Rapid review on protective immunity post infection with SARS-CoV-2: update 3

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Introduction

What do we know about protective immunity from studies on reinfection with COVID-19, and correlates of immunity at 12 or more months post infection?

Understanding the extent and limits of protective immunity against COVID-19 has important implications for the COVID-19 pandemic and response. Immunity arising from infection with coronaviruses in general varies tremendously, from a few months for the seasonal coronaviruses associated with the common cold, to 2-3 years for the emerging coronaviruses such as SARS-CoV-1 and MERS[1]. For SARS-CoV-2 (COVID-19), it is known that most people develop immune responses following infection, however, for how long and to what extent the post infection immune response protects individuals from another COVID-19 infection is not yet clear. Previous versions of this report from February, April and August 2021 summarized the evidence on protective immunity post infection and post-vaccine and can be requested through ocsoevidence-bcscdonneesprobantes@phac-aspc.gc.ca. Due to the expanding evidence base, reviews on protective immunity post infection and post-vaccination have been done separately for update 3 (Oct 2021) and will be done separately for subsequent updates. All reports on protective immunity post infection or post-vaccination can be requested through ocsoevidence-bcscdonneesprobantes@phac-aspc.gc.ca. Evidence on individuals who were both infected and vaccinated are summarized in the immunity post vaccination review. This review looks at the evidence on protective immunity post infection only and summarizes the risk of reinfection and the durability of immune response markers ≥12 months post infection.

Reinfection with SARS-CoV-2 appears to be uncommon but there are challenges to studying this. First is the challenge of diagnosis. The use of nucleic acid amplification testing (e.g., RT-PCR) is excellent for identifying the presence of virus in making the initial diagnosis, but it will also be positive in the presence of non-infectious virus particles (RNA fragments) so, on its own, it cannot confirm reinfection. To address this, several definitions of reinfection have been proposed and are being used both in the literature and by public health organizations (e.g., European Centre for Disease Prevention and Control (ECDC), Pan American Health Organization (PAHO). For the purposes of this review, the definition from PAHO was used where a confirmed case of reinfection is defined as subsequent COVID-19 infection in an individual who has at least one documented negative RT-PCR test between infections and genomic sequence data from both episodes to distinguish two different genetic clades or viral lineages[2]. A suspected case of reinfection is defined by PAHO as a clinical or lab confirmed initial infection with a positive RT-PCR test >90 days from first infection or an infection occurring <90 days after the first infection with epidemiological evidence of re-exposure to SARS-CoV-2 and where infection by another

agent has been ruled out[2]. Some longitudinal cohort studies define a suspected case as a participant with a positive serological test after the first wave in the spring of 2020 for their primary COVID-19 infection. There are also challenges in assessing long-term immunity from COVID-19 post infection. This arises because immune responses are variable and not everyone who recovers from COVID-19 develops detectable antibody levels after infection. Specifically, a small proportion of individuals who are infected with SARS-CoV-2 do not appear to have detectable neutralizing antibody levels, but still recover from infection; the reasons for this are not fully understood[3]. Evidence suggests that neutralizing antibodies as well as memory B-cell (i.e., immune cells that produce virus targeting antibodies) and memory T-cell (i.e., immune cells that guide the cell mediated adaptive immune responses) activity specific to SARS-CoV-2 are good indicators of protective immunity. In addition, the variety of assays used to measure antibodies and T-cell or B-cell response complicates the assessment of long-term immunity as their results are not directly comparable. The association between measured long-term immune markers and protection from reinfection from both the wild-type and emerging variants is largely unknown. This rapid review summarizes the evidence on protective immunity in humans post infection from recent studies on risk of reinfection, and persistence of antibodies and other immune response markers for ≥12 months following initial SARS-CoV-2 infection published before October 22, 2021. Due to the abundance of human data, animal models of disease and in vitro studies were not included.

Key points

Forty-nine studies were identified, including 23 on risk of reinfection and 26 on the kinetics and durability of antibodies and other immune response markers at >12 months from initial SARS-CoV-2 infection and nine rapid or systematic reviews. The review is divided into two sections including reinfections (n=23) in people with prior infection. As well as studies that capture immune response markers 12-16 months post infection (n=26).

Risk of reinfection post infection

The best evidence to date on protective immunity post infection comes from reinfection data reported in 23 prospective cohort studies with >1000 participants, Table 1. Many of these cohorts are on-going and represent reinfections caused by original variants, variants of concern (VOC) or variants of interest (VOI). However, few studies had genotype data and reported the VOC or VOI data separately; results were extracted when provided.

- In a UK longitudinal study, the risk of reinfection was the same for original variants and Alpha[4,5], but an uptick in reinfection was identified during the time Delta

became dominant. Further research is needed to determine if this increase in reinfection was due to waning immunity, and/or lack of cross protection or increased infectivity of the Delta variant[6].

