) according to manufacturer's guidelines. When findings regarding the two target genes (ORF1ab, E) were positive according to specific real-time RT-PCR, a sample was defined as positive if the viral genome was detected at the cycle threshold value (Ct-value) of 36.7 or less (initial infection), while the Ct-value of greater 36.7 was defined as indicating a negative test result or recovery (i.e., the disappearance of signs and symptoms in a previously RT-PCR positive patient). The anti-nucleocapsid IgG antibody level was assessed using a commercially available SARS-CoV-2 IgG test kit (Pishtaz TebDiagnostics, Tehran, Iran) targeting the IgG antibody against the nucleocapsid (N) antigen of the SARS-CoV-2 virus. Based on themanufacturer's formula, the following cut-offs were applied: 1.1, positive; 0.9 to 1.1, equivocal; and less than 0.9, negative.	**Absolute (/crude) reinfection events:** 26 patients (14 male and 12 female patients, aged 10–60 years old) were re-infected after recovery with the rate of 3.13%; of these, 25 patients were in the IgG-negative group, and only one patient was IgG-positive. The occurrence of reinfection in the group ranged from 26 to 138 days after recovery from the initial infection. The degree of disease severity in the reinfection period was worse in most patients than during the first instance of COVID-19. The average Ct value of the first infection in those that were re-infected was 31.47. The average Ct value upon reinfection was 22.88. **Conclusion/relevance** A lack of anti-nucleocapsid IgG in patients who have recovered from COVID-19 may lead some to become infected. Also, an immunocompetent male patient showed a serum IgG level of 5.87 s/ca against SARS-CoV-2 nucleocapsid after recovery but was reinfected 138 days later.

			The vast majority of patients who showed detectable levels of anti-nucleocapsid IgG after COVID-19 were thus mostly protected from reinfection, although the time period of the immunity conferred by IgG against SARS-CoV-2 nucleocapsid has not been concluded. While there was just one case of asymptomatic reinfection 4.5 months after the initial recovery amongst patients with detectable anti-nucleocapsid IgG levels, 25 of the 87 patients negative for anti-nucleocapsid IgG were reinfected within one to three months after their first infection.
Armstrong 2021 US DOI: 10.1016/j.lana.2021.100054 Repeat positive SARS-CoV-2 RNA testing in nursing home residents during the initial 9 months of the COVID-19 pandemic: an observational retrospective analysis Retrospective cohort study	**Population:** 6,079 nursing home residents with a previous SARS-CoV-2 infection surviving beyond 90 days of their initial infection. 11,644 SARS-CoV-2 unique cases were recorded among nursing home residents in total. Median follow-up: NR Maximum follow-up: 9 months (304 days) (15 March 2020 to 15 December 2020) **Patient demographics:** Residents with repeat positive tests (n=156) were of a median age of 75 years (range 36–105), 91 were female (58%).	**Primary endpoint:** Repeat RT-PCR positive test results in nursing home residents. **SARS-CoV-2 confirmation:** SARS-CoV-2 RT-PCR and antigen test positivity was determined by each individual laboratory following product guidance specific for each test and platform. Initial positive tests were all RTPCR-based In the case of repeat positive tests which were initially obtained via antigen-based tests, confirmatory RT-PCR results were obtained and reported, when available. **Serological confirmation:** Not conducted **Additional testing:** Not conducted	**Absolute and relative risk of reinfection** Residents with repeat positive tests represented approximately 2.6% (156/6,079) of nursing home residents surviving beyond 90 days of their initial SARS-CoV-2 diagnosis since the start of the pandemic, with a median time to repeat positivity of 135 days (range 90– 245 days). Of these 156 patients who had a repeat positive test, 67% (98/147) had symptom at the time of initial positive test and 35% (44/124) had symptoms at time of the repeat positive test. Deaths were reported in 12.8% (20/156) of residents following the repeat positive test. Of the repeat positive tests, 27.5% (14/51) had Ct values <33, where reported. **Conclusion:** The analysis suggests that repeat positive testing in nursing home populations may exceed those reported in younger age groups. Repeat positive tests beyond 90 days may accompany severe

Published	Proportion fully vaccinated: 0% (study ended prior to vaccination commencement) **Definition of reinfection**: Tested positive for SARS-CoV-2 by RNA-based testing ≥ 90 days after initial positive results **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		outcomes, and should be prospectively investigated with genomic, virologic and additional data, when feasible. The high frequency of repeat positive tests in this group, as compared to younger populations or community dwelling elderly, suggest that immunity may wane more quickly following natural immunity in this demographic.
Banham 2021 DOI: 10.1681/ASN.2021020188 Haemodialysis Patients Make Long-Lived Antibodies against SARS-CoV-2 that May Be Associated with Reduced Reinfection UK Retrospective cohort study Published	N=256 Antibody positive during 1st wave (March to July 2020) N=734 Antibody negative during 1st wave (Total N=990) Average follow up: 6 months Maximum follow up: 305 days (10 months) **Definition of re-infection:** Minimum of 2 months between positive antibody and subsequent PCR test **Demographics (n=990):** Male, 579 (58.5%) Age, median (IQR), 65 (54-75) years	**Primary endpoint:** RT-PCR reinfection **Test parameters:** **Molecular testing:** RT-PCR (not further information provided) **Serology testing** Antibodies against SARS-CoV-2 spike glycoprotein were examined by ELISA in surplus serum from routine clinical samples taken during the first wave. Antibodies (combined IgG, IgA and IgM (IgGAM)) against the SARS-CoV-2 spike glycoprotein were measured using a CE marked, validated, commercially available ELISA (Product code: MK654, The Binding Site (TBS), Birmingham), as per manufacturer's instructions. Prior validation of this assay has shown it demonstrates 100% sensitivity in individuals with PCR-proven disease 7 days post symptom onset	**Risk of reinfection:** 10/237 (4.2%) in seropositive versus 80/700 (11.4%) in seronegative group. **Relative risk of reinfection** Risk ratio, 0.37 (95% confidence interval, 0.19 to 0.70) in seropositive group. **Conclusion/relevance** SARS-CoV-2 antibodies in patients on haemodialysis are well maintained and associated with reduced risk of subsequent SARS-CoV-2 infection

	Charlson Comorbidity Index, median (IQR), 7 (5-8) **Analysis period:** 10 March 2020 to 9 January 2021 **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR	(n=59 hospitalised, n=31 community) and 97.8% specificity based on 270 individual negative pre2019 samples from commercial sources	
Breathnach 2021 DOI: 10.1016/j.jinf.2021.05.024 Prior COVID-19 protects against reinfection, even in the absence of detectable antibodies UK Prospective cohort study Published	N = 224 (RNA-positive, Antibody negative in first wave) N = 2,087 (RNA positive, Antibody positive in first wave) (total laboratory records N= 49,450 patients. 47,139 with no lab evidence of COVID 19 in first wave, 2,054 of these infected in second wave (4.36%). Of the 49,450 patients, 2,311 RNA +ve in first wave, 2,087 were RNA +ve and antibody positive while 224 were RNA +ve but antibody negative). Minimum follow up: 4 months Maximum follow up: 9 months **Definition of re-infection** Initial SARS-CoV-2 infection through laboratory detection of RNA, in the first wave between March and May 2020, but with negative serology	**Primary endpoint:** SARS-CoV-2 RNA test (PCR or other nucleic acid amplification technology) confirmed re-infection in those in the sample RNA-positive, antibody negative in first wave. Re-infection for those in the sample RNA positive, antibody positive in first wave is also reported. **Test parameters:** SARS-CoV-2 RNA test (PCR or other nucleic acid amplification technology). Serology testing carried out to determine the presence of antibodies. **Comparators:** A comparator group of patients with no evidence of infection in the first wave –i.e. negative serology with either a negative or no RNA assay performed - was used to calculate the relative risk of infection in those with and without prior infection. A second comparator group was also examined, who were RNA-positive and antibody-positive in the first wave.	**Risk of reinfection** RNA-positive antibody-negative patients: 2 out of 224 patients reinfected. 0.89% (with ≥90 days between infection events). RNA-positive antibody-positive patients: 18 out of 2,087 patients reinfected. 0.86% (with ≥90 days between infection events). **Relative risk of reinfection* (or Odds Ratio)** RNA-positive antibody-negative patients compared to those with no lab evidence of COVID 19 in first wave: 0.20 (95% CI: 0.05 to 0.81). RNA-positive antibody-positive patients compared to RNA-positive antibody negative patients: 1.04 (95% CI: 0.24 to 4.43). *Relative to those with no previous evidence of infection. **Conclusion/relevance** There was a significantly reduced risk of infection in those with prior SARS-CoV-2 infection but

	results in June and July. SARS-CoV-2 RNA test results (PCR or other nucleic acid amplification technology) between August 2020 and January 2021 were reviewed to identify patients with likely reinfection in the second wave of the UK pandemic. Repeat positive results within 90 days were discounted. **Demographics:** NR Vaccination status: stopped study before rollout of vaccination programme. **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		without detectable antibodies, compare to those with no previous evidence of infection. Our results indicate that antibodies (as detected by routine laboratory assays) are not essential for protection against reinfection.
Caralis 2021 DOI: https://doi.org/10.1177/215013272098 2752 Case Reports of COVID 19 Recurrence US	N=600 patients who tested positive for SARS-CoV-2. Follow up: 6 months (April 12, 2020 to October 21, 2020). **Definition of re-infection:** After 2 months or more re-presented with a positive PCR test of the SARS-CoV-2. **Demographics:** NR	**Primary endpoint:** Reinfection with SARS-CoV-2 confirmed by PCR test. **Test parameters:** The SARS-CoV-2 RNA was detected from nasopharyngeal swab (NPS) during the acute phase of infection. The agent was detected by the BioFire RP2.1 (multiplex PCR technology).	**Risk of reinfection** 1.2% **Absolute (/crude) reinfection events** 7 reinfections. The patients re-tested were COVID-19 PCR positive again an average of 94.9 days (range 62-172 days) from their original presentation and first COVID-19 PCR positive test. **Characteristics of reinfected**

Retrospective cohort study Published	Vaccination status: NR **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		Ages varied widely from 27 to 72 years of age. None of the patients were from community living centres or assisted living facilities. There were 2 women, 2 African Americans, and 4 Hispanics. Three patients could be considered immunocompromised (psoriatic arthritis, renal/liver transplant and HIV (undetectable viral load), and sarcoidosis). Two of those patient were receiving long-term immunosuppressive therapy (Adalimumab, Tacrolimus/Sirolimus). Three patients were insulin-requiring diabetics. Of the seven cases of reinfection: in three cases they presented as asymptomatic at time of reinfection, another two reported fatigue and one reported both fatigue and loss of taste. The final patient report fever and a headache at time of reinfection. **Conclusion/relevance** Patients had tested negative by PCR or had evidence of antibodies in between the 2 episodes. The majority of patients were asymptomatic on the second presentation and were found incidentally on prescreen for procedures, surgery.
Cavanaugh 2021 DOI: 10.15585/mmwr.mm7032e1 Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19	N = 738 previously infected (246 'case-patients' and 492 'controls') Maximum follow-up: 16 months Minimum follow-up: 4 months **Analysis period:** Initially infected during March to December 2020. Follow up period 1 May to 30 June 2021.	**Primary endpoint:** SARS-CoV-2 reinfection. **Test parameters:** nucleic acid amplification test (NAAT) or antigen test.	**Relative risk of reinfection* (or Odds Ratio)** Using conditional logistic regression, ORs and CIs were used to compare no vaccination and partial vaccination with full vaccination among case-patients and controls. Kentucky residents with previous infections who were not vaccinated had 2.34 times the odds of reinfection compared with those who were fully vaccinated (OR= 2.34; 95% CI = 1.58–3.47).

Vaccination — Kentucky, May–June 2021 US Case Control Study Published	**Demographics:** 60.6% female. **Age group, yrs** **Case** **Control** 18–29 46 (18.7) 89 (18.1) 30–39 37 (15.0) 83 (16.9) 40–49 43 (17.5) 80 (16.3) 50–59 44 (17.9) 88 (17.9) 60–69 27 (11.0) 51 (10.4) 70–79 28 (11.4) 58 (11.8) ≥80 21 (8.5) 43 (8.7) Case-patients and controls were matched on a 1:2 ratio based on sex, age (within 3 years), and date of initial positive SARS-CoV-2 test (within 1 week). **Vaccination status:** Among case-patients, 20.3% were fully vaccinated, compared with 34.3% of controls. 6.9% of case-patients were partially vaccinated, compared with 7.9% of controls. Case-patients were considered fully vaccinated if a single dose of Janssen (Johnson & Johnson) or a second dose of an mRNA vaccine (Pfizer-BioNTech or Moderna) was received ≥14 days before the reinfection date. For controls, the same definition was applied, using the reinfection date of		Partial vaccination was not significantly associated with reinfection (OR = 1.56; 95% CI = 0.81–3.01).The lack of a significant association with partial versus full vaccination should be interpreted with caution given the small numbers of partially vaccinated persons included in the analysis (6.9% of case-patients and 7.9% of controls), which limited statistical power. **Conclusion/relevance** The lower odds of reinfection among the partially vaccinated group compared with the unvaccinated group is suggestive of a protective effect and consistent with findings from previous studies indicating higher titers after the first mRNA vaccine dose in persons who were previously infected,. These findings suggest that among persons with previous SARS-CoV-2 infection, full vaccination provides additional protection against reinfection.

	the matched case-patient. Partial vaccination was defined as receipt of ≥1 dose of vaccine, but either the vaccination series was not completed or the final dose was received <14 days before the case-patient's reinfection date. For controls, the same definition was applied. **Eligibility criteria and definition of reinfection:** Kentucky residents aged ≥18 years with SARS-CoV-2 infection confirmed by positive nucleic acid amplification test (NAAT) or antigen test results reported in Kentucky's National Electronic Disease Surveillance System (NEDSS) during March–December 2020 were eligible for inclusion. A case-patient was defined as a Kentucky resident with laboratory-confirmed SARS-CoV-2 infection in 2020 and a subsequent positive NAAT or antigen test result during May 1–June 30, 2021. Control participants were Kentucky residents with laboratory-confirmed SARS-CoV-2 infection in 2020 who were not reinfected through June 30, 2021. **Definition of reinfection:**		

	120 days (4 months) minimum between positive tests **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		
Cohen 2021 DOI: https://doi.org/10.1681/ASN.2021030387 Antibody Status, Disease History, and Incidence of SARS-CoV-2 Infection Among Patients on Chronic Dialysis Prospective cohort study US Published	N = 2,337 adults with end stage kidney disease (ESKD) ▪ N (IgG+/Hx+) = 87 ▪ N (IgG+/Hx-) = 134 ▪ N (IgG-/Hx+) = 17 ▪ N (IgG-/Hx-) = 2,099 Hx+ represents documented medical history of COVID-19 before; Hx- represents no medical medical history of COVID-19 before 6679 patient-months of follow-up since visit 2 (which occurred approx. 3 months after baseline assessment). Mean follow up: 2.86 months, since visit 2 (which occurred approx. 3 months after baseline assessment). Maximum follow-up: approx. 6 months (from baseline assessment) **Demographics**	**Primary endpoint:** Two outcomes were considered. First, any SARS-CoV-2 infection, whether detected during routine clinical surveillance or via a PCR test at Visits 3, 4, or 5. Secondly, only those SARS-CoV-2 infections detected during routine clinical surveillance (hereafter termed clinically manifest COVID-19), because these represent symptomatic infections. **Test parameters:** Patients could undergo PCR testing during the follow-up period via two mechanisms. First, patients could undergo PCR testing as part of their routine care, in response to clinical circumstance (symptomatology or known exposure, as detected by clinic entrance screening) Second, patients underwent monthly surveillance PCRs as part of the study protocol. PCR testing was conducted primarily using saliva samples. Saliva samples were collected using the SDN-1000 Whole Saliva Collection Device (Spectrum Solution, Inc). If a patient was unable to produce a saliva sample, a swab sample (nasal or mid-turbinate) was instead collected in 0.9% physiologic saline. Nucleic acids were extracted using a chemagic 360 Instrument (PerkinElmer, Inc.). SARS-CoV2 RNA in both sample types was detected using the New	**Risk of reinfection:** IgG+/Hx+ = 2.5% IgG+/Hx- = 3.4% IgG+ and/or Hx+ = 5.9% **Unadjusted relative risk of reinfection (or Odds Ratio)** Any SARS=CoV-2 Infection ▪ IgG+ 0.55 (95% CI: 0.32 to 0.95) relative to IgG- ▪ Hx+ 0.53 (95% CI: 0.24 to 1.19) relative to Hx- ▪ IgG+ and/or Hx + 0.51 (95% CI: 0.30 to 0.88) relative to IgG-/Hx- ▪ IgG+/Hx+ 0.61 (95% CI: 0.27 to 1.36) relative to IgG-/Hx- ▪ IgG+/Hx+ 0.51 (95% CI: 0.25 to 1.04) relative to IgG-/Hx- Clinical Manifestation of COVID-19 ▪ IgG+ 0.21 (95% CI: 0.07 to 0.67) relative to IgG-

	Overall: mean age 59.5, 40.4% female. Baseline IgG +: mean age 58.9, 42.5% female. Exposure was ascribed on the basis of the presence or absence of IgG against SARS-CoV-2 at baseline, and separately, a history of documented COVID-19 before study entry. **Definition of re-infection** NR **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR	Coronavirus Nucleic Acid Detection Kit (PerkinElmer, Inc.).	▪ IgG+ and/or Hx + 0.20 (95% CI: 0.06 to 0.62) relative to IgG-/Hx- ▪ IgG+/Hx+ 0.35 (95% CI: 0.11 to 1.09) relative to IgG-/Hx- The above relative risk estimates were not meaningfully affected by statistical adjustment for baseline clinical and demographic factors **Absolute (/crude) reinfection events** IgG+/Hx+ = 6 reinfections IgG+/Hx- = 8 reinfections IgG+ and/or Hx+ = 14 reinfections **Conclusion/relevance** Presence of anti–SARS-CoV-2 IgG (versus its absence) at baseline was associated with lower risk of any SARS-CoV-2 infection (incidence rate ratio, 0.55; 95% confidence interval, 0.32 to 0.95) and clinically manifest COVID-19 0.21 (95% confidence interval, 0.07 to 0.67). Among patients with ESKD, naturally acquired anti–SARS-CoV-2 IgG positivity is associated with a 45% lower risk of subsequent SARS-CoV-2 infection, and a 79% lower risk of clinically manifest COVID-19. Baseline anti–SARS-CoV-2 IgG seropositivity was associated with a lower risk of SARS-CoV-2 infection during follow-up. This association was more potent for clinically manifest COVID-19 during follow-up: 0.21 (95% CI, 0.07 to 0.67). Risk of any SARS-CoV-2 infection during follow-up was not statistically different between participants

			with baseline IgG+/Hx- (i.e., undetected and likely asymptomatic infection) versus IgG+/Hx+ (i.e., clinically detected prior infection).
Cohen 2021 DOI: 10.1101/2021.07.20.21260855 SARS-CoV-2 incidence, transmission and reinfection in a rural and an urban setting: results of the PHIRST-C cohort study, South Africa, 2020-2021 South Africa Prospective cohort Study Preprint	**Population** N= 406 RT PCR or serology positive for SARS-CoV-2 ≥1 (Total cohort n=1,189) Follow-up: 37 and 35 weeks of follow-up depending on site **Definition of re-infection** Possible reinfection defined as >28 to 90 days between rRT-PCR-positive specimens (no sequence data available) or between first seropositive specimen and rRTPCR -positive specimen; probable reinfection as >90 days between rRT-PCR -positive specimens (no sequence data available) or between first seropositive specimen and rRT-PCR -positive specimen; and confirmed reinfection as distinct Nextstrain clades on sequencing or variant PCR between rRTPCR-positive specimens meeting the temporal criteria for possible or probable The proportion of reinfections was calculated as the number of individuals with re-infection divided by the total number of individuals with evidence of prior infection.	**Primary endpoint** Proportion of SARS-CoV-2 reinfections and relative risk of reinfection. **Test parameters:** **RT-PCR** - Mid-turbinate nasal swabs were collected twice-weekly from consenting household. Members irrespective of symptoms and tested for SARS-CoV-2. Specimens were tested by rRT-PCR using the Allplex™ 2019-nCoV kit and a BioRad CFX96 thermal cycler according to manufacturer instructions. From March 2020, samples were tested using the Allplex™ SARS-CoV-2/FluA/FluB/RSV kit. A cycle threshold (Ct) value of <40 on ≥1 of 3 SARS-CoV-2 PCR targets (E,N and RdRp genes) was considered positive. **Testing for Variants** - All confirmed positive samples were tested to identify variants of concern using the Allplex™ SARS-CoV-2 Variants I assay (Seegene Inc). This assay targets the RdRp gene, HV69/70 deletion, N501Y and E484K mutations, thus identifying the B.1.351/P1 (beta/gamma) and B.1.1.7 (alpha) variants. **Antibody test** - Serum was collected every two months. Serologic evidence of SARS-CoV-2 infection was tested by using the Roche ElecsysR Anti-SARSCoV-2 assay, which was performed on the Cobas e601 instrument.	**Risk of reinfection:** 3% (12/406) experienced a re-infection. Of 12 repeat infection episodes, 6 (50%) were classified as possible and 5 (42%) as probable and 1 (8%) confirmed. **Relative risk of reinfection:** Documented infection on rRT-PCR or serology prior to the start of the second wave was associated with 84% protection against infection in the second wave (relative risk (RR) 0.16, 95% CI 0.07 to 0.35. Attack rate in individuals with previous infection was 3% [6/211] vs 18% [177/978] in individuals without previous infection. **Absolute (/crude) reinfection events** Of the 12 reinfections identified during follow up, 4 at the rural site and 8 at the urban site. Median age was 25 years (range 10-70 years), 9 (75%) were female, 3 of 10 with available data were HIV-infected and 1 (1/12) had non-HIV underlying illness. **Conclusion/relevance** Approximately 3% of individuals experienced at least one repeat episode of infection within 9 months of follow up, and infection in the first wave was 84% protective against infection in the second wave. Infection with SARS-CoV-2 Beta variant, was

	Analysis period: Study was conducted from 16 July 2020 to 31 March 2021 in one rural and one urban community. **Demographics:** For the subset of patients who tested positive for SARS-CoV-2 at least once (n=406): Rural participants 167/406 (41%) Urban participants 239/406 (59%) Age <5yrs 35/406 (8.6%) Age 5-12yrs 83/406 (20.4%) Age 13-18yrs 74/406 (18.2%) Age 19-39yrs 102/406 (25.1%) Age 40-59yrs 81/406 (20.0%) 60+yrs 31/406 (7.6%) Male 142/406 (35.0%) Female 264/406 (65.0%) HIV 73/394 (18.5%) Underlying illness 39/406 (9.6%) BMI underweight or normal weight 199/406 (49%) BMI overweight or obese 207/406 (51%)	**Clinical description** Of 254 PCR-confirmed episodes with available data, 17% (n=43) were associated with ≥1 symptom, of which 21% (9/43) were medically attended. Among 222 included households, 161 (73%) had ≥1 SARS-CoV-2-positive individual. 83% of SARS-CoV-2 infections were asymptomatic.	associated with a similar symptomatic fraction to non-variant infection.

	Predominant variant in circulation: Of those with known variant type, 8% (6/80) in the first wave and 95% (142/150) in the second wave were Beta variant). **Incidence of SARS-CoV-2:** In this cohort 406/1189 (34%) tested positive for SARS-CoV-2. The household cumulative infection risk was 16%.		
Comelli 2021 DOI: https://doi.org/10.3390/ijerph18168748 Nasopharyngeal Testing among Healthcare Workers (HCWs) of a Large University Hospital in Milan, Italy during Two Epidemic Waves of COVID-19 Milan, Northern Italy Retrospective observational study Published	**Population** n = 160 positive HCWs from first wave were included in second wave of study. Two study waves (first wave comprising 3378 HCWs (242 positive) and second wave comprising 4465 HCWs (545 positive)). Median follow up: Median time elapsed between the first positive test in the 1st wave and the first positive test in the 2nd wave was 235 days (inter-quartile range 220–253) **Definition of re-infection** Positive nasopharyngeal swab occurring more than 90 days since the first positive nasopharyngeal swab. **Analysis period:**	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection. **Time interval:** Surveillance program for HCWs ran from October 2020 to end January 2021. Reinfection was diagnosed if there was more than 90 days between tests. **Test parameters:** *SARS-CoV-2 confirmation:* Two PCR assays identified the virus by multiplex rRT-PCR targeting three viral genes (E, RdRP and N). The first assay was performed with STARMag Universal Cartridge kit on Nimbus/starlet instrument, and amplification with Allplex® 2019-nCoV assay. The second assay employed a GeneFinder® COVID-19 Plus RealAmp Kit on ELITech InGenius® instrument Cycle quantification values (Cq) were calculated. A cut off of 35 Cq was used. *Serological confirmation:*	**Risk of reinfection:** Nine of 160 HCWs who tested positive in the 1st wave and who repeated NPS during 2nd wave were positive (5.6%, 95% CI: 2.6 to 10.4%). 8 of these had a high Ct value (>35 and positive only for the E gene, possibly indicative of persistent viral shedding): the reinfection rate drops to 1/160 if these are excluded (0.6%, 95%CI 0.2 to 3.4%). The one remaining probable reinfection case had a Ct of 20.8 and was positive for SARS-CoV-2 gene E, N and RdRP. **Risk of reinfection over time:** Median time elapsed between the first positive test in the 1st wave and the first positive test in the 2nd wave was 235 days (inter-quartile range 220–253). **Relative risk of reinfection:** NR **Conclusion/relevance**

	HCWs tested in two waves - 1st wave (24 February 2020 to 1 July 2020) and 2nd wave (from 1 August 2020 to 31 January 2021). **Demographics:** Subgroup not reported on. Proportion fully vaccinated: NR **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:B** NR	SARS-CoV-2 serology was performed with LIAISON SARS-CoV-2 S1/S2 IgG test on LIAISON XL. *Clinical description:* 2 of 9 symptomatic at reinfection.	Risk of reinfection here was found to be broadly consistent with other studies (less than 1%).
Davido 2021 DOI: https://doi.org/10.1093/jtm/taab058 SARS-CoV-2 reinfections among hospital staff in the greater Paris area Paris, France Retrospective cohort study Published	**Population** 236 previously infected HCWs from two earlier waves (71/264 and 165/1847). Median follow up: NR Maximum follow up: approx. 1 year **Definition of re-infection** • Subsequent RT-PCR positive to SARS-CoV-2 >45 days after the initial presentation if the second test is accompanied by compatible symptoms or epidemiological exposure. • Subsequent RT-PCR positive to SARS-CoV-2 >90 days after the initial presentation if the second test is performed among an	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection. **Time interval:** >45 days if symptomatic, >90 if asymptomatic. **Test parameters:** *SARS-CoV-2 confirmation:* TaqPath™ COVID-19 RT-PCR Kit for B1.1.7 variant (from January 2021). From June 2020: • Alinity-m SARS-CoV-2 AMP Kit® for RdRp and N genes • Xpert® Xpress SARS-CoV-2 for E and N genes • BioFire® Respiratory Panel 2.1 plus for S and M genes.	**Risk of reinfection:** 0 recorded (5 suspected of 236 positive cases (2.1%) – 2 false positive, 3 persistent shedding). None of these 5 suspected reinfections involved the Alpha (B.1.1.7) variant of concern. **Relative risk of reinfection:** NR **Conclusion/relevance** Low reinfection rate (0%) felt to be consistent with international literature.

	asymptomatic HCW with a close contact with a person known to have a laboratory-confirmed COVID-19. **Analysis period:** 1 March 2020 to 1 March 2021. **Demographics:** Mean age 39; 71.6% Female Proportion fully vaccinated: NR **Predominant variant in circulation:** NR. The UK variant was uncommon in France at the time of the study ("only reported a few HSMs infected by the UK variant. None of them was suspected case of reinfection. This may be partly explained by the scarcity of the UK variant in France at the time of the study"). **Incidence of SARS-CoV-2:** NR	From March to June 2020: ▪ Non-commercial RT-PCR targeting RdRp gene *Clinical description:* Two asymptomatic and three symptomatic at time of testing.	
Dobano 2021 DOI: https://doi.org/10.1186/s12916-021-02032-2 Persistence and baseline	**Population** 173 HCWs previously infected with COVID-19. Median follow up: NR Maximum follow-up: 12.5 months **Definition of re-infection** Interval >90 days between tests as per CDC guidelines.	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection. **Time interval:** >90 days for likely reinfections. <90 days for suspected reinfections. **Test parameters:** *SARS-CoV-2 confirmation:* Not detailed.	**Risk of reinfection:** 4 of 173 (2.3%) potential reinfections (three likely reinfections, one suspected). Symptomatic reinfection of 2/173 (1.16%). Two symptomatic reinfection cases were seronegative at baseline, one asymptomatic was seropositive with low antibodies, and one had unknown serostatus.

determinants of seropositivity and reinfection rates in health care workers up to 12.5 months after COVID-19 Barcelona, Spain Prospective cohort study Published	**Analysis period:** September 2020 to April 2021 (participants included during March – April 2020). **Demographics:** Median age 47.91 (IQR:41-58); 79.2% Female. Proportion fully vaccinated: Fully vaccinated workers were excluded from the study. **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR	*Serological confirmation:* Levels of IgM, IgA, and IgG to RBD and S recombinant proteins expressed from donated plasmids were quantified in plasma by Luminex. Plates were treated according to protocol. Median fluorescence intensity was reported for each analyte on a Flexmap 3D® reader.	Age range of reinfected: 29 – 58 years. All reinfected were female **Relative risk of reinfection:** NR **Antibody titres:** Not reported. **Conclusion/relevance** Despite heterogeneity in antibody levels induced by SARS-CoV-2 infection, most HCW patients remained seropositive for anti-S antibodies up to 12.5 months after COVID-19. The findings that after PCR reversion, 2 out of 13 seronegative individuals had another symptomatic episode, and that one low responder had a second (asymptomatic) infection, are consistent with a protective role of antibodies.
Finch 2021 SARS-CoV-2 infection and reinfection in a seroepidemiological workplace cohort in the United States DOI:10.1101/2021.05.04.21256609 United States Prospective Cohort	**Population** N=309 tested seropositive (out of n=4411) Follow-up: six months **Definition of re-infection:** Possible reinfection was defined as a new positive PCR test more than 30 days after initial seropositive result **Analysis period:** Between April 2020 and February 2021.	**Primary endpoint** Proportion of SARS-CoV-2 infection and reinfections, odds ratio and adjusted odds ratio for reinfection. **Test parameters:** Serological samples were taken during four rounds of testing between April - September 2020. SARS-CoV-2 IgG receptor-binding domain (RBD) antibody testing with an in-house ELISA assay with 82·4% sensitivity and 99·6% specificity. PCR testing were widely available for employees, with data available from April 2020 - January 2021.	**Rate of reinfection** 14 possible reinfections out of 309 seropositive individuals (4.5%) **Time to reinfection** 14 possible reinfections with a median time of 66.5 days between initial seropositive test and PCR positive test. **Odds ratio for reinfection:** 14 possible reinfections out of 309 seropositive individuals. Adjusted odds ratio of 0.09 (95% CI: 0.005 to 0.48).

Preprint	**Demographics:** No demographics available for subset of patients. For cohort n= 4411 Age range: 18-71 years **Predominant variant in circulation:** Unclear **Seroprevalence of SARS-CoV-2 in cohort:** Adjusted seroprevalence 8.2% (95% CI: 7.3 to 9.1).		**Conclusion/relevance** The presence of SARS-CoV-2 antibodies at baseline is associated with around 91% reduced odds of a subsequent PCR positive test (over a sixth month period).
Flacco 2021 DOI: https://doi.org/10.1093/pubmed/fdab346 Rate of reinfections after SARS-CoV-2 primary infection in the population of an Italian province: a cohort study Italy Retrospective cohort study Published Journal of Public Health	**Population** N= 7173 Mean follow-up: 201 days (>6 months) Minimum follow-up: 90 days Maximum follow-up: 414 days (>12 months) **Definition of re-infection:** Positive PCR test occurring ≥90 days after recovery of the first infection, and with ≥2 consecutive negative test results between episodes. Minimum interval between tests: 90 days. **Analysis period:**	**Primary endpoint:** The incidence of a reinfection, defined as a new positive PCR test occurring ≥90 days after complete resolution of the first infection, and with ≥2 consecutive negative test results between episodes. **Time interval:** ≥ 90 days after compete resolution of the first infection Cases where the subjects younger than 1 year old, the second positive PCR test <90 days, or deceased within 90 days after the resolution of the first infection were excluded. **Test parameters:** PCR samples were tested through nasopharyngeal swabs by the accredited laboratories of Pescara Local Health Unit.	**Risk of reinfection:** 0.33% **Absolute (/crude) reinfection events** 24 participants tested positive among 7173 subjects. Nine of the re-infected subjects received a first vaccine dose during the follow-up. Four reinfections required hospitalisation, one was lethal. Most of the reinfections (n = 13) occurred 6–9 months after the resolution of the first infection; no new infection was detected 12 or more months later and among the 832 minors. Four of the reinfected subjects (0.06%) had a symptomatic COVID-19 requiring hospitalisation, and one died (a 77-year-old woman). **Relative risk of reinfection:** NR The mean age and the proportion of subjects with ≥1 comorbidity were substantially higher among those who were reinfected than those who were

	Study period: March 2020 to May 2021. Subjects who were aged ≥1 year with positive PCR tests of SARS-CoV-2 infection from 3 March 2020 (date of the first positive real-time RT-PCR test) to 90 days before 21 May 2021 (date of data extraction and end of follow-up) in the Province of Pescara, Italy were identified. **Demographics:** Mean age 46.3, 48.0% males 1478 (20.6%) were diagnosed with ≥1 comorbidity over the previous 10 years. Proportion fully vaccinated: None 1783 participants who received the first vaccine dose during the follow-up. **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		not (mean age: 54.5 ± 18.4 versus 46.3 ± 21.8 years and 41.7% versus 20.6%, respectively). **Conclusion/relevance** The study observed a 0.33% reinfection rate among general population who recovered from a previous infection (symptomatic or asymptomatic) during the first 15 months of SARS-CoV-2 pandemic. Most of the episodes were asymptomatic or paucisymptomatic, and only one subject deceased after the second infection (0.01%). Their findings are in line with previous evidence on a low risk of SARS-CoV-2 reinfection.
Gallais 2021 DOI:	**Population** 393 previously infected HCWs and 916 non-infected HCWs (total of 1309). **Definition of re-infection:**	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection. **Time interval:** Assessed at one month after onset of first case. Thereafter at M3-6, M7-9, and M11-13). **Test parameters:**	**Risk of reinfection:** One of 393 was reinfected (0.3%) over a nine month course (incidence of 0.40 per 100 person-years). First infection Ct=17, second infection Ct=34.