- Large prospective cohorts of suspected reinfections from the US, UK, Denmark, France, and South Africa suggest past SARS-CoV-2 infection provides protective immunity in 82-99% of individuals – although the follow up time varied from enrollment (1.5-13 months) and settings (e.g., hospitals, workplaces, military)[4,5,7,8,9,10,11,12,13,14,15,16,17]. Across studies, the proportion of individuals seropositive at baseline that became infected again (i.e., suspected reinfections) was lower than the proportion of seronegative individuals that became infected during follow-up (0.2-10% vs. 0.8-48%)[7,8,9,10,13,15,16,17,18].
    - Healthcare workers with positive SARS-CoV-2 anti-spike IgG responses at baseline had lower rates of PCR-positive tests during 6-7 months of follow-up compared to healthcare workers who were seronegative at the start of the study (0.13-1.27 vs. 1.08-4.29 per 10,000 days at risk)[7,13], as well as overall lower risk (RR 0.35, 95%CI: 0.15-0.85)[17]. A longer follow-up study (13 months) among healthcare workers found a similar trend (0.40 vs. 12.2 cases per 100 person-years)[10].
- Two studies from Nicaragua and Switzerland that looked at only symptomatic reinfections found past SARS-CoV-2 infection provided protective immunity in 78-93% of individuals followed up to 6-8 months[19,20].
- The included studies reported that higher antibody titers mounted post-COVID-19 infection were correlated with protection from reinfection for up to 13 months of follow-up.
    - There is evidence for a higher risk of reinfection among those who had low IgG titers or no detectable neutralizing antibody activity against SARS-CoV-2. For example, young healthy adults with high titers had an HR 0.45 (95%CI 0.32-0.65) against reinfection during high SARS-CoV-2 circulation at a US military facility in May-November 2020[15].
    - There were few reinfection cases with antibody titers taken close to reinfection. In a large prospective cohort study, there were two cases of reinfection at 7 months post infection where the 5 month sera had no detectable neutralizing antibodies[6,21].
- In four cohort studies, time to reinfection was highly variable, ranging from 90 to 374 days[4,20,22,23]. This was similar to a systematic review of confirmed SARS-CoV-2 reinfection cases that ranged from 20->350 days[24].

- Reinfection cases across prospective cohorts were more likely to be asymptomatic (~50-84%) compared to cases experiencing their first infection (19.2-68%)[4,25].

Immune response markers ≥12 months post infection

Twenty-six studies with follow-up of >30 participants 12-16 months post infection provide evidence that many individuals have detectable immune markers beyond 12 months after infection, however this varies by what targets were measured and what type of test was used as well as study design (Table 2).

- Six correlational studies reported positive correlations between humoral immunity markers (e.g. antibody titers) and cellular immune markers (T-cells and B-cells) taken between 12-16 months[26,27,28,29,30,31]. Within humoral markers, there was a weaker correlation between neutralizing antibodies (NAbs) and N-protein IgG[26,27,28].
- In eleven correlational studies, there was a positive correlation between cases that had more severe COVID-19 (or an acute infection that lasted longer than 10 days) and higher levels of humoral and T-cell activity taken between 12-16 months[7,28,31,32,33,34,35,36,37]. No correlation between memory B-cells activity and COVID-19 severity was reported[38].
- Six studies documented that a cellular immune response following infection was linked to memory B-cells (i.e., immune cells that produce virus targeting antibodies) or T-cells (i.e., immune cells that guide cell-mediated adaptive immune responses) [26,27,31,38,39,40]. It is likely these immune cells (B-cells and T-cells) are good indicators of some long-term immunity to subsequent reinfections.
    - Memory B-cell (n=1 study) and T-cell (n=5 studies) activity was shown to be elevated above baseline and in some cases was still increasing in both magnitude and breadth (meaning the cells continued to diversify in their function) 12-15 months post infection[26,27,31,38,39,40]. This suggests that despite waning circulating antibodies ≥12 months after recovering from SARS-CoV-2 acute infection, protective immunity may still be strong.
    - CD8+ T-cells were found to remain stable or decrease from peak levels up to 12 months post infection, whereas other studies found CD4+ T-cell responses continued to increase, indicating that antibody production via CD4+ cell activation persisted[27,31,39].
    - A preliminary study reported unique T-cell signatures at 6-15 months post-acute infection were correlated to post COVID-19 condition cases, where symptoms or sequelae lasted for more than 3 months post COVID-19 diagnosis[40].

- Long-term antibody kinetics in post COVID-19 infection were described in 25 studies conducted from 12-16 months post symptom onset. These studies found that the majority of individuals remained positive for circulating SARS-CoV-2 specific neutralizing antibodies (NAbs), S protein and/or RBD IgG antibodies 12 to 16 months from infection with overlapping ranges reported at monthly time points.
    - Six studies reported NAbs were detectable in 84%-99% of cases at 12-16 months[27,28,33,35,41,42].
    - Five studies reported S-protein IgG levels were detectable in 57-100% of cases at 12-13 months post infection[10,26,30,35,42].
    - Six studies found that RBD IgG antibodies continued to increase for up to 8 months before stabilizing, and 81% -100% of participants remained RBD-IgG positive at 12-16 months[27,33,36,43,44,45]. Conversely, one study found only 19% RBD-IgG positivity between 7-13 months, however S2-IgG and overall positivity was >85%, suggesting there may have been a test sensitivity issue with the RBD target antigen[46].
    - Seven studies identified that N-protein IgG and other classes of antibodies waned more rapidly and positivity was highly variable in 20-100% of cases at 12-16 months compared to NAbs, S protein, and RBD antibodies[27,33,36,38,43,44,45].
    - Four studies found that total IgG positivity was 62-95% at 12 months, longitudinal analysis between 6-12 months showed the total IgG levels were stable and the correlation with disease severity was smaller compared to results under 6 months[29,32,37,47].
- Other correlates of higher humoral or cellular immune markers were reported across studies:
    - One study found that symptoms of anosmia and dysgeusia (loss of smell and taste) were associated with higher anti-S protein and/or RBD IgG[43].
    - Five studies found that cases age >60 years or <18 years were associated with higher antibody titers[28,35,41,45,47].