https://doi.org/10.1016/j.ebiom.2021.103561 Evolution of antibody responses up to 13 months after SARS-CoV-2 infection and risk of reinfection Strasbourg, France Prospective longitudinal cohort study Published	Not stated. Confirmed by positive RT-PCR. **Analysis period:** Up to 13 months with recruitment between April and May 2020. **Demographics:** Median age 39 (IQR: 30-51); 76.8% Female. Proportion fully vaccinated: 14.6% (vaccination ongoing throughout study). **Predominant variant in circulation:** NR. Three waves - March to June 2020, September 2020 – January 2021 and from March 2021 onwards, with the last wave due to the B1.1.7 variant. **Incidence of SARS-CoV-2:** NR	*SARS-CoV-2 confirmation:* Performed in house with SARS-CoV-2 specific primers and probes targeting two regions on the viral RNA-dependent RNA polymerase (RdRp) gene. *Serological confirmation:* Biosynex (COVID-19 BSS IgG/IgM) Lateral Flow Assay (LFA), and the EDI Novel coronavirus COVID-19 IgG ELISA. Confirmed on Abbott Architect SARS-CoV-2 IgG II Quant assay. *Additional testing:* Live-virus neutralisation assay was performed on sera collected at M11-13 from a panel of 28 COVID-19 positive HCW, including 13 who had received a single dose of COVID-19 vaccine *Clinical description:* One reinfected person was asymptomatic.	**Relative risk of reinfection:** The incidence of SARS-CoV-2 infections was 12.22 and 0.40 per 100 person-years in COVID-19-negative and COVID-19-positive HCW, respectively, indicating a relative reduction in the incidence of SARS-CoV-2 reinfection of 96.7%. (hazard ratio (HR): 4.053 (95% CI: 2.437 to 6.743); $p < 0.0001$. [Note: includes those who were in baseline seronegative group who seroconverted, if restricted to infection confirmed by RT-PCR, HR changes to 3.966 (95%CI: 2.099 to 7.494; $p < 0.0001$)]. **Antibody titres:** Anti-RBD titers decayed by 0.07, 0.04 and 0.02 log BAU/mL per month from M1 to M3-6, M3-6 to M7-9 and M7-9 to M11-13. **Conclusion/relevance:** This study suggests that COVID-19 positive patients develop a humoral immune response that reduces the risk of SARS-CoV-2 reinfection within at least one year.
Gazit 2021 DOI: 10.1101/2021.08.24.21262415 Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus	**Population** Overall, group 1 - 673,676 individuals 16 years and older were eligible for the study group of fully vaccinated SARS-CoV-2-naïve individuals (no prior infection); group 2- 62,883 were eligible for the study group of unvaccinated previously infected individuals; group 3- 42,099 individuals were eligible for the study	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection or breakthrough infection. **SARS-CoV-2 Confirmation** RT-PCR (further information on assay used not provided) **Additional tests** Not conducted	**Relative risk of reinfection:** *Model 1 – previously infected vs. vaccinated individuals, with matching for time of first event* After adjusting for comorbidities, we found a statistically significant 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection as opposed to reinfection (P<0.001). Apart from age ≥60 years (OR 2.7, 95% CI, 1.68 to 4.34), there was no statistical evidence that any of the

breakthrough infections Israel Retrospective cohort study Preprint	group of previously infected and single-dose vaccinated. **Three different models:** *Model 1 – previously infected vs. vaccinated individuals, with matching for time of first event (either the time of administration of the second dose of the vaccine or the time of a positive RT-PCR test result, both occurring between January 1, 2021 and February 28, 2021).* Reference group – the group 1 participants: fully vaccinated (BioNTech/Pfizer mRNA BNT162b2), without prior infection (n=16,215 matched in model 1) *Age years, mean* (SD), 36.1 (13.9) *Female, no. (%)*, 7,428 (45.8) *Comorbidities, no (%),* Hypertension, 1,569 (9.7) CVD, 647 (4) Diabetes Mellitus, 877 (5.4) Immunocompromised, 420 (2.6) Obesity (BMI ≥30), 3,073 (19) CKD, 271 (1.7)		assessed comorbidities significantly affected the risk of an infection during the follow-up period. 191 breakthrough symptomatic infections and 8 symptomatic reinfections occurred. After adjusting for comorbidities, a 27.02-fold risk (95% CI, 12.7 to 57.5) for symptomatic breakthrough infection as opposed to symptomatic reinfection was observed (P<0.001). None of the covariates were significant, except for age ≥60 years. Nine cases of COVID-19-related hospitalisations were recorded, 8 of which were in the vaccinated group and 1 in the previously infected group. No COVID19-related deaths were recorded. *Model 3 - previously infected vs. partially vaccinated (1 dose) and previously infected individual* Those previously infected and received a single dose of the vaccine had a significant 0.53-fold (95% CI, 0.3 to 0.92) decreased risk for reinfection vs. those infected without vaccination, as 20 had a positive RT-PCR test, compared to 37 in the previously infected and unvaccinated group. No covariates were statistically significant for infection. Symptomatic disease was present in 16 single dose vaccinees and in 23 of their unvaccinated counterparts. One COVID-19-related hospitalisation occurred in the unvaccinated previously infected group. No COVID-19-related mortality was recorded.

	COPD, 97 (0.6) Cancer, 636 (3.9) Comparator group – the group 2 participants: unvaccinated, with previous infection (n=16,215 matched in model 1) *Age years, mean* (SD), 36.1 (13.9) *Female, no. (%)*, 7,428 (45.8) *Comorbidities, no (%),* Hypertension, 1,276 (7.9) CVD, 551 (3.4) Diabetes Mellitus, 635 (3.9) Immunocompromised, 164 (1) Obesity (BMI ≥30), 3,076 (19) CKD, 196 (1.2) COPD, 65 (0.4) Cancer, 324 (2) *Model 2 –previously infected vs. vaccinated individuals, without matching for time of first event (i.e., either vaccination or infection)*		A sub-analysis was conducted, where the single-dose vaccine was required to be administered after the positive RT-PCR test. This subset represented 81% of the previously-infected-and-vaccinated study group. When performing this analysis, a similar, though not significant, trend of decreased risk of reinfection was observed, with an OR of 0.68 (95% CI, 0.38 to 1.21, P-value=0.188). **Relative risk over time** *Model 2 –previously infected vs. vaccinated individuals, without matching for time of first event* 640 breakthrough infections and 108 reinfections occurred. After adjusting for comorbidities, a 5.96-fold increased risk (95% CI, 4.85 to 7.33) increased risk for breakthrough infection as opposed to reinfection could be observed (P<0.001). Apart from SES level (0R 1.07, 95% CI: 1.03 to 1.11) and age ≥60 (OR 2.2, 95% CI: 1.66 to 2.92), that remained significant in this model as well, there was no statistical evidence that any of the comorbidities significantly affected the risk of an infection. 484 symptomatic breakthrough infections and 68 symptomatic reinfections occurred. There was a 7.13-fold (95% CI, 5.51 to 9.21) increased risk for symptomatic breakthrough infection than symptomatic reinfection. COVID-19 related hospitalisations occurred in 4 and 21 of the reinfection and breakthrough infection groups, respectively.

	Reference group - the group 1 participants: fully vaccinated (BioNTech/Pfizer mRNA BNT162b2), without prior infection (n=46,035 matched in model 2) *Age years, mean* (SD), 36.1 (14.7) *Female, no. (%)*, 22,661 (49.2) *Comorbidities, no (%),* Hypertension, 4,304 (9.3) CVD, 1,830 (4) Diabetes Mellitus, 2,300 (5) Immunocompromised, 849 (1.8) Obesity (BMI ≥30), 8,610 (18.7) CKD, 814 (1.8) COPD, 292 (0.6) Cancer, 1,364 (3) Comparator group - the group 2 participants: unvaccinated, with previous infection (n=46,035 matched in model 2) *Age years, mean* (SD), 36.1 (14.7) *Female, no. (%)*, 22,661 (49.2)		Vaccinated individuals had a 6.7-fold (95% CI: 1.99 to 22.56) increased to be admitted compared to recovered individuals. Being 60 years of age or older significantly increased the risk of COVID-19-related hospitalisations. No COVID-19-related deaths were recorded. **Absolute risk of reinfection** *Model 1 – previously infected vs. vaccinated individuals, with matching for time of first event* 238/16,215 (1.47%) breakthrough infections and 19/16,215 (0.12%) reinfections occurred. *Model 2 –previously infected vs. vaccinated individuals, without matching for time of first event* 640/46,035 (1.39%) breakthrough infections and 108/46,035 (0.23%) reinfections occurred. *Model 3 - previously infected vs. partially vaccinated (1 dose) and previously infected individual* 20/14,029 (0.14%) of the partially vaccinated and previously infected group had a positive RT-PCR test, compared to 37/14,029 (0.26%) in the previously infected and unvaccinated group. **Conclusion/relevance** This study demonstrated that natural immunity confers longer lasting and stronger protection against infection, symptomatic disease and hospitalisation caused by the Delta variant of SARS-CoV-2, compared to the BNT162b2 two-dose vaccine-induced immunity. Individuals who were both previously infected with SARS-CoV-2 and

	Comorbidities, no (%), Hypertension, 4,009 (8.7) CVD, 1,875 (4.1) Diabetes Mellitus, 2,207 (4.8) Immunocompromised, 527 (1.1) Obesity (BMI ≥30), 9,117 (19.8) CKD, 1659 (1.4) COPD, 218 (0.5) Cancer, 1,044 (2.3) *Model 3 - previously infected vs. partially vaccinated (1 dose) and previously infected individual* Reference group - the group 2 participants: unvaccinated, with previous infection (n=14,029 matched in model 3) *Age years, mean* (SD), 33.2 (14) *Female, no. (%)*, 7,467 (53.2) *Comorbidities, no (%),* Hypertension, 892 (6.4) CVD, 437 (3.1) Diabetes Mellitus, 529 (3.8)		given a single dose of the vaccine gained additional protection against the Delta variant.

	Immunocompromised, 127 (0.9) Obesity (BMI ≥30), 2,599 (18.5) CKD, 137 (1) COPD, 30 (0.2) Cancer, 241 (1.7) Comparator group – the group 3 participants: partially vaccinated (1 dose of BioNTech/Pfizer mRNA BNT162b2), with previous infection (n=14,029 matched in model 3) *Age years, mean* (SD), 33.2 (14) *Female, no. (%)*, 7,467 (53.2) *Comorbidities, no (%),* Hypertension, 1,004 (7.2) CVD, 386 (2.8) Diabetes Mellitus, 600 (4.3) Immunocompromised, 145 (1) Obesity (BMI ≥30), 2,772 (19.8) CKD, 162 (1.2) COPD, 53 (0.4) Cancer, 267 (1.9)		

	Median follow-up: NR Maximum follow-up: for models 1 and 3 = 225 days (1 Jan until 14 Aug 2021) Maximum follow up: for model 2 = 531 days (1 Mar 2020 until 14 Aug 2021) **Definition of re-infection** RT-PCR confirmed infection between 1 January and 28 February 2021 and again between 1 June and 14 August 2021 (minimum of ~90 days between two positive tests). **Analysis period:** Study period: 1 March 2020 – 14 August 2021 (outcomes were evaluated between 1 June 2021 and 1 August 2021). The study population included members of the Maccabi Healthcare Services healthcare system aged 16 or older who were fully vaccinated prior to 28 February 2021, who had a documented SARS-CoV-2 infection by 28 February 2021, or who had both a documented SARS-CoV-2 infection by 28 February 2021 and received one dose of the vaccine by 25 May 2021, at least 7 days before the study period.		

	The fully vaccinated group was the comparison (reference) group in our study. Groups 2 and 3, were matched to the comparison group 1 in a 1:1 ratio based on age, sex and residential socioeconomic status. **Predominant variant in circulation:** Delta variant (during the period of outcome evaluation that is 1 June until 14 August 2021). **Incidence of SARS-CoV-2:** NR		
Gehring 2021 DOI: https://doi.org/10.21203/rs.3.rs-688656/v1 An Epidemiological Cohort Study of SARS-CoV-2 and COVID-19 in German Healthcare Workers – Interim Analysis after Six Months of Follow-up Mainz, Germany	**Population** n = 98 (HCWs antibody positive at baseline from a total of 3,664 in a cohort of HCWs). Median follow up: 101 days for entire cohort. NR for antibody positive at baseline. **Definition of re-infection:** NR for reinfection specifically. Virologically confirmed COVID-19 disease was defined according to the US Food and Drug Administration (FDA) guidance as an acute illness with positive SARS-CoV-2 RT-PCR test and at least one symptom suggestive of COVID-19.	**Primary endpoint:** Assess the seroprevalence and seroconversion rates of SARSCoV-2 infection, as measured by anti-SARS-CoV-2 antibodies, and the rate of virologically confirmed COVID-19 disease before the introduction of COVID-19 vaccines. **Time interval:** 5 months. **Test parameters:** *SARS-CoV-2 confirmation:* RT-PCR testing performed in own hospital laboratory (details NR). *Serological confirmation:* Serum samples were collected at baseline and in all follow-up visits for serological two-step testing of anti-SARS-CoV-2 IgG and IgM antibodies: first using ARCHITECT® i2000SR (Abbott Laboratories), and if positive or borderline-positive, re-tested using Elecsys® Anti-SARS-CoV-2 (Roche Diagnostics).	**Risk of reinfection:** 0 recorded. **Relative risk of reinfection:** NC **Antibody titres:** NR. Out of 98 HCWs who were seropositive at baseline, ~ 11% and ~ 15% seroreverted by weeks 6 and 12 of follow-up, respectively. Out of 98 seropositive healthcare workers at baseline, 12 subjects later seroreverted by follow-up visit 2 and 14 seroreverted by follow-up visit 3. **Conclusion/relevance:** Although an apparent waning in humoral immune response against SARS-CoV-2 was observed, evidence of reinfections was not detected.

Prospective cohort study Published	**Analysis period:** August 2020 – January 2021 **Demographics:** NR for antibody positive at baseline. For total cohort: Mean age 39.1; 75.3% Female Proportion fully vaccinated: Study completed before vaccination. **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		
Glück 2021 DOI: 10.1007/s15010-021-01703-9 Immunity after COVID-19 and vaccination: follow-up study over 1 year among medical personnel Germany Prospective cohort study Published	N = 136 hospital employees who recovered from a RT-PCR-confirmed COVID-19 episode between April and June 2020. Follow-up: approx. 12 months. **Demographics:** Majorly directly involved in patient care, of younger/middle age. Median age 38 (IQR, IQR 29–49) years, 64% female Generally healthy (15/130 (12%) with a chronic condition according to self-assessment. None of the study participants required inpatient care during the acute COVID-19-illness. 10/130 (8%), 50/130 (38%) and 70/130 (54%) of	**Primary endpoint:** SARS-CoV-2 reinfection, SARS-CoV-2-specifc antibody levels, spikeprotein-reactive memory T cells. **Time intervals and testing parameters:** After written informed consent, directly after recovery, and after approximately 12, 30 and 48 weeks, participants were asked to provide a serum sample (S-Monovette, Sarstedt, Nümbrecht, Germany), and additionally at approximately 30 weeks also a heparin-anticoagulated whole-blood sample for analysis of cellular immunity (LH Monovette, Sarstedt, Nümbrecht, Germany). At each blood sampling date, participants were asked to report their COVID-19-specifc symptoms in structured questionnaires. SARS-CoV-2-specifc antibody levels were measured by ELISA over 1 year among 136 health care workers infected during the first COVID-19 wave and in a	**Absolute (/crude) reinfection events:** 0 reinfections observed **Risk or reinfection:** During the whole observation period, none of the study participants developed a symptomatic reinfection. Only 7/136 (5%) of study participants developed no measurable antibody response directly after infection. Nearly 1 year after symptom onset (median 333 (IQR 320–345) days) the proportion of seronegative individuals increased to 21/98 (21%). Levels of SARS-CoV-2-specifc IgM- and IgA-antibodies showed a rapid decay over time, whereas IgG-antibody levels decreased more slowly. Among individuals with history of COVID-19, booster vaccination induced very high IgGand to a lesser degree IgA-antibodies. Antibody levels

	study participants rated their symptoms during the acute COVID-19 illness as severe, moderate and minor, respectively. **Analysis Period:** Between 9 April 2020 and 3 June to 29 April 2021. **Vaccination status:** Between December 31, 2020 and April 29, 2021, 56/136 (41%) of study participants received a single dose vaccination; 19 (34%), 17 (30%) and 20 (36%) received the Vaxzevria (Oxford/Astra-Zeneca), Comirnaty (BioNTech) and Spikevax (Moderna), vaccines respectively. **Definition of reinfection:** NR **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR	subgroup after booster vaccination approximately 1 year later**.**	were significantly higher after booster vaccination than after recovery from COVID-19. **Conclusion/relevance** No reinfections were observed among the study participants, but given the generally low reinfection rates, the number of individuals included is clearly insufficient for drawing conclusions which of the studied immunological parameters might indicate protection from reinfection. Such parameters are an important topic of current multicentre studies with considerably higher numbers of participants.
Graham 2021 DOI: https://doi.org/10.1	**Population** N= 36 509 reported a positive swab test before 1 October 2020. (out of 1,767,914 users)	**Primary endpoint:** The proportion of infections on COVID Symptoms or disease duration, rates of reinfection, and transmissibility associated with B.1.1.7 variant in the UK.	**Risk of reinfection:** 0.7% (95% CI 0.6% to 0.8%) **Absolute (/crude) reinfection events**

016/S2468-2667(21)00055-4 Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study England Ecological study Published	Median follow-up: NR Maximum follow-up: NR Data was collected for complete 13 weeks (from Sept 28 to Dec 27, 2020) **Definition of re-infection** Possible reinfection: The second positive PCR test was reported more than 90 days after the first positive PCR test, with a period of reporting no symptoms for more than 7 days before the second positive test. The proportion of possible reinfections among individuals who reported their first positive test before Oct 1, 2020 was calculated. **Analysis period:** Study period: From Sept 28 to Dec 27, 2020. **Demographics:** Mean age 48.4 59.2% Female Proportion fully vaccinated: NR **Predominant variant in circulation:** The SARS-CoV-2 variant B.1.1.7 **Incidence of SARS-CoV-2:** NR	**Time interval:** The presence of two reported positive tests separated by more than 90 days. **Test parameters:** Swab result (by PCR or Lateral-flow test)**.** The proportion of SARS-CoV-2 infections with the Alpha variant across the UK was estimated with use of genomic data from the COVID-19 Genomics UK Consortium and data from Public Health England on spike-gene target failure (a proxy measure for the Alpha variant) in community cases in England.	Of the 36 509 individuals who reported a positive swab test before Oct 1, 2020, possible reinfections were identified in 249 users for whom there was a period of at least 7 symptom-free days in between positive tests. But there was no evidence that the frequency of reinfections was higher for the B.1.1.7. **Conclusion/relevance** 249 potential reinfection cases were observed, accounting for a very low incidence of reinfection rate 0.7%. The reinfection rate did not vary across regions or time, which is consistent with the hypothesis that reinfection is no more likely associated with the B.1.1.7 variant. No change in symptoms or disease duration was found in the context of SARS-CoV-2 B.1.1.7 variant. Reinfection occurrences were more positively correlated with the overall regional rise in cases (Spearman correlation 0.56 to 0.69 for South East, London, and East of England) than with the regional increase in the proportion of infections with the B.1.1.7 variant (Spearman correlation 0.38 to 0.56 in the same regions), suggesting B.1.1.7 does not substantially alter the risk of reinfection.

Havervall 2021 DOI: https://doi.org/10.1111/joim.13387. Robust humoral and cellular immune responses and low risk for reinfection at least eight months following asymptomatic to mild COVID-19 Stockholm, Sweden Prospective longitudinal cohort study Published	**Population** n = 252 of 370 HCWs antibody positive at baseline assessed for reinfection with weekly PCR testing. 48 uninfected HCWs included in testing as controls. Total cohort consists of 2149 HCWs and 118 hospitalized COVID-19 patients. **Definition of re-infection** NR **Analysis period:** 12 consecutive weeks between December 7th and Feb 26th, 2021. Participants were included between April 9th – June 8th, 2020. **Demographics:** For subset of 370 HCW ≥ 8 months post infection median age 44 years (IQR 34-53 years). Proportion fully vaccinated: NR (those who were vaccinated were not considered to be risk of infection/reinfection). **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection. **Time interval:** Followed for 12 weeks, having been positive for at least seven months. **Test parameters:** *SARS-CoV-2 confirmation:* Participants collected nasal and oropharyngeal swabs and saliva in a 1 ml tube with storage buffer. Samples were mixed with Trizol, RNA were extracted using PSS magLEAD 12gC, after which RT-qPCR was performed. *Serological confirmation:* Serological assays were performed utilizing a bead-based high-throughput multiplex assay based on the FlexMap3D (Luminex Corp.) platform. Based on a separate method validation using 331 positive control samples collected at least 17 days after symptom onset or positive qPCR-test and 2090 negative control samples collected before 2020, the sensitivity and specificity were determined to be 99.7% (330 of 331 positive, 98.3-100.0, 95% CI) and 98.1% (2050 of 2090 negative, 97.4-98.6, 95% CI).	**Risk of reinfection:** 1% (3/252) among anti-spike IgG positive HCW (0.13 cases per 100 weeks at risk) compared to 23% (11/48) among anti-spike IgG negative HCW (2.78 cases per 100 weeks at risk). **Relative risk of reinfection:** The incident rate ratio was 0.05 (95% CI 0.01-0.18), with a protective effect of 95.2% (95% CI 81.9-99.1%) for HCWs that were seropositive at baseline. **Antibody titres:** NR for reinfection subgroup study. **Conclusion/relevance:** Findings support a broad immune memory for at least eight months following asymptomatic to mild COVID-19. The presence of antispike IgG is associated with a reduced risk of reinfection up to nine months following asymptomatic to mild COVID-19.

Kohler et al 2021 DOI:10.1101/2021.06.09.21258422 Impact of baseline SARS-CoV-2 antibody status on syndromic surveillance and the risk of subsequent Covid-19 – a prospective multicentre cohort study Northern and Eastern Switzerland Prospective cohort study Preprint	**Population** N= 144 seropositive at baseline from n=4818 health care workers (HCW); 2713 HCW with ≥1 SARS-CoV-2 test during follow-up, whereof 67 HCW were seropositive at baseline. Median Follow-up: median follow-up of 7.9 months **Definition of re-infection:** We cannot definitely confirm that the three seropositive HCWs with positive SARS-CoV-2 NPS were indeed re-infected with a new strain. However, the long latency between the episodes, new onset of symptoms (two cases), and a negative PCR between episodes (one case) strongly support our hypothesis of re-infection (rather than persistence of viral RNA for more than 6 months). **Analysis period:** 22 June to 20 October 2020 recruitment. Followed up until 9 March 2021. **Demographics:** Median age for seropositive group vs seronegative group at baseline: 35.8 (2.9 % female) vs 39 (97.1% female)	**Primary endpoint** Proportion of reinfected cases. Risk of reinfection for those with positive serology compared to those with negative serology at baseline. **Test parameters:** *Serology testing:* Detection of total antibodies directed against the nucleocapsid-(N)-protein of SARS-CoV-2 (ECLIA, Roche Diagnostics). *PCR testing/rapid antigen tests:* Self-reported.	**Risk of reinfection** 4.5%, 3 out of 67 seropositive patients who underwent testing tested positive during follow up. 20.7% 547 of the 2646 seronegative tested participants. **Relative risk of reinfection:** RR of 0.22 (95%-CI: 0.07 to 0.66, P=0.002) for a positive SARS-CoV-2 test after positive baseline serology. Baseline seropositive HCWs, compared to baseline seronegative HCWs, less frequently reported impaired olfaction/taste (6/144, 4.2% vs. 588/4674, 12.6%, RR 0.33, 95% CI: 0.15 to 0.73), chills (19/144, 13.2% vs. 1040/4674, 22.3%, RR 0.59, 95% CI: 0.39 to 0.90), and limb/muscle pain (28/144, 19.4% vs. 1335/4674, 28.6%, RR 0.68 95% CI: 0.49 to 0.95). **Time to re-infection:** Three cases with presumable re-infection after positive baseline serology were all diagnosed in January 2021 after a follow-up (i.e. time from baseline serology to second positive SARS-CoV-2 test) of 198, 200, and 220 days. **Symptomology of reinfection:** One of the three re-infected HCWs was asymptomatic at time of re-infection. All three were between 40 and 55 years of age. Two male and one female **Conclusion/relevance**

	Comorbidity for seropositive group vs seronegative group at baseline: 58/144 (40.3%) 1661/4674 (35.5%)). Gender female in seropositive group: 108/144 (75%) Gender female in seronegative group: 3655/4674 (78%) **Proportion vaccinated**: None. Participants only included up to first dose of any SARS-CoV-2 vaccine or the end of the observation period, whichever came first. **Predominant variant in circulation:** Although no sequencing data for available, reinfections occurred in January 2021, when the proportion of the B.1.1.7 variant was estimated to account for less than 20% of all SARS-CoV-2 isolates in Switzerland **Seroprevalence of SARS-CoV-2:** At baseline in this cohort 3% (144/4818)		We conclude that anti-nucleocapsid antibodies convey an approximately 80% protection against symptomatic SARS-CoV-2 infection, at least for a period of 8 months and in a setting where "new variant" mutations were not widely present at the end of follow-up.
Kojima 2021 DOI: 10.1101/2021.07.03 .21259976 Incidence of Severe Acute Respiratory Syndrome Coronavirus-2	**Population** (1) SARS-CoV-2 naïve (no prior infection) and unvaccinated (n=4,313) (2) previous SARS-CoV-2 infection, unvaccinated (n=254)	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection/breakthrough infection. **Test parameters:** *SARS-CoV-2 confirmation* PCR assays were performed on a Food and Drug Administration-authorised test. The workforce was screened daily.	**Risk of reinfection/breakthrough infection:** Group 1 (SARS-CoV-2 naïve (no prior infection) and unvaccinated) had an incidence of 25.9 per 100 person years (95% CI: 22.8 to 29.3). A total of 254 infections occurred among 4,313 individuals (5.9%). Group 2 (previous SARS-CoV-2 infection and unvaccinated) had an incidence of 0 per 100

infection among previously infected or vaccinated employees US Retrospective cohort study Preprint	(3) fully vaccinated (either the BNT162b2 or mRNA-1273 vaccines) without previous infection (n=739) Median follow-up: NR Maximum follow-up: 221 days for groups 1 and 2, and 419 days for group 3. **Definition of re-infection** NR **Analysis period:** Study period: 8 May 2020 until 15 December 2020 (for groups 1 and 2), and from 8 May 2020 until 1 July 2021 for group 3. **Demographics:** Median age 29 years (IQR, 23.6-39.9 years); **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** Group 1 (SARS-CoV-2 naïve (no prior infection) and unvaccinated) had an incidence of 25.9 per 100 person years (95% CI: 22.8-29.3).	*Other testing* Not conducted.	person-years (95% CI: 0 to 5.0). No reinfections occurred (0%). Group 3 (fully vaccinated) had an incidence of 1.6 per 100 person-years (95% CI: 0.04 to 4.2). A total of 4 breakthrough infections occurred among 739 individuals. **Relative risk of reinfection:** The IRR of reinfection among those with previous infection compared to SARS-CoV-2 naïve (no prior infection) was 0 (95% CI: 0 to 0.19). The IRR of those vaccinated compared to SARS-CoV-2 naïve (no prior infection) was 0.06 (95% CI: 0.02 to 0.16). The IRR of those vaccinated compared to prior SARS-CoV-2 was not estimable due to zero events in the previously infected group. **Conclusion/relevance** Previous SARS-CoV-2 infection and vaccination for SARS-CoV-2 were associated with decreased risk for infection or re-infection with SARS-CoV-2 in a routinely screened workforce. There was no difference in the infection incidence between vaccinated individuals and individuals with previous infection. Further research is needed to determine whether results are consistent with the emergence of new SARS-CoV-2 variants
Kute 2021 DOI: 10.6002/ect.2021.0284	**Population** N=1,350 kidney transplant recipients recovering from COVID-19	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection. **Test parameters:**	**Risk of reinfection** 13/1,350 (0.9%); 6 of whom subequently died (46%).

A Multicentre Cohort Study of Indian Centers on Reoccurring SARS-CoV-2 Infections in Kidney Transplant Recipients India Retrospective cohort study Published	Median follow-up: 135 days (4.5 months) Maximum follow-up: NR **Definition of re-infection** Two successive SARS-CoV-2 RT-PCR tests >48 hours apart were negative before the second episode (RT-PCR confirmed) parallel with clinical convalescence **Analysis period:** April 2020 – May 2021 **Demographics (n=13 reinfected):** Median ages (IQR), 46 (28-50) years Men, 8 (62%) Comorbidities were present in 11 patients (84.6%) and included arterial hypertension (84.6%; n = 11), diabetes (23%; n = 3), allograft dysfunction (84.6%; n = 11), hypothyroid (15.4%; n = 2), heart disease (15.4%; n = 2), hepatitis C virus (7.7%, n = 1), and retransplant (15.4%; n = 2). Multiple comorbidities were present in 8 patients (61.5%), with hypertension and diabetes being the most common. **Predominant variant in circulation:**	*SARS-CoV-2 confirmation* RT-PCR from nasopharyngeal (nasal) and oropharyngeal (throat) swabs in the first and second infections. *Other testing* Not conducted.	Eleven patients had both (first and second) COVID-19 episodes after transplant; 2 had their first COVID-19 episode before transplant while on dialysis and a second episode after transplant. Median time interval from transplant to first episode of COVID-19 diagnosis was 9.2 months (IQR, 2.2-46 months). The median time interval between the first episode and the second episode based on COVID-19-positive RT-PCR tests was 135 days (IQR, 71-274 days) without symptoms. **Ct values** ***Median (IQR)*** First episode, 24 (24-26) Second episode, 24 (18-26) **Conclusion/relevance** Recurrent episodes of COVID-19 were symptomatically more severe than the first episode in this population of kidney transplant recipients

	NR **Incidence of SARS-CoV-2:** NR		
Lawandi 2021 DOI: https://doi.org/10.1093/cid/ciab671 Suspected Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCOV-2) Reinfections: Incidence, Predictors, and Healthcare Use Among Patients at 238 US Healthcare Facilities,1 June 2020 to 28 February 2021 US Retrospective cohort study Published Clinical Infectious Diseases	**Population** N= 131,773 patients received ≥1 positive SARS-CoV-2 PCR result Median follow-up: NR Maximum follow-up: 12 months **Definition of re-infection:** Suspected reinfection was defined as ≥2 positive SARS-CoV-2 PCR test results no less than 90 days apart. **Analysis period:** Study period: 1 March 2020 to 28 February 2021. Adult patients aged ≥18 years who underwent SARS-CoV-2 polymerase chain reaction (PCR) testing at a participating healthcare facility were identified from a subset of 247 healthcare. Facilities. Patients with a sole SARS-CoV-2 infection were compared with those with a suspected reinfection. **Demographics of suspected reinfection patients:** Mean age: 45, 64.8% Female	**Primary endpoint:** The incidence and associated healthcare utilisation of suspected SARS-CoV-2 reinfection**;** the evolution and predictors of reinfection risk over time. **Time interval:** The last recorded positive PCR test result (for the index encounter) was the start date for the 90-day interval before the reinfection risk period. Patients with positive SARS-CoV-2 PCR test result occurred after 30 November 2020 were excluded**.** **Test parameters:** Patients underwent SARS-CoV-2 polymerase chain reaction (PCR) testing at a participating healthcare facility.	**Risk of reinfection:** Incidence of suspected reinfection: 0.2% **Absolute (/crude) reinfection events** 235 out of 131,773. More patients with suspected reinfection were female (64.8%, (hazard ratio for suspected reinfection in women vs men, 1.579 [95% CI: 1.283 to 1.941]; P < .001). There was no significant difference in cumulative risk of reinfection between patients <65 versus ≥65 years of age, nor by geographic region or testing rate. Patients with suspected reinfection were less likely to have received remdesivir and corticosteroids during their index infection ((remdesivir, 2.8% vs 7.1%, respectively [P = .007]; corticosteroids, 11.0% vs 23.3% [P < .001]). The same proportions of patients with suspected reinfections were diagnosed for acute respiratory failure for their suspected reinfection and for their index infection encounters (5.1% vs 5.1%; P = .21). Six patients with suspected Reinfections (2.6%) needed intensive care unit admission and/or non-invasive positive pressure ventilation, and <5

	Comorbid conditions ▪ Any 51 (32.5%) ▪ Cancer <5 ▪ Stage 3 CKD 11 (7.0%) ▪ COPD 7 (4.5%) ▪ Immunocompromise <5 ▪ Obesity/overweight 19 (12.1%) ▪ Pregnancy <5 ▪ Diabetes 30 (19.1%) ▪ Asthma <5 ▪ Interstitial lung disease <5 ▪ Heart failure 18 (11.5%) ▪ Cerebrovascular disease <5 ▪ Hypertension 19 (12.1%) Proportion fully vaccinated: NR **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** 8.8% (131,773 out of 149,2545)		patients needed mechanical ventilation within a day after admission. Of patients with suspected reinfection, 7 died during their suspected reinfection encounter (2.8%). **Conclusion/relevance** 253 patients (0.2%) had suspected reinfection. Women displayed a higher cumulative reinfection risk. Healthcare burden and illness severity were similar between index and reinfection encounters. But patients tend not to be markedly sicker in subsequent episodes. The majority of reinfections required the same level of care as the initial infection. Geographic differences in reinfection rates, stratified by month were not identified.
Leidi 2021 DOI: 10.1101/2021.08.06.21261419 Occupational risk of SARS-CoV-2 infection and reinfection during the second pandemic surge: a cohort study.	**Population** N=784 seropositive individuals from a total of n=10,457 essential workers; n=3,057 workers requiring sustained physical proximity; n=3,645 requiring regular brief contact; n=3,755 classified as "other essential occupations". Mean follow-up: 27.6 weeks (193 days) for seropositive cohort and 27.9 (195 days) weeks for seronegative cohort.	**Primary endpoint:** The number of virologically-confirmed (RT-PCR or antigen) infections from serological assessment, according to baseline antibody status, and stratified by three pre-defined occupational groups (occupations requiring sustained physical proximity, involving brief regular contact or other. **Test parameters:** *SARS-CoV-2 confirmation* RT-PCR or RADT on nasopharyngeal swabs *Serological confirmation*	**Absolute Risk of reinfection:** After a follow-up period of over 27 weeks, 5 (0.6%) seropositive and 830 (8.5%) seronegative individuals had a positive SARS-CoV-2 test, with an incidence rate of 0.2 (95% CI 0.1 to 0.6) and 3.2 (95% CI 2.9 to 3.4) cases per person-week, respectively. Incidences were similar across occupational groups. All infections in seropositive individuals were considered likely reinfections by adjudicators.