Overview of the evidence

Reinfection studies: This review focuses on the highest level of evidence: large prospective cohorts (sample size >1000), some of which were large, multi-center studies as they have the lowest risk of bias and have the highest generalizability. However, multivariable analyses to account for potential confounding factors were not included in

some of these studies and may bias the results. Retrospective cohorts of medical record data or routinely collected surveillance data on COVID-19 were not captured because of their higher risk of bias due to the retrospective nature of the study, missing data, and possible confounding factors. Only four studies reported on VOCs; more prospective cohort studies are needed to assess protective immunity against VOCs.

Long-term immunity studies mainly include longitudinal evidence from observational studies, particularly of prospective cohort, large case series and cross-sectional design, which are at moderate to high risk of selection biases and confounding. For example, most studies reported clinical infection severity among study participants, but many did not analyse or control for risk factors that may explain some of the heterogeneity in correlates of immunity. Differences in study participant demographics, baseline immune status, clinical severity of infections, investigated immune outcomes, follow-up time and measurement methods likely contributed to some of the observed heterogeneity. Variability may have come from the application of different antibody and immune cell detection methods with different test sensitivity and specificity parameters.

Knowledge gaps in the current literature include:

- Lack of understanding of how the immunological measures (e.g., neutralizing antibody titers) correlate to protection and risk of reinfection.
- The correlation of specific antibodies, B-cells and T-cells reactive against SAR-CoV-2 in protecting against reinfection have not been definitively identified in humans.
- Evidence is accumulating on variants of concern including Alpha and Delta and prospective studies are being conducted to evaluate long term immunity. However, as vaccination coverage increases there will be fewer unvaccinated people to participate in prospective cohorts to study long term immunity post infection.

Risk of reinfection post infection

The summary below provides the best evidence to date from recently published large prospective cohort studies on risk of reinfection. Case reports, case series, retrospective cohorts and smaller prospective cohorts (with samples sizes <1000) were excluded from this review. Studies with these designs published prior to April 9, 2021 have been summarized in earlier versions of this review available through ocsoevidence-bcscdonneesprobantes@phac-aspc.gc.ca. High level points are listed below and detailed outcomes for each study are located in Table 1.

Results of reinfection studies (n=23)

Highlights from the current literature include:

- Previous infection resulting in antibodies seems to be associated with protection from reinfection for up to 13 months, however there has been a small proportion of people that have become reinfected. Reasons for reinfection or lack of protective immunity are not well understood.
- No large prospective cohort studies conducted a genomic analysis to ascertain confirmed reinfection among cases. Thus, evidence on reinfection in this review includes only suspected reinfection estimates.
- Four studies provided reinfection evidence on VOCs.
    - Alpha variant: Two studies reporting on the SIREN cohort (Jun 2020-Jan 2021) from the UK did not find any evidence that increased prevalence of Alpha adversely affected reinfection rates during follow-up[4,5]. Analysis suggested that the protective effect of previous infection after 4-9 months follow-up was similar when Alpha was dominant (Incidence Rate Ratio [IRR] 0.18, 95% CI 0.15–0.23) compared to the original variant (IRR 0.13, 95%CI 0.10–0.17, p=0.05)[4].
    - Delta variant: During the time when the Delta variant became dominant, the SIREN cohort study in the UK found that reinfections increased from 7 cases in April/May 2021 to 44 cases in June/July 20216.
    - Beta variant: In the placebo arm of a randomized controlled trial for the Novavax vaccine (used in India), there was no difference in infection or reinfection between seronegative and seropositive individuals, among which the majority of cases (92.7%) were caused by the Beta variant. This indicates that prior infection was not protective against reinfection with the Beta variant[48].
- Thirteen studies of suspected reinfections from the US, UK, Denmark, France, and South Africa suggest past SARS-CoV-2 infection provides protective immunity in 82-99% of individuals across a range of follow-up times from enrollment (1.5-13 months) and settings (e.g., hospitals, workplaces, military) compared to those without past SARS-CoV-2 infection; hazard ratio 0.15-0.41; odds ratio 0.09-0.25; incidence rate ratio 0.002-0.26; risk ratio 0.35-1.14[4,5,7,8,9,10,11,12,13,14,5,16,17].
- Two studies from Nicaragua and Switzerland that looked at only symptomatic reinfections suggest past SARS-CoV-2 infection provides protective immunity in 72-93% of individuals up to 6-8 months follow-up[19,20].
- Adults with end-stage kidney disease treated with hemodialysis, assessed over 5 months, were found to have much lower protection against reinfection; presence of

SARS-CoV-2 antibodies at baseline was associated with only a 45% lower risk of subsequent SARS-CoV-2 infection (IRR 0.55, 95%CI 0.32-0.95)[49].