Retrospective cohort study Switzerland Preprint	Maximum follow-up: approx. 269 days (from 1 May 2020 until 25 January 2021). **Definition of re-infection** Positive RT-PCR or RADT in seropositive individuals were clinically investigated by two independent adjudicators and classified as likely or unlikely reinfections. **Analysis period:** Study period: participants recruited from a sero-survey cohort between May and September 2020. Follow-up occurred until 25 January 2021. **Demographics:** *Seropositive individuals (n=748)* Women, 423 (57%) Mean age (SD), 43.9 (10.9) years *Seronegative individuals (n=9,709)* Women, 5,399 (55.6%) Mean age (SD), 44.5 (10.6) years Proportion fully vaccinated: 0% (patients recruited prior to commencement of vaccination programme, no information on vaccination uptake during the follow-up period). **Predominant variant in circulation:**	Seropositivity was first assessed by the detection of IgG antibodies against the S1 domain of SARS-CoV-2 spike protein using a commercially available ELISA (Euroimmun, Lübeck, Germany, #EI 2606-9601 G, cut-off for positivity ≥4.0, for negativity <0.8). Cases with intermediate results were tested for total Ig antibodies (IgG/A/M) against the virus nucleocapside protein using the Elecsys® anti-N assay (Roche Diagnostics, Rotkreuz, Switzerland, #09 203 079 190, cut-off for positivity >1.1, for negativity <0.8). Finally, still indeterminate cases were subject to a recombinant immunofluorescence assay (rIFA). This algorithm was designed to minimize false positive and false negative results at the individual level based on commercially available tests at the time of recruitment as well as practical constrains given the large number of participants. **Additional testing** Not conducted	**Adjusted estimates** Seropositive essential workers had a 93% reduction in the hazard (HR of 0.07, 95% CI 0.03 to 0.17) of having a positive test during follow-up compared with seronegative workers, with no significant between-occupational group differences. **Conclusion/relevance** A ten-fold reduction in the hazard of being virologically tested positive was observed among anti-SARS-CoV-2 seropositive essential workers regardless of their sector of occupation, confirming the seroprotective effect of a previous SARS-CoV2 exposure at least six months after infection.

	NR **Incidence of SARS-CoV-2:** Serological assessment (May to September 2020) took place during low SARS-CoV-2 incidence (<300 weekly cases), but follow-up assessment took place during very high incidence (peaking >6,500 weekly cases in early November).		
Mei 2021 DOI: https://doi.org/10.3389/fmed.2021.617689 Health Issues and Immunological Assessment Related to Wuhan's COVID-19 Survivors: A Multicenter Follow-Up Study China Retrospective study Published	**Population** N= 3,677 COVID-19 survivors Median follow-up: 144 days (>4 months) Minimum follow-up: 135 days Maximum follow-up: 157 days **Definition of re-infection:** Survivors with positive PCR test for SARS-CoC-2 during follow-up **Analysis period:** Study period: from January 18 to July 24, 2020. All patients with confirmed COVID-19 infection who were discharged from four hospitals (Wuhan No.1 Hospital, Wuchang Hospital, Zhongshang Hospital, and Hubei Province Hospital) in Wuhan, China were included.	**Primary endpoint:** Post-COVID-19 sequelae among the discharged patients and related potential risk factors. **Time interval:** Within the maximum follow-up 157 days. **Test parameters:** RT-qPCR for SARS-CoV-2 was performed on nasopharyngeal / oropharyngeal swabs twice for each patient with at least a 24-h interval between samples. Both sequential tests must be negative before discharge from hospital. During follow up RT-qPCR for SARS-CoV-2 was performed on nasopharyngeal/ oropharyngeal swabs for viral detection. Viral RNA was extracted from the patients' nasopharyngeal/oropharyngeal swabs. CT imaging and SARS-CoV-2 retesting occurred, or upon personal requests, or for other reasons such as entering medical facilities and community centers. Also, the patient was tested at least once during Fangcang-medical monitoring.	**Risk of reinfection:** 1.2% (45 out of 3677) **Absolute (/crude) reinfection events** Median age: 57 years; 68.9% female. The median duration between initial hospital discharge and retest positivity was 32.0 days (IQR = 28.0–40.0, range = 9–58). 21 survivors in this retest-positive subgroup were asymptomatic During their intial hospitalizaiton,19 of the 45 survivors had mild disease, 24 had severe condition, and two had critical condition. 24 had at least one symptom associated with COVID-19, the most common being dyspnea, cough, and chest tightness. All 45 retest-positive survivors were alive were alive at the end of the follow up with no new viral transmission was observed. **Antibody titres:** Two of the 45 retest-positive survivors had both IgG and IgM antibodies, 26 were IgG-positive and IgM-negative, two were IgG-negative and IgM-

	Demographics: Mean age 59; 54.1% female Proportion fully vaccinated: NR **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR	The colloidal gold-based immunochromatographic strip assay (IGCSA) was used for immunoglobulin G (IgG) and immunoglobulin M (IgM) detection.	positive, and the remaining 15 were negative for both antibodies. During follow-up, a dramatic reduction of anti-SARS-CoV-2 IgG (88.0%, 95% CI: 84.2 to 90.4) and IgM (93.2%, 95% CI: 88.5 to 96.4) antibodies was observed. **Conclusion/relevance:** 1.2% rate of COVID-19 retest positivity among all COVID-19 survivors, with no new viral transmission. Persistent and often severe morbidity is prevalent among COVID-19 survivors. Individuals with post-viral sequelae may have reduced quality of life, including lost productivity, and may continue to strain health care systems.
Murillo-Zamora 2021 DOI: https://doi.org/10.1186/s12879-021-06643-1 Symptomatic SARS-COV-2 reinfection: healthcare workers and immunosuppressed individuals at high risk Mexico	N = 99,993 recovered SARS-CoV-2 patients (adults aged 20 years or above). Mean follow up – 82.7 days. Adults whose symptoms appeared from March to June 2020 and who recovered to primary infection were analysed. **Definition of re-infection** Symptomatic reinfection of SARS-COV-2 and was defined by the reappearance of symptoms of COVID-19 at 28 days or more after initial laboratory-confirmed illness and a positive RT-qPCR result during second-time illness.	**Primary endpoint:** The main binary outcome was symptomatic laboratory-confirmed reinfection of SARS-COV-2. **Test parameters:** laboratory-confirmed (quantitative reverse transcription polymerase chain reaction, RT-qPCR).	**Risk of reinfection** The overall risk of SARS-COV-2 symptomatic reinfection was 0.21%. **Adjusted relative risk of reinfection (or Odds Ratio)** Increasing age was associated with a reduced risk of reinfection (RR per year=0.99997, 95% CI: 0.99814 to 0.99958). Severe primary illness was associated with a reduced risk of reinfection (RR=0.9989, 95% CI: 0.9981 to 0.9997). When compared with homemakers, healthcare workers (RR=1.0042, 95% CI: 1.0030 to 1.0055) and other healthcare-related employees

A nationwide and retrospective cohort study Published	**Demographics of cohort (n=99,993):** Mean age 42.2, 50.9% female. Comorbid diseases: ▪ Obesity 18.5% ▪ Type 2 diabetes mellitus 13.1% ▪ Arterial hypertension 17.8% ▪ Immunosuppression 1.2% ▪ Chronic kidney disease 1.5% ▪ Chronic obstructive pulmonary disease 1.1% ▪ Asthma 3.1% ▪ Cancer (any site) 0.3% Vaccination status: NR **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		(RR=1.0025, 95% CI: 1.0012 to 1.0039) showed an increased reinfection risk. High-risk conditions included the personal history of immunosuppression (RR=1.0038, 95% CI: 1.0011 to 1.0065) or chronic kidney disease (RR=1.0039, 95% CI: 1.0016 to 1.0063). **Characteristics of SARS-CoV-2 reinfected** Mean age 39.2+/- 10.4 years, 52.9% female. **Absolute (/crude) reinfection events** n=210 and the incidence density was 2.5 reinfections per 100,000 person-days. The mean elapsed days (±standard deviation) between both COVID-19 episodes was 61.0±31.0 and ranged from 28 to 116 days. Mild subsequent illness was documented in 169 patients (80.5%), and severe disease in 41 of reinfected subjects and the observed fatality rate was 4.3% (n=9). **Conclusion/relevance** The results suggest that symptomatic SARS-COV-2 reinfection is a rare phenomenon. Patients with SARS-COV-2 reinfection were younger and were more likely to be healthcare professionals or other related employments. They were also more likely to have had milder symptoms at primary disease and had a significantly higher prevalence of chronic kidney disease or immunosuppression (any cause except for type 2 diabetes mellitus or kidney disease).

Narrainen 2021 DOI: 10.7861/clinmed.2021-0225 The protective effect of previous COVID-19 infection in a high-prevalence hospital setting UK Retrospective Cohort Study Published	N=115 individuals previously infected (N=538 healthcare workers on wards with COVID-19 outbreaks. N=423 individuals with no evidence of previous infection) Median follow-up: 131 days (approx. 4.4 months). Minimum follow-up: 99 days (approx. 3.3 months). Maximum follow-up: 168 days (approx. 5.6 months). **Demographics:** Median 40 years, 88% female. Included individuals had a similar exposure risk. PPE use was the same on all wards. **Analysis period:** Initial infection - 1 March 2020 to 31 July 2020 Follow-up period - 29 September 2020 and 20 November 2020. **Definition of reinfection:** Individuals were included if they worked on a ward during a period of high prevalence (an outbreak ward) and had close clinical contact with patients.	**Primary endpoint:** laboratory confirmed COVID-19 re-infection **SARS-CoV-2 confirmation** From March 2020 onwards, symptomatic HCWs were tested for SARS-CoV-2 using PCR testing of combined nasal and oropharyngeal or oropharyngeal swabs (according to the assay used). Criteria for testing changed throughout the pandemic in line with evolving evidence and overall capacity for testing. Screening for infection occurred on a number of occasions in outbreak areas when it became apparent that transmission during asymptomatic infection was common. Testing capacity limited screening on some occasions. Screening of asymptomatic staff typically occurred at a one-off time point as soon after unexpected or widespread transmission had been identified, as testing capacity allowed. PCR testing was performed on a number of platforms according to availability, capacity and urgency of the test result. Assays used include an in-house assay (E gene), the Cepheid GeneXpert (N2 gene and E gene), Luminex Aries (ORF1ab gene and N gene), Genmark Eplex (N gene), Seegene Startlet (E gene, RdRP gene and N gene), Roche (ORF1ab gene and E gene), Perkin Elmer (ORF1ab gene and N gene) and the Bosphore (ORF1ab gene and E gene). In the early phase of the pandemic, the majority of samples were processed on the in-house assay. Later on, the majority of samples were processed on the Seegene. **Serological testing**	**Risk of reinfection** One out of 115 individuals previously infected developed infection compared with 104 out of 423 individuals with no evidence of previous infection. The single case of reinfection occurred in a symptomatic individual who tested positive by PCR at the beginning of April 2020 (Roche assay, ORF1/a not detected. E gene CT value 37), by antibody serology in June (level 146 on Roche Elecsys Anti-SARS-CoV-2 assay) and again by PCR (Aries, ORF1/a CT value 23. N gene CT value 25) in late October, tested because of presence of new symptoms. **Relative risk of reinfection* (or Odds Ratio)** The attack rate was 0.87% in the 'evidence of previous infection' group compared to 24.59% in the 'no evidence of previous infection' group (odds ratio 0.027, 95% CI 0.004– 0.195, p<0.001) **Conclusion/relevance** Prior SARS-CoV-2 infection offers significant protection against reinfection and this protection lasts 4 months for the majority of individuals.

	Reinfection was defined as infection during the second wave in the 'evidence of previous infection' group. Individuals were categorised according to infection status following the first wave of infections in the area (1 March 2020 to 31 July 2020) as: • 'Evidence of previous infection' – a positive PCR result or a positive antibody test or • 'No evidence of previous infection' – a negative antibody test and no evidence of a previous positive PCR result. Individuals were further categorised according to infection status after a period of high prevalence in their ward during the second wave (29 September 2020 to 20 November 2020) as: • 'Infected in the second wave' – a positive PCR result or • 'Not infected in the second wave' – a negative PCR result or no PCR test carried out. This equates to a minimum gap of 60 days between first positive antibody/PCR test and second positive PCR test	SARS-CoV-2 antibody assay testing programme was conducted in the health board during the period from 2 June 2020 to 7 July 2020. Serum anti-SARS-CoV-2 antibody was detected using either the EUROIMMUN Anti-SARS-CoV-2 ELISA assay or the Roche Elecsys Anti-SARS-CoV-2. A cut-off index ≥1.0 is considered reactive or positive for anti-SARS-CoV-2 antibodies.	

	Predominant variant in circulation: NR **Incidence of SARS-CoV-2:** NR		
Peghin 2021 DOI:10.1007/s10096-021-04335-x Low risk of reinfections and relation with serological response after recovery from the first wave of COVID-19 Italy Prospective longitudinal study Published	N = 546 Patients diagnosed of COVID-19 with positive PCR tests were included. Median follow up: 10 months **Analysis period**: March 2020 to February 2021 **Demographics** 53.5% female, median age 53 years Comorbidities, number, n (%) ▪ 0 - 259 (47.4) ▪ 1 - 163 (29.8) ▪ 2 - 69 (12.6) ▪ 3 - 35 (6.4) ▪ ≥ 4 - 20 (3.7) **Definition of re-infection** Clinical reinfection was defined as clinical recurrence of symptoms compatible with COVID-19, accompanied by a positive PCR test (Ct < 35), more than 90 days after the onset of the primary infection, supported by close contact exposure or outbreak settings, and no evidence of another cause of infection.	**Primary endpoint:** RT-PCR-confirmed SARS-CoV-2 reinfection. **Test parameters:** Monthly serological follow-up during the first 4 months, and then at 6, 8, and 10 months after. Serum concentrations of the anti-SARS-CoV-2 specific antibodies IgG and IgM were assessed using iFlash-SARS-CoV-2 (Shenzhen YHLO Biotech Co., Ltd., China, distributed in Italy by Pantec SRL). In accordance with the manufacturer's instructions, the IgM and IgG thresholds for positivity were considered to be 10.0 kAU/L. Participants with symptoms were referred for a PCR test for SARS-CoV-2. Systematic SARS-CoV-2 PCR test was performed at regular intervals (every 2/4 weeks) only for healthcare workers (HCWs) in accordance to Hospital and Nursing homes/long-term facility protocols.	**Risk of reinfection** 1.1%. **Absolute (/crude) reinfection events:** 6 out of 546 patients. **Antibody titer:** One patient had a high-titer serological response against SARS-CoV-2 at the time of reinfection. **Conclusion/relevance** All had a previous history of mild COVID-19 (all were healthcare workers) and reinfection occurred a median of 9 months (IQR 8.2–10.2) after the onset of the first episode. Reinfection rates did not differ significantly in seronegative. (2/56, $n = 3.6\%$), seroreverted (2/137, 1.5%), or seropositive (2/353, 0.6%) patients ($p = 0.085$) but were significantly higher in HCWs than in non-HCWs (6/119, 5.0% versus 0/385, $p < 0.001$). All reinfections were mild ($n = 5$) or asymptomatic ($n = 1$). Only one patient had a high-titer serological response against SARS-CoV-2 at the time of reinfection.

	Epidemiological reinfection was defined as any positive PCR test (Ct < 35) more than 90 days from first episode, regardless of symptoms. **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		
Peltan et al 2021 DOI: 10.1371/journal.pone.0251214 Evaluation of potential COVID-19 recurrence in patients with late repeat positive SARS-CoV-2 testing Retrospective cohort study US Published	N=23,176 RT-PCR positive patients Median follow up: 85.5 (74–107) days. Max follow up: 222 days (7.5 months) **Analysis period**: 11 March to 31 July 2020 **Demographics (N=114 population)** Age, median (IQR) 40 (20-56) Female sex, 64 (56.1%) **Definition of re-infection** A positive SARS-CoV-2 RT-PCR performed ≥60 days after the initial positive assay, and adjudication of the clinical likelihood of acute COVID-19 at the time of both the initial positive test and the recurrent positive test.	**Primary endpoint:** RT-PCR recurrence. **Test parameters:** RT-PCR. Study used a range of assays (CDC, Quidel, Cepheid, Thermo Fsichser Scientific, Hologic, Biofire, Roche), targeting a range of genes N, ORF, E, S, according to manufacturer's guidance.	**Risk of reinfection** 10/23,176 (0.04%) – probable or possible recurrence based on virologic data 114/23,176 (0.49%) – clinical likelihood of recurrence **Absolute (/crude) reinfection events:** Recurrent COVID-19 was probable by purely *clinical criteria* in 14 patients (12.3%), possible in 30 (26.3%), and unlikely in 70 (61.4%). Based on stringent final determination criteria, 4 patients were deemed probably recurrence, 6 were deemed possible recurrence. The incidence of probable or possible COVID-19 recurrence was therefore 4.3 (95% CI 2.1–7.9) cases per 10,000 COVID-19 patients. Median interval to the recurrent positive test was 85.5 (74–107) days. Ct values on repeat positive SARS-CoV-2 RT-PCR increased in most 95/114 (83%) patients **Antibody titer:** NR

	"Probable" or "possible" recurrence by clinical assessment was *confirmed* by the final recurrence likelihood only if a Ct value obtained ≥60 days after initial testing was lower than its preceding Ct or if the patient had an interval negative RT-PCR. All other patients were classified as "unlikely" recurrence. **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		**Conclusion/relevance** Only 0.04% of all COVID-19 patients in this health system experienced probable or possible recurrence; 90% of repeat positive SARS-CoV-2 RT-PCRs were not consistent with true recurrence.
Rennert 2021 DOI: https://doi.org/10.1093/cid/ciab454 Risk of SARS-CoV-2 reinfection in a university student population US Retrospective cohort study Published	N= 2,010 Positive PCR test at baseline. Follow up – ranges from approx. 2.8 months to 8.5 months. **Analysis period**: Initial tests period: 19 August to 5 October 2020. Follow-up period: 28 December 2020 to 1 May 2021. Reinfections without a confirmatory negative test between original infection and reinfection were excluded. **Demographics** Mean age 20.30, 51.4% female.	**Primary endpoint:** Reinfection confirmed through negative polymerase chain reaction test between original infection and reinfection. **Test parameters:** Repeated SARS-CoV-2 testing was mandated for all students. PCR tests: anterior nasal swabs or saliva tests.	**Risk of reinfection** 1.6% **Adjusted relative risk estimates (for covariates)** 0.12 (95% CI: 0.09 to 0.17) relative to the negative group for the autumn 2020. Adjusted for age, gender, testing compliance (measured as percentage of eligible periods tested), and residential status. We estimated protection against repeat infection as 1 – adjusted RR of SARS-CoV-2 infection. **Absolute (/crude) reinfection events** 33 reinfection cases. **Conclusion/relevance**

	Definition of re-infection NR **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		Median time to reinfection was 129 days (range: 86-231 days).
Ringlander 2021 DOI: https://doi.org/10.1080/23744235.2021.1957143 Recurrent and persistent infection with SARS-CoV-2 – epidemiological data and case reports from Western Sweden, 2020 Sweden Retrospective cohort study Published	N = 6,014 Mean follow up: 7 months. **Analysis period**: From 6 February to 31 August 2020. **Demographics** Mean age of patients tested twice >50 days apart 62.1 years. **Definition of re-infection** A negative PCR result in between two positive PCR results, and/or more than two mutations per month in serial samples, determined by SARS-CoV-2 whole genome sequencing, indicate a new infection, rather than intra-host evolution in persistent infection. Patients were included if >50 days passed between samples and if they had at least one initial SARS-CoV-2 positive sample.	**Primary endpoint:** reinfection with SARS-CoV-2 confirmed by whole genome sequencing. **Time interval:** Sequences of SARS-COV-2 from samples were taken with more than 50 days intervals. **Test parameters:** Tests were performed on nasopharyngeal, oropharyngeal and lower respiratory samples by either an in-house one-step real-time PCR or the Roche Cobas 6800 assay (Roche Diagnostics, Rotkreuz, Switzerland). **Serological confirmation** Samples with cycle threshold above 36 were not eligible for sequencing as our experience from sequencing clinical samples is that samples with higher values, i.e. low amount of virus, do not provide a full and representative consensus sequence. RNA was extracted from nasopharyngeal samples using a total nucleic acid extraction kit on the MagnaPure LC 2.0 instrument (Roche Life Sciences, Branchburg, NJ).	**Risk of reinfection:** 0.02% **Absolute (/crude) reinfection events:** 1/6014 patients testing positive during the period. The incidence was 1.34 (95% CI, 1.26–1.42) per 10,000 person-weeks, i.e. one case during a follow-up of 74,776 person-weeks. Fifteen patients with two SARS-COV-2 PCR positive samples >50 days apart were not eligible for whole genome sequencing, due to low viral loads in the second samples. Of the 5 patients with cycle threshold values low enough to qualify for whole genome sequencing 1 concluded reinfection, 3 concluded persistent infection and 1 was a technical failure. **Conclusion/relevance** One patient had a second infection with a different viral strain. There were eight nucleotide differences between the virus genomes from the two time points, and SARS-CoV-2 PCR was negative in a sample taken in between. At the time of reinfection, the patient had very low levels of

	Predominant variant in circulation: NR **Incidence of SARS-CoV-2:** NR	The five subjects with sequenced samples are described regarding timing of sampling and results from sequencing.	IgG antibodies to the SARS-CoV-2 N antigen routine test, in clinical diagnostics interpreted as uncertain results as they were in the range between negative and positive cut-off values, and low titres of neutralizing antibodies. The re-infected patient had mild symptoms during the second episode, which might reflect partial immunity.
Rivelli 2021 DOI:10.1101/2021.09.07.21263100 Incidence of COVID-19 reinfection among Midwestern healthcare employees US Prospective cohort Study Preprint	**Population** N= 2,625 with at least one positive PCR test. Median Follow-up: 167.6 days (5.6 months). **Definition of re-infection** Defined by CDC guidelines : subsequent COVID-19 infection ≥ 90 days from prior infection Participants with more than two documented SARS-CoV-2 positive PCR results, the second documented infection that was closest to 90 or more days from the prior infection was also included. **Analysis period:** From March 1 2020 to January 10, 2021. The entire study period was counted as 315 days (the number of days between earliest positive PCR test result and study end). **Demographics:**	**Primary endpoint**: Incidence of COVID-19 reinfection. **Test parameters:** PCR assay: Aptima Panther SARS-CoV-2 Assay. Antibody assay: SARS-CoV-2 IgG Abbott Architect. Assay (sensitivity of 98.7% and specificity of 99.2%.)	**Risk of reinfection:** 5.94% (156/2625) experienced reinfection. Incidence rate of COVID-19 reinfection was 0.35 cases per 1,000 person-days. Cumulative incidence of reinfection within 10 months was 5.94% overall, 6.70% among COVID-clinical participants, 6.23% among clinical participants, and 1.73% among non-clinical participants. **Time to re-infection:** Median days were 126.50 (105.50-171.00) to reinfection. Number of days post 90-day reinfection cut-off duration for reinfection: • 0-29 Days: 67 (42.95%) • 30-59 Days: 27 (17.31%) • 60-89 Days : 31 (19.87%) • 90+ Days : 31 (19.87%) **Demographics of reinfected:** Median age 36.5 (29-46), mean age 37.83 (10.64). Males 14 (8.97%), female 142 (91.03%).

	▪ Age: ≥ 18 years ▪ Mean Age (SD): 38.26 (11.62) years ▪ Median Age (IQR): 36 (29-47) years ▪ Male: 361 (13.75%) ▪ Female: 2264 (86.25%) ▪ Ethnicity: ▪ Non-Hispanic White: 1970 (77.69%) ▪ Hispanic: 183 (7.21%) ▪ Non-Hispanic Asian: 181 (7.13%) ▪ Non-Hispanic Black: 94 (3.70%) ▪ Non-Hispanic Mixed: 108 (4.25%) ▪ Non-Hispanic American Indian: 3 (0.12%) **Proportion vaccinated**: none **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		**Conclusion/relevance** COVID-19 reinfectionis rare, even among a sample of healthcare workers with frequent exposure. Participants working in COVID-clinical and clinical units experiencing 3.77 and 3.57 times, respectively, greater risk of reinfection relative to those working in non-clinical units.
Ronchini 2021 DOI: 10.1101/2021.09.24.21263978 Italy	**Population** N=266 infected individuals in the pre-vaccination period (of a total of 1,493 included) (N=2,029 individuals included post-vaccination, however unclear how	**Primary endpoint**: reinfection in the positive cohort or a primary infection in the negative cohort, determined by PCR test **Test parameters:** **SARS-COV-2 detection in respiratory specimens**	**Risk of reinfection:** 8/266 (3%) putative reinfections. 7 of the 8 re-infected subjects were IgG+ at the time of enrolment. All Ct values > 30, where reported. When considering only individuals testing positive for more than one SARS-CoV-2 gene in the PCR

Lower probability and shorter duration of infections after Covid-19 vaccine correlate with anti-SARS-CoV-2 circulating IgGs Prospective cohort study Preprint	many of those were previously infected). Maximum follow up: 6 months for pre-vaccination cohort **Definition of re-infection** A possible reinfection was defined as a participant with two positive PCR samples with a negative PCR between the two positive PCR samples and considering a positive PCR after 60 or more days. **Analysis period:** Pre-vaccination period: April 2020 until January 2021. Post-vaccination period: January to June 2021 **Demographics (pre-vaccination cohort):** Age, median (IQR), 41 (31-49) Male, 499 (34.4%) **Proportion vaccinated**: Unclear **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR	quantitative PCR (qPCR) detection of viral genes, using the Allplex SARS-CoV-2 Assay (Seegene) on nasopharyngeal or saliva samples **Serological tests for SARS-COV-2** Humoral immunity was measured by testing levels of IgGs against the receptor binding domain (RBD) of the spike protein using an in-house ELISA assay. assay showed high sensitivity (95.2 %) and specificity (97.6%) that allowed monitoring IgG levels over time in healthy people as well as in Covid-19 patients with accuracy and reproducibility.	assay, the frequencies of re-infection decreased significantly to 1% (2/266, **Relative risk of reinfection:** Subjects that were IgG+ at the time of enrolment had 66% significantly lower probability of having a positive swab (OR=0.34, 95%CI: 0.14- 0.80, P=0.014 **Conclusion/relevance** The probability of infection after vaccination is rare and significantly less frequent compared to reinfection after natural immunity, in particular in responders, which are the vast majority. However this study was not designed to compared vaccine and natural immunity-induced immunity.
Rovida 2021 Italy	**Population:**	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection.	**Absolute and relative risk of reinfection** During the 6-month survey, 1.78% seropositive subjects (26/1,460) developed secondary SARS-

DOI: 10.1016/j.ijid.2021.07.003 Incidence of SARS-CoV-2 infection in health care workers from Northern Italy based on antibody status: immune protection from secondary infection- A retrospective observational case-controlled study Retrospective cohort study Published	N=1,460 seropositive individuals (and 8,150 seronegative controls) from a cohort of 9,610 healthcare workers Median follow-up: N/R Maximum follow-up: Approx. 6 months (June to November 2020) **Patient demographics:** 2,567 males and 7,043 females. Median age 47 years, range 21-70 years **Definition of reinfection**: Detection of SARS-CoV-2 RNA ≥60 days following previous positive serology (anti-spike IgG antibodies) **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR	**SARS-CoV-2 confirmation:** Performed as per the laboratory of each hospital. Nasopharyngeal samples were collected every 7-14 days from healthcare workers dependent on the hospital (serial testing). In all centres, nasopharyngeal sampling was done for all the symptomatic individuals and contacts. **Serological confirmation:** Chemiluminescent assay (Liason SARS-CoV-2 S1/S2 IgG, Diasorin, Saluggia, Italy) to measure SARS-CoV-2 anti-S1 and anti-S2 IgG antibodies. Neutralising antibody serum titer was determined using seropositive and seronegative samples. **Additional testing:** Not conducted	CoV-2 infection while 6.63% seronegative controls (540/8,150) developed primary infection (odds ratio: 0.26; 95% CI: 0.17 to 0.38). **Antibody titres:** Data on anti-Spike IgG antibody quantitative levels were available for 313 seropositive subjects without and 7 seropositive subjects with a SARS-CoV-2 secondary infection. No significant difference in IgG levels was observed. Secondary infection was associated with low or absent serum neutralising titer ($p < 0.01$), however this is based on samples from 20 individuals in total (7 who had a secondary infection and 13 who did not). **Absolute estimates (for covariates):** Where symptom status reported, secondary infection was mildly symptomatic in 45.8% cases (11/26) vs 71.4% symptomatic primary infections (279/391) (odds ratio: 0.34; 95% CI: 0.16 to 0.78). **Conclusion:** Immunity from natural immunity appears protective from secondary infection; therefore, vaccination of seronegative subjects might be prioritised.
Sabetien 2021 Iran DOI: 10.21203/rs.3.rs-772662/v1	**Population:** Of a total 13,749 healthcare workers tested, 5,349 healthcare workers contracted COVID-19 and 8,400 did not, during the time frame.	**Primary endpoint:** PCR-confirmed (or clinically assessed) SARS-CoV-2 reinfection, relapse and re-positivity. **SARS-CoV-2 confirmation:** RT-PCR assays were performed according to the protocol established by the WHO and previous	**Absolute and relative risk of reinfection** 97 cases of reinfection from 5,349 previously infected were detected (1.8%). There was no significant difference among the symptoms of patients with COVID-19 reinfection compared with HCWs with Relapse/Repositivity (P

High Post-infection Protection after COVID-19 Among Healthcare Workers: A Population-Level Observational Study Regarding SARS-CoV-2 Reinfection, Reactivation, and Re-positivity and its Severity Retrospective cohort study Pre-print	Median follow-up: NR Maximum follow-up: up to 10 months (304 days) (20 April 2020 to 20 February 2021) **Patient demographics:** Age; mean ± SD ▪ 35 ± 7.18 [35.70 ± 7.43 in reinfected group] Gender; n (%) ▪ Male 53 (37.6), Female 88 (62.4) [males 36 (37.9) and females 59 (62.1) in reinfected group] Comorbid diseases; n (%) ▪ yes 25 (17.4), no 119 (82.6) [yes 17 (17.5) and no 80 (82.5) in reinfection group] Proportion fully vaccinated: NR **Definition of reinfection**: Any positive RT-PCR test >90 days after primary infection, or < 90 days plus if clinical symptoms of the first episode resolved and two PCR tests were negative before the new episode. **Predominant variant in circulation:** NR	studies. Clinical assessment was also used to diagnose COVID-19. **Serological confirmation:** Not conducted. **Additional testing:** Not conducted.	= 0.650). Also, there was no significant difference among the symptoms in the first episode, second episode, and overlap between the two episodes among the reinfection and Relapse/Repositivity group (P = 0.442, 0.054, and 0.162, respectively). There was also no significant difference regarding the need for hospitalisation, frequency of hospitalisation during the first and second episode, and overlapping of hospitalisation among the reinfection and Relapse/Repositivity group (P = 0.120, 0.458, 0.085, and 0.194 respectively). There was also no significant difference in the need for ICU admission among the two groups (P = 0.247). As established, there was no significant difference among the clinical presentation of HCWs with reinfection compared to the relapse/repositivity group. **Adjusted reinfection rates:** The adjusted rate ratio (RR) of infection was 0.052 (95% CI: 0.043 to 0.064) among those who previously tested positive compared with those who had previously only tested negative. The estimated protection against repeat infection after a previous SARS-CoV-2 infection was 94.8% (95% CI: 93.6 to 95.7. **Conclusion:** Re-positivity, relapse, and reinfection of SARS-CoV-2 are quite rare in the population of HCWs. Also, after the first episode of infection, estimated protection of 94.8% was achieved against repeat infections.