- Ten studies found that previous COVID-19 diagnosis (clinical or laboratory confirmed) had a lower proportion, 0.2-10%, of suspected SARS-CoV-2 infections at 1.5 - 13 months follow-up compared to 10.8-48% among cases with no evidence of previous infection (seronegative or PCR negative at baseline) [,8,9,10,13,15,16,17,18,50].
    - One study of US Marine recruits found that reinfection was less likely among those with higher baseline IgG titres than lower to no baseline titres (hazard ratio 0.45, 95%CI 0.32-0.65, p<0.001) 15. This study also found that recruits with reinfections had viral loads ~10-times lower than first-time infected participants (p=0.004)[15].
    - Two reinfection cases had serology conducted at 5 months post infection prior to reinfection at 7 months, both cases had virus NAb levels below the estimated threshold for predicting immune protection[6,21].
    - Healthcare workers with positive SARS-CoV-2 anti-spike IgG responses had lower rates of PCR-positive tests after 8 months of follow-up compared to healthcare workers with no IgG responses at the start of the study (0.13 vs. 1.09 per 10,000 days at risk)[7]. A longer follow-up study (13 months) among healthcare workers found a similar trend (0.40 vs. 12.2 per 100 person-years)[10].
- In one US study, the incidence rate of COVID-19 reinfection in a cohort of healthcare workers was 0.35 cases per 1,000 person-days. Participants working with patients in COVID-19 clinical and non-COVID-19 clinical units were 3.77 and 3.57 times at greater risk of reinfection compared to those working in non-clinical units (administrative personal with no patient exposure), respectively[23].
- In four studies that measured time to reinfection, the reported range was 90-374 days[4,20,22,22]. These estimates only include suspected reinfection cases. They may have data points that are misclassified and instead represent persistent viral shedding or recurrence, both of which have been reported in the literature. A systematic review of confirmed cases of SARS-CoV-2 reinfections reported highly variable time to reinfection ranging from 20 days to >350 days[24].
- Three studies found that cases of reinfection were more likely to be asymptomatic (49.7-84% vs. 19.7-68%, respectively)[4,15] or mild compared to individuals with COVID-19 for the first time[7,10,16].

- Across two studies that only recorded symptomatic reinfections, only one reported cases that were admitted to hospital[51]. The other study demonstrated 10/15 symptoms were reported less frequently by participants who had been seropositive from a previous infection at baseline. The difference was statistically significant only for anosmia and dysgeusia (RR 0.33, 95%CI 0.15–0.73, P=0.004), chills (RR 0.59, 95%CI 0.39–0.90, P=0.01), and limb/muscle pain (RR 0.68 95%CI 0.49-0.95, P=0.02)[20].

Immune response markers ≥12 months post infection

This section summarizes 26 studies that report on immune responses measured between 12-16 months following SARS-CoV-2 infection. The included studies were limited to studies that reported >30 participants ≥12 months after SARS-CoV-2 infection (Table 2). Twenty-five studies looked at circulating serum antibody levels and/or seropositivity after infection, one study reported exclusively on T-cell activity and six studies reported on multiple cellular and humoral immune markers (i.e., B-cells and/or T-cells and antibodies) in the same sample. The majority of included studies were prospective cohorts or case series that followed the serology of RT-PCR confirmed COVID-19 cases over time. High-level points are listed below and detailed outcomes for each study are located in the Appendix (Table 2).

Overall, there was a lot of variability across studies due to differences in study participants, COVID-19 infection severity, frequency and duration of follow-up, investigated immune outcomes and measurement methods, which limit the synthesis of results across studies.

Key outcomes from B-cell and T-cell immune responses at 11 -15 months post infection (n=6)

Memory B-cells and T-cells following a natural infection likely confer some long-term immunity to reinfection[1,38,52]. There were six studies that measured B-cell and T-cell responses post infection. The viral antigen targets, activity, and counts of these memory cells were most frequently measured by flow cytometry cell analysis techniques, however various assays were also used. The variability of molecular biology techniques and the viral antigen markers used across studies limit the comparability of study results.

- Five studies on B- and T-cell activity found that for many individuals there is an established and sustained polyfunctional response (e.g., T-cells produce multiple cytokines resulting in a more effective response) at 12-15 months post COVID-19[26,27,38,39,40]. In two of these studies, the memory B-cells and T-cells have been shown to have diversified over time resulting in strong activity against a range of variants[38,39].

- Only one study reported on memory B-cell activity 12 months post COVID-19. B-cells were stable and had expanded clonality resulting in the expression of broad and potent antibodies with exceptional activity against a range of variants[38].
- T-cells are immune cells classified by surface receptors CD4+ or CD8+. The primary role of T-cells can be separated into the production of antibodies via B-cell activation (CD4+ T-cells) or the destruction of infected cells presenting certain antigens (CD8+ T-cells)[39]. The included studies isolated peripheral blood mononuclear cells (PBMCs) from serum samples then measured T-cell numbers, phenotypes or activity after simulation with various SARS-CoV-2 peptide sequence pools (i.e., amino acids that make up viral proteins)[26,31]. The variability and/or the lack of detail on peptide sequences used in simulation studies limit the comparability of study results. Increasingly studies also report Interferon-γ (IFNγ), interleukin-2 (IL-2), and/or Tumor Necrosis Factor α (TNFα) from commercial kits to measure T-cell reaction against antigens based on secreted cytokines[26].
- Five studies report on T-cell outcomes in previously infected cases 12-15 months post infection and show long-term polyfunctional and cytotoxic T-cells responsive to SARS-CoV-2[26,27,31,39,40].
    - The breadth and magnitude of memory T-cell responses were maintained and increased in three studies 12 months post infection[27,31,39]. The magnitude of detectable T-cells in two studies decreased between 6-12 months[26,39], but in two studies was reported to be stable[27,31].
    - In three studies at 12 months 76-92% of participants had detectable T-cell responses (CD4+/CD8+) against SARS-CoV-2[27,31,39] or had T-cell activity measured by detectable SARS-C0V-2 specific helper T-cells (80%), Interferon- γ (IFNγ) (65%) and interleukin-2 (IL-2) (43%)[26].
    - Two studies reported a positive correlation between CD8+ or CD4+ T-cell activity and NAbs, IgG and IgM seropositivity or titers[26,27].
    - Four studies showed a positive correlation with T-cell response at 12 months and more severe disease[27,31,39,40], length of acute infection (>10 days)[26], and older age (>60 years) [26]. Preliminary results from one study showed at 15 months post COVID-19 distinct immunologic profiles characterized by differentiated proportions of monocytes (a type of white blood cell involved in adaptive immunity)[40]. Those with post COVID-19 condition had significantly elevated levels of intermediate (CD14+, CD16+) and non-classical monocytes (CD14Lo, CD16+) compared to healthy, not infected, controls[40].