	Incidence of SARS-CoV-2: NR		
Schuler 2021 DOI:10.1128/Spectrum.00087-21 Mild SARS-CoV-2 Illness Is Not Associated with Reinfections and Provides Persistent Spike, Nucleocapsid, and Virus-Neutralizing Antibodies US Prospective cohort study Published	**Population** N=653 (N=129 had a history of COVID 19 at enrolment, 209 had a negative RT-PCR test and 315 had no history of clinical illness or positive RT-PCR test). Mean time from a positive RT-PCR to enrolment was 51 days. Mean time to follow-up (visit 2) was 126 days. **Definition of re-infection:** NR For reinfection analyses, the first date of vaccination was considered to be the end of the observation period, so these results only include data from the time individuals were unvaccinated. **Analysis period:** Over two visits, 3 to 6 months apart, between May 2020 and February 2021. **Demographics:** Entire cohort (n=653) ▪ Mean Age (SD): 40.7 (12.1) ▪ Median age (IQR): 39 (31, 51) ▪ Female: 472 (72%) ▪ Male: 176 (27%)	**Primary endpoint** Reinfection of COVID-19 and the persistence of antibodies against SARS-CoV-2 after mild infection. **Test parameters:** Antibody test: Nucleocapsid (N) antibodies were detected via the Elecsys (Roche) SARS-CoV-2 total antibody assay ("N immunoassay") on a Cobas e411 analyzer and spike (S1-RBD or "S") antibodies were detected via the ADVIA Centaur (Siemens) SARS-CoV-2 total (COV2T) assay ("S immunoassay") on an ADVIA Centaur XPT analyzer. A COVID-19 antibody lateral flow assay (LFA) from Healgen Scientific (COVID-19 IgG/IgM rapid test cassette, or "Healgen") was used to evaluate the presence of IgM antibodies.	**Risk of reinfection** 0.00% **Absolute(/crude) reinfection risk of events** No initially seropositive subjects experienced a subsequent COVID-19 infection during the follow-up compared to 15 infections among initially seronegative subjects (infection rates of 2.05 per 10,000 days at risk [P = 0.0485]). **Antibodies** Among the RT-PCR-positive subjects, 91% were found to have N antibodies and 90% S antibodies with the higher complexity tests. Seven subjects produced only detectable N antibodies, and 7 others produced only S antibodies. Among the RT-PCR-negative subjects, 1% had N antibodies and 2% S antibodies with these tests. Among the RT-PCR-positive subjects who produced N and/or S antibodies, the mean levels were unchanged at follow-up. Furthermore, there was no evidence of an overall decrease in the N or S antibody levels at later times, and only one subject had a significant decrease in N and S antibodies during the study. **Conclusion/relevance** In this prospective cohort study, no subject with a known SARS-CoV-2 infection had a reinfection during the observation period. In addition, those subjects with who were found to have N or S antibodies to SARS-CoV-2 on lab-based immunoassays but who did not have a known

	▪ Other/unknown: 6 (1%) ▪ Race: ▪ White: 543 (83%) ▪ Asian: 57 (9%) ▪ Other/unknown: 52 (8%) ▪ Unknown/not reported: 6(1%) ▪ Mean BMI (SD): 27.7 (8.2) Median BMI (IQR): 25.7 (22.8, 29.9) Positive at baseline (n=129) ▪ Mean Age (SD): 42.8 (12.4) ▪ Median age (IQR): 43 (32, 52) ▪ Female: 92 (71%) ▪ Male: 36 (28%) ▪ Other/unknown: 1 (1%) ▪ Race: ▪ White: 104 (81%) ▪ Asian: 10 (8%) ▪ Other/unknown: 15 (11%) Pre-existing medical conditions: ▪ Yes: 39 (30%) ▪ No: 89 (69%) ▪ Unknown/not reported: 1 (1%) ▪ Mean BMI (SD): 30.2 (12.0) ▪ Median BMI (IQR): 27.3 (23.8, 34.0) Proportion of vaccinated: 169 (26%) at the time of visit 2; vaccinated individuals were not included in follow-up analysis as the currently		positive RT-PCR at enrolment also had no infections during the observation period.

	approved vaccines induce an S protein antibody response. **Predominant variant in circulation:** NR **Seroprevalence of SARS-CoV-2:** NR		
Shrestha 2021 DOI: 10.1101/2021.06.01.21258176 Necessity of COVID-19 vaccination in previously infected individuals US Retrospective cohort study Preprint	**Population** N=52,238 employees in total; n=2,579 previously infected and n=49,659 not previously infected. n=1,359 of 2,579 (53%) previously infected individuals remained unvaccinated. N=20,804 of 49,659 (42%) not previously infected individuals remained unvaccinated. Vaccination occurred using either the Pfizer-BioNTech, Moderna or Johnson & Johnson vaccines. A person was considered vaccinated 14 days after receipt of the second dose of the vaccine. Median follow-up: for previously infected 10 months. Maximum follow-up: 5 months for those without previous infection. Up to 1 year for those with previous infection, but reinfection would only	**Primary endpoint:** Time to SARS-CoV-2 infection defined by a positive nucleic acid amplification test (PCR) for SARS-CoV-2. **Test parameters:** *SARS-CoV-2 confirmation* PCR testing (unspecified). *Other tests* Not conducted.	**Absolute Risk of reinfection:** 2,139 infections occurred in those not previously infected and who remained unvaccinated (2,139/20,804; 10.28%). 15 breakthrough infections occurred in those not previously infected, but fully vaccinated (15/28,855; 0.05%). 0 reinfections occurred in those previously infected (0/2,579; 0%). **Relative risk of reinfection:** The cumulative incidence of SARS-CoV-2 infection among previously infected unvaccinated subjects did not differ from that of previously infected subjects who were fully vaccinated, and that of previously uninfected subjects who were fully vaccinated. For all three of these groups, the cumulative incidence of SARS-CoV-2 infection was much lower than that of subjects who were not previously infected and who remained unvaccinated. **Risk of reinfection over time** For the previously infected subjects the median duration (from start of the study on 16 December

	be detected in the same latter 5 month period. **Definition of re-infection** A minimum of 90 days between two positive tests. **Analysis period:** Study period: 16 December 2020 until 15 May 2021, with historic PCR results available from 12 March 2020. **Demographics:** *Previously infected (n=2,579)* Age, years, mean ± SD, 39 years ±13 Proportion fully vaccinated by end of study: 1,220 (47%). *Not previously infected (n=29,659)* Age, years, mean ± SD, 42 years ±13 Proportion fully vaccinated by end of study: 28,855 (58%). **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** When vaccination campaign began in December 2020, the epidemic in Ohio was at the peak of its third wave (with approximately 22% test positivity rates). This fell to a test		2020) since prior infection was 143 days (IQR 76 – 179 days), and none of these individuals had SARS-CoV-2 reinfection over the following five months, suggesting that SARS-CoV-2 infection may provide protection against reinfection for 10 months or longer. **Adjusted estimates** In a Cox proportional hazards regression model, after adjusting for the phase of the epidemic, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI: 0.015 to 0.061) but not among those previously infected (HR 0.313, 95% CI: 0 to Infinity). **Conclusion/relevance** Individuals who have had SARS-CoV-2 infection are unlikely to benefit from COVID-19 vaccination, and vaccines can be safely prioritised to those who have not been infected before.

	positivity rate of ~4% 75 days after initiation of the vaccination campaign.		
Slezak 2021 DOI: https://doi.org/10.1016/j.cmi.2021.07.030 Rate and severity of suspected SARS-Cov-2 reinfection in a cohort of PCR-positive COVID-19 patients US Retrospective cohort study Published	**Population** N= 75,149 initial PCR positive at baseline Median follow-up: NR Maximum follow-up: 270 days (9 months) **Definition of re-infection:** Suspected reinfection was defined as a positive PCR test for SARS-CoV-2 >90 days after the first positive test. **Analysis period:** From first positive SARS-CoV-2 PCR test between 1 March 2020 and 31 October 2020 to 31 January 2021. All members of Kaiser Permanente Southern California(an integrated healthcare organisation) with first positive SARS-CoV-2 PCR test between 1 March 2020 and 31 October 2020 were identified. **Demographics:** 52.9% Female 66.1 % Hispanic 8.1% aged <18 years 14.6% aged ≥ 60 years	**Primary endpoint:** The burden and severity of suspected reinfection with severe acute SARS-CoV-2. **Time interval:** Subsequent positive SARS-CoV-2 tests (suspected reinfection) were taken no less than 90 days after initial infection. **Test parameters:** PCR were undertaken to test SARS-CoV-2 for participants at baseline and follow-up.	**Cumulative risk of reinfection:** 0.8% (95% CI: 0.7 - 1.0%) at 270 days following initial infection. **Hazard ratios:** Adults were significantly more likely to have a suspected reinfection than children (age 18-39: HR 2.71, 95% CI: 1.38 to 5.31, age 40-59: HR 2.22, 95% CI: 1.12 to4.41, age 60: HR 2.52, 95% CI: 1.23 to5.17). **Absolute (/crude) reinfection events** Higher hospitalisation rate at suspected reinfection (36/315, 11.4%) than initial infection (4094/75 149, 5.4%). Suspected reinfection rates were higher in females (1.0%, 95% CI: 0.8% to 1.2% versus 0.7%, 95% CI: 0.5% to 0.9%, p 0.002); immunocompromised patients (2.1%, 95% CI: 1.0% to 4.2% versus 0.8%, 95% CI: 0.7% to 1.0%, p 0.004); and lower in children than adults (0.2%, 95% CI: 0.1% to 0.4% versus 0.9%, 95% CI: 0.7 to 1.0%, p 0.023). Patients hospitalized at initial infection were more likely to have suspected reinfection (1.2%, 95% CI: 0.6 to 1.7% versus 0.8%, 95% CI: 0.7 to 1.0%, p 0.030). Patients with initial infections later in 2020 were more likely to have suspected reinfection (150-day incidence 0.4%, 95% CI: 0.2% to 0.5% September - October versus 0.2%, 95% CI: 0.1%

	1.3% had an immunocompromising condition 5.4% hospitalized at initial infectiom **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** 10.7%		to 0.3% March - May and 0.3%, 95% CI: 0.2% to 0.3% June - August, p 0.008). Adults were significantly more likely to have a suspected reinfection than children. **Conclusion/relevance** Reinfection with SARS-CoV-2 was low (0.8%). Women, adults, immunocompromised subjects, and those previously hospitalized for coronavirus 2019 (COVID-19) were the significant independent predictors of suspected reinfection.
Vitale 2021 DOI:10.1001/jamainternmed.2021.2959 Assessment of SARS-CoV-2 Reinfection 1 Year After Primary Infection in a Population in Lombardy, Italy Italy Retrospective study Published	**Population** N = 1,579 Positive PCR test at baseline; n=12968 negative result at baseline and during follow-up; n=528 negative result that converted to positive during follow-up. Median follow-up: 280 days Maximum follow-up: 314.5 days (10.5 months) for baseline positive PCR participants; 12 months for the study cohort. Minimum follow-up: 7 months for the study cohort. **Definition of re-infection:** A second RT-PCR positivity beyond 90 days after complete resolution of the first infection and with at least 2 consecutive negative test results between episodes. **Analysis period:**	**Primary endpoint:** The incidence of SARS-CoV-2 primary infection and reinfection. **Time interval:** Reinfection was considered 90 days after initial infection. **Test parameters:** Diagnostic reverse-transcriptase–polymerase chain reaction PCR were undertaken for primary infection and reinfection.	**Risk of reinfection:** 0.31% (95% CI: 0.03% to 0.58%), 5 out of 1579. **Absolute (/crude) reinfection events** One patient was hospitalized. Two patients work in hospitals. One patient underwent transfusions every week. One patient retired in a nursing home. The mean (SD) interval between primary infection and reinfection was longer than 230 (90) days. **Cumulative risk of reinfection:** The cumulative incidence during follow-up, we confirmed that the 2 cohorts were significantly different (hazard ratio, 0.06; 95% CI: 0.05 to 0.08; log-rank test P < .001). **Adjusted Relative risk of reinfection:** New infection cohorts and reinfection cohorts were significantly different. With those previously infected are less likely to become reinjected

	February 2020 to February 28 2021 **Demographics:** Mean age: 62, 48.8% Female **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** 3.9% (95%CI, 3.5%-4.2%); 528 out of 13 496 persons who initially were not infected with SARS-CoV-2.		relative to those with no history of infection. Incidence rate ratio, 0.07 (95% CI: 0.08 to 0.08; log-rank test P < .001) adjusted for age, sex, ethnicity, and the sanitarian area. **Conclusion/relevance:** Patients who have recovered from COVID-19 have a lower risk of reinfection. Natural immunity to SARS-CoV-2 appears to confer a protective effect for at least a year, but its protection against other variants remain unknown.
Wilkins 2021 DOI: https://doi.org/10.1017/ice.2021.367 Serologic Status and SARS-CoV-2 Infection over 6 Months of Follow Up in Healthcare Workers in Chicago: A Cohort Study US Prospective cohort study Published	**Population** n = 316 (HCWs antibody positive at baseline from a total of 6,510 in a cohort of HCWs). Median follow up: 216 days for entire cohort (6-7 months). NR for antibody positive at baseline. **Definition of re-infection** Participants who were seropositive at baseline were considered to be at risk for possible reinfection 90 days after their antibody test until the end of follow-up or to the first positive PCR test plus 1 or more of the following characteristics: in-home exposure to someone infected with SARS-CoV-2, consistent symptoms, or a physician diagnosis of active infection.	**Primary endpoint:** PCR-confirmed SARS-CoV-2 reinfection. **Time interval:** Six months. **Test parameters:** *SARS-CoV-2 confirmation:* NR *Serological confirmation:* Serum samples were tested on the ARCHITECT i2000SR Immunoassay System from Abbott Laboratories at enrolment and on the Abbott Alinity Immunoassay System at follow-up. Concordance across the two analysers was verified following the College of American Pathologist guidelines and by the study team using 20 positive and 20 banked negative serum samples from baseline with 100% concordance.	**Risk of reinfection:** 8 of 316 (2.5%) were possible reinfections as per definition. (20 participants had positive PCR during follow up). Possible reinfection rate was 1.27 per 10,000 days at risk (95% CI: 0.55 to 2.51). **Relative risk of reinfection:** Crude incidence rate ratio was 0.30 (95% CI: 0.15 to 0.60) for participants who were seropositive at baseline compared with those who were seronegative at baseline. **Adjusted estimates (for covariates)** When adjusted for age, sex, race, and occupation, incidence rate ratio was 0.26 (95% CI: 0.13 to 0.53). **Antibody titres:** NR. 4 of the 8 possible reinfections were persistently seropositive and 4 had seroreverted.

	Analysis period: Recruited between May 26 and July 10 and assessed for follow up between November 9 and January 8, 2021 (Max: 7 months). **Demographics:** Mean age of seropositive subgroup NR; 81% Female. The sample mean age was 41 (SD 12) 79.6% female. Proportion fully vaccinated: Study completed before vaccination. **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		**Absolute (/crude) reinfection events** Among these 8 cases of possible reinfection during follow-up, 5 were asymptomatic and no cases were severe and none reported a history of immunosuppression. **Conclusion/relevance:** Loss of detectable antibody was common during the 6 months follow-up but was not associated with significantly higher rates of possible reinfection than those who were persistently seropositive. Similar to other reports of reinfection in HCWs, all cases of possible reinfection that we observed in seropositive HCWs were not severe.
Yoo et al. 2021 DOI: https://doi.org/10.1101/2021.05.14.21257231 Patient Characteristics in Cases of Reinfection or Prolonged viral shedding in SARS-CoV-2	**Population** N= 234,866 Positive PCR test at baseline Median follow-up: NR Minimum follow-up: 42 days **Definition of re-infection:** Potential reinfection or prolonged viral shedding (RPVS) cases was defined as having no less than two positive diagnostic tests via RT-PCR for SARS-Cov-2 separated by 42 or more days with at least one serological test	**Primary endpoint:** The frequency and characteristics of people with a testing pattern indicative of SARS-CoV-2 reinfection or prolonged viral shedding. **Time interval:** Two positive RT-PCR tests separated by more than 42 days, with a positive IgG test in between. 42 days was selected to account for the typical length of viral shedding. **Test parameters:**	**Risk of reinfection:** 0.034%; 79 had two positive RT-PCR tests separated by more than six weeks, with a positive IgG test in between out of a cohort size of 234,866. **Absolute (/crude) reinfection events** RPVS patients exhibit a higher frequency of comorbidities related to a compromised immune system (such as, high cholesterol, hypertension, anxiety, arthritis, obesity, diabetes etc.) than the general population who have a positive PCR test.

US Retrospective cohort study Preprint	(IgG) indicating the presence of antibodies between diagnostic tests. **Analysis period:** NR Patients whose insurance, either commercial or Medicare provided by a single US based insurer and had positive RT-PCR results were identified. Patients who had a negative RT-PCR test result reported the same day, had less than two positive RT-PCR tests separated by at least 42 days and did not have a positive IgG test between two positive RT-PCR results were excluded. **Demographics:** Median age 56 for the RPVS cohort. Median age 42 for the Non-RPVS cohort. **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR	RT-PCR was performed to identify infection and reinfection of SARS-Cov-2. IgG was undertaken to test the presence of antibodies between diagnostic tests.	RSVP patients tended to be older than those COVID-19 patients without this pattern (median age 56 vs. 42). In particular, 75% of cases are from age group above 44 suggesting a possible increased susceptibility to an RPVS state with age. **Relative risk of reinfection:** NR **Conclusion/relevance:** A very low possible SARS-CoV-2 reinfection rate (0.034%) based on patterns of positive RT-PCR and positive antibody tests were identified with assessment of test accuracy. The median number days between a positive IgG test and a subsequent positive RT-PCR test is 21 (IQR 24.5). Comorbid conditions associated with a compromised immune system rank high on the list for patients with potential reinfection. While the testing pattern alone was not sufficient to distinguish potential reinfection from prolonged viral shedding, we were able to identify common traits of the patients identified through the pattern.
Young-Xu 2021 DOI: 10.1101/2021.09.27.21264194 SARS-Cov-2 Infection versus	**Population** N=5,622 previously infected individuals who remained unvaccinated. (N=47,102 in total; N=9,539 patients with SARS-CoV-2 infection during the first two months of 2021 (matched to	**Primary endpoint:** RT-PCR confirmed SARS-CoV-2 infection during follow-up, COVID-related hospitalisation, and deaths **Test parameters:** RT-PCR (no other information provided)	**Risk of reinfection:** *Total population:* Reinfection rate (in those not vaccinated), 28/5,622 (0.50%) Break through infection rate for Moderna, 25/14,458 (0.17%)