Key outcomes from circulating antibodies immune responses at 12-14 months post infection (n=25)

Humoral immunity, also called antibody-mediated immunity, generally refers to circulating antibodies that are directed at viral antigens[1,52]. Among included studies, circulating antibodies in serum samples were measured by antibody affinity assays, pseudovirus neutralization assays, flow cytometry, and other molecular biology-based techniques. Variation between assays was noted in several studies with large disagreement between results in some analyses; this was an important source of between study heterogeneity in at least four studies[53,54,55,56]. An example of this was a diagnostic test accuracy study that reported the Euroimmun assay missed 40% of positives in 8-month samples found by Roche assays[55]. The range of reported antibody outcomes included total antibodies, neutralizing antibodies (NAbs), antibody class (i.e., IgG, IgM, IgA) which were frequently further described by subclass (i.e., IgG1, IgG3), and/or binding affinity to SARS-CoV-2 viral antigens. Many studies often specified the viral antigen targets of the measured Ig antibodies, including the spike (S) protein, S1 or S2 subunit of the S protein, nucleocapsid (N), envelope (E), membrane (M) proteins, receptor binding domain (RBD) proteins, and accessory proteins (i.e., open reading frame (ORF) proteins).

Studies found most previously infected individuals had some detectable SARS-CoV-2 specific antibodies at 12-16 months from infection, but seroprevalence of specific antibody targets was variable. Longitudinal trends in humoral immune markers post infection across include studies are outlined below, by viral antigen and clinical severity.

- Three studies reported NAbs, anti-S protein and anti-RBD protein IgG were highly correlated, whereas anti-N IgG decreased rapidly and only was only weakly correlated with other circulating antibodies[26,31,57].
- Two studies found that seroreversion at 12 months was inversely associated with peak IgG for both S and N proteins[30,41].
- Three studies identified that antibodies had a steep decline over the first 6 months and then a much slower decline after 6 months[27,28,35].
- Neutralizing antibodies (NAbs) target the SARS-CoV-2 S protein and/or the RBD to neutralize the binding of the virus to ACE2 receptors of potential host cells. Seven studies found a range of study level results for proportion seropositive over time.
    - 16 months= 88%[33]
    - 15 months= 88%[33]
    - 14 months= 88%[33]

        - 13 months= 72-100%[33,35]
        - 12 months= 48-99%[26,27,28,33,41,42]
    - In one study, two-phase exponential decay modelling of neutralizing titers found that hospitalized patients had a steep decline in the first phase (half-life 26 days) and a slower decrease in the second phase (half-life 533 days) whereas those with mild or asymptomatic infection had no significant difference in slope, their titer peak was lower and their slow decline was similar to the second phase of severe cases[58].
    - One study on pseudo typed neutralization assays against variants indicated that more than half of participants tested generated 50% inhibition against Alpha, Beta, Gamma, Delta, and Lambda[33]. With severe or moderate disease, high neutralization titers against Alpha and Delta (82-100%) were maintained with lower neutralization for Beta, Gamma, and Kappa (64-100% positivity at 12-13 months), however neutralization was much lower for those who experienced mild disease[28,29,35].
- Six studies reported on S protein IgG levels which remained detectable up to 13 months[10,26,30,35,42,46] despite declining levels (82.8% decrease months 1-12) noted in three with longitudinal sampling[30,42,46].
        - 13 months= 96-100%[35]
        - 12 months= 57-97%[10,26,30,42]
    - Anti-S protein IgG levels were higher among those with severe disease compared to mild or asymptomatic disease at 12-13 months[30,35].
- Nine studies reported on RBD IgG antibodies up to 16 months[27,28,29,33,36,38,43,45] which continued to increase from baseline (within 3 months post COVID-19) up to 8 months and stabilize from 6-12 months[27,44,55].
        - 16 months= 91%[33]
        - 15 months= 100%[33]
        - 14 months= 97%[43]
        - 13 months= 91-97%[33,26]
        - 12 months= 81-95%[27,33,38,44,45]
    - In three studies, titers were higher in patients who had severe COVID-19[33,36,43]. In one study, cases that developed a loss of taste and smell had higher RBD IgG titers at 14 months[59].

- In three studies, there was a correlation between RBD Ig antibodies (all Ig classes), and the neutralization activity targeting SARS-CoV-2[27,28,29]. This association was consistent among those with mild to severe infections.

- One study indicated that N protein IgG and other classes of antibodies waned more rapidly than NAbs, S protein, RBD antibodies[28,30]. In seven studies, compared to other target antibodies, N-protein were highly variable and usually had lower levels of positivity compared to NAbs, S protein, RBD antibodies at ≥12 months[10,28,30,33,34,35,60]
    - 16 months= 91%[33]
    - 13 months= 91-97%[33,35]
    - 12 months= 20-100%[10,30,33,34,60]
  - In four studies, Anti-N protein seropositivity beyond 12 months was correlated with severe COVID-19[28,34,35,60].
  - In three studies, compared to other humoral immune markers, there were weak correlations between NAbs and N- protein IgG[26,31,57].
- In two studies IgG titers were reported to gradually decrease up to 6 months, but then remain stable 6-12 months post infection with seroreversion rates reported as 3-18% at ≥12 months[37,41].
    - 12 months: 62% -95.3% positivity[29,32,37,47]
    - At 7-13 months positivity was 88.1% in one small study[46]
- Other correlates of higher humoral or cellular immune markers were reported across studies.
  - In 11 studies, IgG antibody and NAb titers were higher among those with severe COVID-19 and lowest among those with asymptomatic COVID-19[27,28,31,32,33,34,35,36,37]. In five studies, the IgG antibody titers from severe cases had a sharper decrease up to 6 months and then the decline was very slow and levels were reported to remain higher than those who had mild COVID-19[33,34,37,44,45,58]. One study indicated at >12 months the difference in IgG or NAb titers between those that had severe and mild COVID-19 were not significant[31].
  - In three studies, higher age of cases (> 60 years old) was associated with higher titers[28,35,47]. In one study the IgG titers were U-shaped with children and older adults having higher titers[45]. This is consistent with another study that reported the children had higher neutralization titers than adults

(p=0.02) and the seroreversion rates at 4-12 months was 3.8% in children and 18% in adults[41].

- Four studies measured neutralization against variants of concern (VOC) or interest (VOI) ≥12 months post COVID-19; these preliminary results are based on small numbers of individuals and more data is needed to improve the confidence in these findings. Follow-up ranged between 10-16 months across studies and results included 52% of participants had low, but detectable neutralizing titers against Beta after >300 days[58]. At 16 months after infection 57% (8/14) of individuals had at least 50% inhibition against all variants (Alpha, Beta, Gamma, Delta, Lambda)[33], which was also in line with studies that had 13 months of follow-up, reported neutralization activity for Delta and Alpha and weaker neutralization for Beta, Gamma, and Kappa[28,35].

Review Literature

Nine relevant rapid and systematic reviews include COVID-19 research from June 2020 – August 2021 on correlates of immunity from previously infected individuals as well as reviews on reinfections (Table 3). These are included as resources for research on time points for immune markers earlier than 12 months and analyses of factors that correlate with a strong immune response to infection or vaccination. There are also systematic reviews reinfection data including summaries of confirmed reinfections typically reported as case reports which are not included in this review.

Methods

A daily scan of the literature (published and pre-published) is conducted by the Emerging Science Group, PHAC. The scan has compiled COVID-19 literature since the beginning of the outbreak and is updated daily. Searches to retrieve relevant COVID-19 literature are conducted in Pubmed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN, Research Square and cross-referenced with the COVID-19 information centers run by Lancet, BMJ, Elsevier, Nature and Wiley. The daily summary and full scan results are maintained in a Refworks database and an excel list that can be searched. Targeted keyword searching was conducted within these databases to identify relevant citations on COVID-19 and SARS-COV-2. Three separate searches were conducted to identify citations relevant to reinfection, breakthrough infections and immunity. Search terms used included: REINFECTION TERMS (reinfect* or re-infect* or recurren* or re-positive).

Immunity terms (month* or longitudinal) across studies with the Immunology tag.

This review contains research published up to October 22, 2021.

Each potentially relevant reference was examined to confirm it had relevant data and relevant data was extracted into the review.

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Evidence tables

Table 1: Large prospective cohort studies (n>1000) evaluating the risk of reinfection with SARS-CoV-2 (n=23)

Study	Method	Key Outcomes
Suspected reinfection caused by VOCs (n=4)		
Public Health England (2021) [6] Prospective cohort UK Jun 2020-Jul 2021	Asymptomatic and symptomatic staff (n=25,661) working at hospital sites participating in the SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) Study were enrolled between June 18 and December 31, 2020 and were followed to estimate the relative incidence of PCR-positive test results according to baseline antibody and/or PCR results. Earlier results from this study are also reported in Hall 2021 [4]. A possible reinfection was defined as a participant with two positive PCR samples 90 or more days apart or an antibody positive participant with a new positive PCR test at least 4 weeks after the first antibody-positive result. A probable case additionally required supportive quantitative serological data or supportive viral genomic data from samples available. As of July 2021 95% of the cohort was vaccinated and thus the number contributing to the reinfection rate was getting smaller.	• Reinfections increased from 7 cases (April/May) to 44 cases (June/July). This increase in reinfections coincides with the Delta variant becoming the dominant variant in the UK. • In 2 cases of reinfection, virus neutralizing antibodies levels were below the estimated threshold for predicting immune protection (neutralization level for 50% protection being 54 U/mL, which equates to a titre of 1:10 or 1:30 in most virus neutralization assays at 5 month post infection samples and reinfection occurred at 7 months [21].
Hall (2021) [4] Prospective cohort	Asymptomatic and symptomatic staff (n=25,661) working at hospital sites participating in the SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) Study were	• On follow-up, 1,704 new infections in the negative cohort and 155 reinfections were identified. Of these, 19.7% of new infections and 49.7% of reinfections were asymptomatic. • The incidence density was 7.6 per