Vaccine-Induced Immunity among Veterans US Retrospective cohort study Preprint	n=14,458 and 23,105 patients fully vaccinated, with no previous infection, with Moderna and Pfizer mRNA vaccines, during the same two months). Median follow-up: NR Maximum follow-up: 229 days (7.5 months) **Definition of re-infection:** Minimum 90 days between positive PCR tests **Analysis period:** Study period: 1 January 2021 – 18 August 2021 A retrospective observational study was conducted comparing two groups whose incident vaccination or infection occurred within the first two months of 2021: (1) SARS-CoV-2-naive individuals who received a full mRNA vaccination - 2 doses of either Pfizer or Moderna vaccine prior to 1 March 2021, (2) newly infected individuals (Jan-Feb 2021) who were subdivided into those have not been vaccinated and those have been vaccinated after their infection. Each previously infected Veteran was matched with up to four vaccinated individuals on the following: state and index event dates (within +/-2 weeks), race/ethnicity, age groups,		Breakthrough infection rate for Pfizer, 57/23,105 (0.25%) *Age 65+* Reinfection rate (in those not vaccinated), 19/2,480 (0.77%) Breaththrough infection rate for Moderna, 16/7,391 (0.22%) Breakthrough infection rate for Pfizer, 30/10,789 (0.28%) *Age < 65* Reinfection rate (in those not vaccinated), 9/3,142 (0.29%) Breaththrough infection rate for Moderna, 9/7,067 (0.13%) Breakthrough infection rate for Pfizer, 27/12,316 (0.22%) **Relative risk of reinfection:** Among individuals ≥65 years, Moderna and Pfizer mRNA vaccines offered stronger protection against infection compared with previous infection, lowering the risk by an additional 66% [HR: 0.34 (95% CI, 0.14-0.78)] and 68% [HR: 0.32 (95% CI, 0.14-0.70)]; stronger protection against hospitalisation, lowering the risk by an additional 61% [HR: 0.34 (95% CI, 0.14-0.78)] and 45% [HR: 0.34 (95% CI, 0.14-0.78)]; and stronger protection against deaths lowering the risk by an additional 95% [HR: 0.05 (95% CI, 0.004-0.62)] and 99% [HR: 0.01 (95% CI, 0.001-0.44)].

	sex, rural/urban, CCI, and VHA priority Outcome assessment period: 1 June – 18 August 2021. **Demographics of total population (n=47,102):** Mean age (SD), 62.87 (14.10) Male, 91.37% Comorbidities: ▪ cancer, 10.66% ▪ cancer (metastatic), 8.75% ▪ coronary artery disease, 11.5.8% ▪ congestive heart failure, 6.6% ▪ chronic kidney disease, 8.49% ▪ chronic obstructive pulmonary disease, 11.53% ▪ cardiovascular disease, 36.43% ▪ dementia, 2.06% ▪ diabetes mellitus (complicated), 9.87% ▪ diabetes mellitus (uncomplicated), 24.82% ▪ hypertension, 41.32% ▪ renal disease, 8.88% ▪ obesity, 11.97%. Proportion vaccinated; 3,917 (41%) of previously vaccinated cohort were		Among younger adults (age < 65), the protections offered by vaccines were statistically equivalent to that provided by previous infection, especially in terms of absolute incidence rate. For those younger than 65 years, using matched, adjusted multivariable Cox model no difference in the hazard of infection was observed (Pfizer-BioNTech: HR: 0.64 [95% CI, 0.24 to 1.69]; Moderna vaccines: HR: 0.35 [95% CI, 0.11 to 1.13]) or when restricted to infections in July and August 2021 (Pfizer-BioNTech: HR: 1.59 [95% CI, 0.41 to 6.11]; Moderna vaccines: HR: 1.04 [95% CI, 0.24 to 4.58]). For those younger than 65, this pattern remained the same. Those previously infected had the highest infection rate, 1.4 per 100,000 patient-days, and those vaccinated with Modern vaccine had the lowest infection rate at 0.7. In between them, those vaccinated with Pfizer vaccine had an infection rate of 1.2. **Adjusted estimates (for covariates)** **Antibody titres:** **Absolute (/crude) reinfection events** Between June and August, a total of 110 (0.23%) participants tested positive for COVID-19 with those previously infected without subsequent vaccination having the highest infection rate – 2.7 per 100,000 patient-days Among those 65 or older, those previously infected had the highest infection rate, 4.8 per 100,000

	subsequently vaccinated and removed from this analysis **Predominant variant in circulation:** Delta variant **Incidence of SARS-CoV-2:** NR		patient-days, followed by Pfizer at 1.5, and Moderna, 1.2. **Conclusion/relevance:** Among older adults (age 65 or older), two-dose mRNA vaccines provided stronger protection against infection, hospitalisation, and death, compared to natural immunity. Among younger adults (age < 65), the protections offered between natural immunity and vaccine-induced immunity were similar.
Zare 2021 DOI: https://doi.org/ 10.1017/S095026882100087X COVID-19 re-infection in Shahroud, Iran: a follow-up study Iran Prospective cohort study Published Epidemiology and Infection	**Population** N = 4,039 Positive PCR test at baseline. (N = 8,734 total) Maximum follow-up: 9 months **Definition of re-infection:** Have clinical symptoms with SARS-CoV-2 PCR-positive test at least 30 days after first positive test. **Analysis period:** 20 March 2020 to 20 November 2020 Patients residing in the Shahroud Iran with suspected respiratory symptoms were tested and followed up. Health status and symptoms among patients initially tested positive were followed up after recovery. **Demographics:** NR	**Primary endpoint:** The recurrence of the infection in recovered individuals over a 9-month period. **Time interval:** Mean time interval between the first infection and re-infection was 134.4 ± 64.5 days (range 41–234 days).Cases where the second positive result was < / = 30 days after the first were excluded. **Test parameters:** RT-PCR for SARS-CoV-2 was performed on nasopharyngeal and oropharyngeal specimens.	**Risk of reinfection:** 0.25% (10 out of 4,039). Or 2.5 per thousand (95% CI: 1.2 to 4.5). **Absolute (/crude) reinfection events:** The mean time interval between the first infection and re-infection was 134.4 ± 64.5 days (range 41–234 days). Of 10 re-infected patients, re-infection occurred in 4 female and 6 male. Four were admitted to the intensive care unit both in primary infection and reinfection period. Four were referred and treated on an outpatient basis in both periods. Two of them had mild symptoms in the primary stage but re-infection was severe for them or vice versa. Three medical staffs were among the patients with reinfection. Four patients over 80 years old with one or more underlying diseases (heart disease, diabetes, gastrointestinal bleeding, fractures, or a history of

	49 tested positive for RT-PCR after recovery. Of these, 39 were excluded due to repeated testing at 1-month interval. **Predominant variant in circulation:** NR **Incidence of SARS-CoV-2:** NR		surgery and lung diseases) had died at the hospital due to COVID-19. The mean age of patients was 64 ± 28 years ranging from 13 to 90. 60% of those reinfected were male. **Relative risk of reinfection:** NR **Conclusion/relevance** A small possibility of re-infection in people recovering from COVID-19, and the severity of its re-infection can vary from mild to very severe and eventually may cause death.

Key: aHR – adjusted hazard ratio; aOR – adjusted odds ratio (adjusted for week group); CI – confidence interval; Ct – cycle threshold value; f/u – follow-up; NAAT – nucleic acid amplification test; NR – not reported; IgA immunoglobulin A; IgG **-** immunoglobulin G; IgM – immunoglobulin M; IQR – inter-quartile range; HCW – healthcare worker; Hx - history of COVID-19; RADT – rapid antigen detection test; RR – relative risk; RT-qPCR – real time reverse transcription polymerase chain reaction; SD - standard deviation WGS – whole genome sequencing

Appendix 3: Quality Appraisal

The National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies, available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Table A5: Quality Appraisal (cohort study) from previous version of evidence summary (version 7.1), table 1 of 2

	Abu-Raddad 2021 [assessment: 'fair']	Breathnach 2021 [assessment: 'fair']	Hall 2021 [assessment: 'good']	Hanrath 2021 [assessment: 'fair']	Hansen 2021 [assessment: 'good']	Harvey 2020 [assessment: 'poor']	Jefferey-Smith 2021 [assessment: 'fair']	Krutikov 2021 [assessment: 'good']	Leidi 2021 [assessment: 'fair']
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?									
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	No – All had an antibody test in the database, but type of test and validity unknown	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	No – All had NAAT, but type of NAAT cannot be determined	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	No; Retrospective study	No; Retrospective study	Yes; Prospective study	No; Retrospective study	No; Retrospective study	No; Retrospective study	No; Retrospective study	Unclear; Prospective study	Unclear
13. Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Not Reported	Yes	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Database analysis; unclear if all confounders measured	Unclear	Yes	No	Yes	Statistical analysis and adjustment for confounders not reported	No	Yes	Unclear

Table A6: Quality Appraisal (cohort study) from previous version of evidence summary (version 7.1), table 2 of 2

	Lumley 2020 [assessment: 'good']	Manica 2021 [assessment: 'fair']	Masia 2021 [assessment: 'fair']	Mohamadreza 2021 [assessment: 'poor']	Papasavas 2021 [assessment: 'fair']	Perez 2021 [assessment: 'fair']	Pilz 2021 [assessment: 'fair']	Qureshi 2021 [assessment: 'fair']	Sheehan 2021 [assessment: 'fair']	Shields 2021 [assessment: 'fair']
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Unclear, Enrolment was not random	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A	N/A	N/A
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	N/A	N/A	N/A	Unclear	Yes	N/A	N/A	N/A	N/A	N/A

9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Testing methodology insufficiently reported	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	Unclear; Prospective study	Unclear	Unclear	No; retrospective	Unclear	No; Retrospective study	No; Retrospective study	No; Retrospective study	No; Retrospective study	Unclear
13. Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	No - only age standardisation in adjusted analyses	Unclear	Unclear	Unclear	No	No	Authors acknowledge confounding by the selection criteria of the analysis	No	Unclear

Table A7: Quality Appraisal (cohort study) from current version of evidence summary (version 8.0), table 1 of 5

	Abdelrahman 2021 [assessment: 'Poor']	Abo-Leyah 2021 [assessment: 'Fair']	Abu-Raddad 2021 [assessment: 'Fair']	Ali 2021 [assessment: 'Fair']	Armstrong 2021 [assessment: 'Fair']	Banham 2021 [assessment: 'Fair']	Breathnach 2021 [assessment: 'Fair']	Caralis 2021 [assessment: 'Poor']	C. Cohen 2021 [assessment: 'Good']	D. Cohen 2021 [assessment: 'Fair']	Comelli 2021 [assessment: 'Fair']
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome	N/A	N/A	No – either fully vaccinate	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

(e.g., categories of exposure, or exposure measured as continuous variable)?			d or unvaccinated only considered								
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	No - Testing methodology insufficiently reported	Yes	Yes	Yes	No – testing varied by lab (could be antigen or PCR)	Unclear how regularly patient were screened in the first wave	Yes	Yes	Yes	No – unclear how documented history or infection obtained	Yes
10. Was the exposure(s) assessed more than once over time?	Yes	No – antibody testing done once	Yes	No – antibody testing done once	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	No - Testing methodology insufficiently reported	No - Testing methodology insufficiently reported	Unclear whether systematic testing done in vaccinated or asymptomatic individuals	Unclear whether systematic testing done in asymptomatic individuals	Unclear whether systematic testing done in asymptomatic individuals	Yes	No - Testing methodology insufficiently reported	Unclear whether systematic testing done in asymptomatic individuals	Yes	Yes	Unclear whether systematic testing done in asymptomatic individuals

12. Were the outcome assessors blinded to the exposure status of participants?	No – prospective study but only those exposed were followed up	Unclear	No – retrospective study	Unclear	No – retrospective study	Unclear	No – retrospective study	No	Unclear	Unclear	No
13. Was loss to follow-up after baseline 20% or less?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	Unclear	Yes	No	No	No	No	No	Yes	Yes	No

Table A8: Quality Appraisal (cohort study) from current version of evidence summary (version 8.0), table 2 of 5

	Davido 2021 [assessment: 'Fair']	Dobano 2021 [assessment: 'Fair']	Finch 2021 [assessment: 'Good']	Flacco 2021 [assessment: 'Fair]	Gallais 2021 [assessment: 'Good']	Gazit 2021 [assessment: 'Fair']	Gehring 2021 [assessment: 'Fair']	Glück 2021 [assessment: 'Poor]	Graham 2021 [assessment: 'Poor']	Havervall 2021 [assessment: 'Fair']	Kohler 2021 [assessment: 'Poor']
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Unclear	No – significantly less than 50% of all eligible participated	Unclear	Unclear
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

see an association between exposure and outcome if it existed?											
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	N/A	N/A	N/A	N/A	N/A	Yes – in relation to number of vaccine doses	N/A	Yes	N/A	N/A	N/A
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	No – may have missed cases tested outside of healthcare setting	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No – all self-report (PCR or lateral flow accepted)	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No – only once
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	No – may have missed cases tested outside of setting	No – only passive monitoring for infection (not systematically monitored in asymptomatic people)	Yes	Unclear whether systematic re-testing done in asymptomatic individuals	Yes	Unclear whether testing done in vaccinated or asymptomatic individuals	No – only self-reported symptomatic individuals were tested	No – unclear how reinfection was measured	No – all self-report (PCR or lateral flow accepted)	No – PCR serial testing was only done on a subset of participants	No – self-report of test results (PCR or antigen) which were usually symp

											tom initiated
12. Were the outcome assessors blinded to the exposure status of participants?	No – retrospective study	No	Unclear	No – retrospective study	No	No – retrospective study	Unclear	Unclear	Unclear	Unclear	Unclear
13. Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	No	Yes	No	No	Yes	No	No	No	No	No

Table A9: Quality Appraisal (cohort study) from current version of evidence summary (version 8.0), table 3 of 5

	Kojima 2021 [assessment: 'Fair']	Kute 2021 [assessment: 'Poor]	Lawandi 2021 [assessment: 'Fair']	Leidi 2021 [assessment: 'Fair']	Mei 2021 [assessment: 'Fair']	Murollo-Zamora 2021 [assessment: 'Fair']	Narrainen 2021 [assessment: 'Fair']	Peghin 2021 [assessment: 'Fair']	Peltan 2021 [assessment: 'Fair']	Rennert 2021 [assessment: 'Fair']	Ringlander 2021 [assessment: 'Fair']	Rivelli 2021 [assessment: 'Fair']
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Unclear	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	No – comparator groups from different time periods	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the	No – only fully vaccinated	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	or unvaccinated considered											
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	Yes	Unclear	Yes	No – serology assessed only once	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	No – systematic testing was not performed	No – not all participants underwent repeat testing	No – RT-PCR or antigen tests accepted. unclear whether all participanst underwent repeat testing	No – retesting only occurred in symptomatic individuals or for specific medical circumstances	No – only conducetd restesting among sympotomatic individuals; also >28 days apart considered reinfection	No – not all HCWs availed of testing	Yes	No – asymptomatic retesting was not undertaken	No – only residential students had mandated testing in Autumn 2020 semester, however conducted sentisivity analysis to deal with this issue.	Non – not all participants underwent repeat testing	No – not all participants underent repeat testing
12. Were the outcome assessors blinded to the exposure status of participants?	No – retrospective study	No - retrospective study	No – retrospective study	No – 2 adjudicators	No	No – retrospe	No – retrospectiv	Unclear	No – retrospe	No – retropse	No – retropsectiv	No – retropsecti

				decided upon possible reinfection cases		ctive study	e study		ctive study	ctive study	e study	ve study
13. Was loss to follow-up after baseline 20% or less?	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	No	No	Yes	No	Yes	No	No	No	Yes	No	No

Table A10: Quality Appraisal (cohort study) from current version of evidence summary (version 8.0), table 4 of 5

	Ronchini [assessment: 'Poor']	Rovida 2021 [assessment: 'Fair']	Sabetian 2021 [assessment: 'Poor']	Schuler 2021 [assessment: 'Poor']	Shrestha 2021 [assessment: 'Fair']	Slezak 2021 [assessment: 'Fair']	Vitale 2021 [assessment: 'Good]	Wilkins 2021 [assessment: 'Fair']	Yoo 2021 [assessment: 'Poor']	Young-Xu 2021 [assessment: 'Fair']	Zare 2021 [assessment: 'Fair']
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	No – comparator population included at different time points	Yes	Yes	No – both patients and healthcare professionals recruited	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No – exposure and outcome were measuredsimultaneously	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

see an association between exposure and outcome if it existed?											
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	No – only considered fully vaccinated	N/A	N/A	N/A	No – only considered fully vaccinated or not accinated	N/A	N/A	N/A	N/A	No - only considered fully vaccinated or not accinated	N/A
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	No – based on PCR or clinical assessment	No – unclear how documented history of SARS-CoV-2 confirmed.	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	No – based on PCR or clinical assessment. Not all participants got retested	No – unclear whether PCR testing was undertaken in all patients	No – PCR re-testing was no undertaken in asymptomatic individuals	No – not all participant would have been retested	Yes	Yes	No – outcome measures intrinsically linked to exposuremeasures	No – unclear if asymptomatic individuals re-tested	No – unclear if asymptomatic individuals re-tested

12. Were the outcome assessors blinded to the exposure status of participants?	Unclear	No – retrospective study	No – retrospective study	Unclear	No – retrospective study	No – retrospective study	No – retrospective study	Unclear	No – retrospective study	No – retrospective study	No – retrospective study
13. Was loss to follow-up after baseline 20% or less?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No – 24% lost to follow-up	Yes	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	No	Unclear	No	Yes	Yes	Yes	Yes	No	Yes	No

Table A11: Quality Appraisal (case-control) from current version of evidence summary (version 8.0) , table 5 of 5

	Cavanaugh 2021 [assessment: 'Fair']
1. Was the research question or objective in this paper clearly stated?	Yes
2. Was the study population clearly specified and defined?	Yes
3. Did the authors include a sample size justification?	No
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Yes
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	No – use of NAAT or antigen test results
6. Were the cases clearly defined and differentiated from controls?	Yes
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible	N/A
8. Was there use of concurrent controls?	Yes
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	Yes
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	Yes
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	No – retrospective study
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	Yes

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