UK Jun 2020-Jan 2021	enrolled between June 18 and December 31, 2020 and followed for 7 months to estimate the relative incidence of PCR-positive test results according to baseline antibody and/or PCR results. A possible reinfection was defined as a participant with two positive PCR samples 90 or more days apart or an antibody positive participant with a new positive PCR test at least 4 weeks after the first antibody-positive result. A probable case additionally required supportive quantitative serological data or supportive viral genomic data from samples available. The effect of the B.1.1.7 variant was included in the analysis by creating a binary variable of when the S-Gene Target Failure (SGTF) PCR accounted for 50% or more of the positive results for each region. Population: 8,278 (32%) participants had evidence of prior infection and were assigned to the positive cohort, 17,383 (68%) participants that had no evidence of prior infection were assigned to the negative cohort. 13,401 (52.2%) participants of the cohort were vaccinated during the follow-up period (between Dec 2020 and Jan 11, 2021). This included 9,468 in the negative cohort and 3,933 in the positive cohort. Once vaccinated participants no longer contributed to the reinfection data.	100,000 in the positive cohort and 57.3 per 100,000 in the negative cohort. • Participants in the positive cohort had 99.8% lower risk of new infection than did participants in the negative cohort, adjusted IRR (aIRR) 0.002 (95% CI 0.00–0.01). • Restricting infections to only those who had COVID-19 symptoms, participants in the positive cohort had a 93% lower incidence of new infection than did participants in the negative cohort, aIRR 0.074 (95% CI 0.06–0.10). • Using the most sensitive definition for reinfection, which included possible or probable cases, participants in the positive cohort had an 84% lower incidence of new infection than did the participants in the negative cohort, aIRR 0.159 (95%CI 0.13–0.19). • Those that had an asymptomatic infection had a higher risk of reinfection compared to those with symptomatic infection (aIRR 0.48 95% CI 0.37–0.63). • The authors did not find any evidence that increased prevalence of the B.1.1.7 variant adversely affected reinfection rates during follow-up. The models suggested that the protective effect of previous infection was similar when Alpha was present (IRR 0.18, 95% CI 0.15–0.23) compared when the original variant was dominant (IRR 0.13 (0.10–0.17), p=0.05).The median interval between the first PCR positive date or date of symptom onset of first infection and the reinfection PCR positive date was 201 days (95-297) or 241 days (90-345), respectively.
Lumley (2021) [5]	Healthcare workers (HCWs) were followed to investigate	Nasal and oropharyngeal swab

Preprint Prospective cohort UK Sep 2020-Feb 2021	and compare the protection from SARS-CoV-2 infection conferred by vaccination (results in Table 2) and prior infection (determined using anti-spike antibody status). Individuals were followed from >60 days after their first positive antibody test to either a positive PCR test or first vaccination. To assess the impact of the B.1.1.7 variant on (re)infection risk, they analysed PCR-positive results with and without S-gene target failure (SGTF), and those confirmed as B.1.1.7 on genome sequencing.	• 294/10,513 (2.7%) seronegative HCWs had symptomatic infection during follow-up vs. 1/1273 seropositive HCW (0.08%). Thus, incidence was 98% lower after 60 days in seropositive HCWs (adjusted IRR: 0.02 (95%CI: <0.01-0.18; p<0.001). • Rates of any PCR-positive result, irrespective of symptoms, were highest in unvaccinated seronegative HCWs (635 cases), with 85% lower incidence in unvaccinated seropositive HCWs (12 cases, aIRR=0.15 (95%CI: 0.08-0.26, p<0.001). • There was no evidence that SGTF changed the extent of protection against any PCR-positive infection in seropositive HCWs (aIRR vs. non-SGTF, 0.43, (95%CI 0.12-1.52; p=0.19). There was also no evidence that B.1.1.7 changed the extent of protection from any PCR-positive infection in those who were seropositive (aIRR vs non-B.1.1.7=0.40 (95%CI 0.10-1.64; p=0.20). • Seronegative HCWs had the highest viral loads (average Ct: 18.3) while unvaccinated seropositive HCWs had the lowest viral loads (average Ct: 27.2).
Shinde (2021) [48] Randomized controlled trial South Africa Aug-Nov 2020	Phase 2b trial of a NVX-CoV2373 nanoparticle vaccine. A total of 4387 participants were randomized and dosed at least once, 2199 with NVX-CoV2373 and 2188 with placebo. Serology at baseline was determined and follow-up RT-PCR testing was conducted. Whole virus genome sequencing was conducted on nasal samples.	Nasal swabs • Of the primary endpoint cases with available whole genome sequencing, 38 (92.7%) of 41 cases were the Beta variant. • Among placebo recipients, the incidence of symptomatic COVID-19 was similar in baseline seronegative vs. baseline seropositive participants during the first 2 months of follow-up: 5.3% (95%CI 4.3-6.6) vs. 5.2% (95%CI 3.6-7.2). This indicates that prior infection was not protective against reinfection with the B.1.351 variant.

Suspected reinfection caused by unspecified or original variants (n=19)		
Banerjee (2021) [51] Preprint **new** Prospective cohort India Oct 2020-Jun 2021	Individuals who tested positive for IgG antibodies in a population-based seroprevalence study (n=1,081) in Oct 2020 were followed up by telephone after 8 months to ascertain reinfections. Reinfection was identified by individuals self-reporting a history of fever, cough, and body ache, or after having coming in contact with a positive patient and RT-PCR was done to confirm reinfection.	• Reinfection was self-reported in 13/1081(1.2%) participants. • All self-reported reinfections were mild with 9 individuals recovering at home and 4 opting for hospital admission. • Of the 13 self-reported reinfection cases, 3 had reported receiving the COVID-19 vaccine prior to developing symptoms.
Massimo (2021) [22] Preprint Prospective cohort Italy Apr 2020-May 2021	COVID-19 recovered patients (n=2723) were recruited as potential convalescent plasma donors and tested for SARS-CoV-2 antibodies and followed for possible reinfection. Reinfection was defined as any confirmed positive RT-PCR test >90 days from first episode, regardless of symptoms, with at least one, negative RT-PCR tests on specimens collected between the first and second episode. Subjects were followed for >4 months. The LIAISON® chemiluminescence immunoassay (CLIA) SARS-CoV-2 S1/S2 IgG (DiaSorin) system was used for antibody screening. The CLIA values are expressed as AU (Arbitrary Units) (≥80 AU correlate with neutralizing antibody titer ≥1:160).	• Two cases of reinfection were reported with 1790 cumulative person-years follow-up. The estimated risk of reinfection was 1.1 x 1000 person-years in this cohort. • The second infection was diagnosed 201 and 347 days after the first one. • Both second infections were asymptomatic and detected during contact tracing or routine occupational screening. • One case was unvaccinated and the other was taken 2 days after the second dose of Comirnaty (BNT162b2) vaccine. • In the unvaccinated case, after the first infection the anti-SARS-CoV-2 CLIA value was 51 AU, after reinfection it rose to 129 AU. For the second case of reinfection only the NA titer was available after first infection and it was 1:40, the CLIA value after vaccination and reinfection was >400 AU.
Gallais (2021) [10] Prospective	Healthcare workers (n=1,309) with a COVID-19 history, proven either by serology (IgM and IgG against RBD or nucleocapsid proteins) at	• This study included 393 convalescent COVID-19 (COVID-19 positive group) and 916 COVID-19 negative HCWs. The COVID-19 positive HCWs included 345 with a history of positive

cohort France Apr 2020-May 2021	screening or by a previous RT-PCR (targeting two regions of the RdRp gene), were recruited and followed for up to 13 months. Participants that were seronegative without a history of positive RT-PCR were also recruited to evaluate incidence of infection during the follow-up period. Because the main objective of this study was to study serology over time, assessment of reinfection was based on participant reports during visits, as no RT-PCR surveillance was planned in the study. Therefore, it cannot be excluded that the COVID-19 positive participants had unnoticed asymptomatic reinfection during follow-up (although none had a significant increase of both anti-S and anti-N levels during follow-up).	SARS-CoV-2 RT-PCR and 48 with positive serology only. • Overall, 69 SARS-CoV-2 infections developed in the COVID-19 negative group for an incidence of 12.22 per 100 person-years. In contrast, there was one reinfection (asymptomatic) in the COVID-19 positive group for an incidence of 0.40 per 100 person-years, indicating a relative reduction in the incidence of SARS-CoV-2 reinfection of 96.7% (p<0.0001). • The one reinfection case experienced mild symptomatic COVID-19 during her first infection with a high viral load (Ct=17) and eventual anti-S and anti-N IgG seroconversion. The second episode occurred 9 months later, was asymptomatic, and was revealed by a low viral load (Ct=34), detected 6 days after exposure. The reinfection was associated with positive anti-S IgM and a rebound of anti-S and anti-N IgG titer 22 days after a second positive RT-PCR.
Cohen (2021) [11] Preprint Prospective cohort South Africa Jul 2020-Mar 2021	Estimated the burden and transmission of SARS-CoV-2 over the two waves un one rural and one urban community. Mid-turbinate nasal swabs were collected twice-weekly from consenting household members irrespective of symptoms and tested for SARS-CoV-2 by real-time RT-PCR (targeting E, N and RdRp genes). Serum was collected every two months and tested for anti-SARS-CoV-2 antibodies. Defined possible reinfection as >28 to 90 days between rRT-PCR positive specimens (no sequence data available) or between first seropositive specimen and rRT-PCR positive specimen; probable reinfection as >90 days between positive	• Among 71,759 samples from 1,189 participants, 834 (1%) were SARS-CoV-2-positive. • By PCR detection and serology combined, 34% (406/1189) of individuals experienced ≥1 SARS-CoV-2 infection episode. • Of 12 reinfections, 6 (50%) were classified as possible and 5 (42%) as probable and 1 (8%) confirmed. Thus 1.5% of the post infection cohort experienced a probably or confirmed 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).

	specimens; and confirmed reinfection as distinct Nextstrain clades on sequencing or variant PCR between rRT-PCR positive specimens meeting the temporal criteria for possible or probable.	
Kohler (2021) [20] **new** Prospective cohort Switzerland Jun 2020-Mar 2021	Across 17 healthcare institutions in Northern and Eastern Switzerland, 4812 HCWs were tested for SARS-CoV-2 antibodies (Jun-Sep 2020) and followed for possible reinfection. Subsequently, participants were tested through nasopharyngeal swabs if they experienced any COVID-19 symptoms such as fever and/or the presence of any respiratory symptom (i.e., shortness of breath, cough, or sore throat). Participants were then asked to fill out a weekly survey to record COVID-19 symptoms and the date/result of any PCR or rapid antigen test. The median follow-up time was 7.9 months [IQR 6.7–8.2].	• At baseline, 144 (3%) participants were seropositive and 4668 (97%) were seronegative. Nasopharyngeal swabs • A positive test result was found in 3/67 (4.5%) participants who were seropositive at baseline and 547/2645 (20.7%) who were seronegative. This translates into a RR of 0.22 (95% CI: 0.07-0.66, P = 0.002) for a positive nasopharyngeal swab after positive baseline serology. • The 3 cases with suspected reinfection were all diagnosed in Jan 2021 after a follow-up (time from baseline serology to 2nd positive test) of 198, 200, and 220 days. 1/3 cases were asymptomatic at the time of reinfection. Full cohort • Including those who did not undergo nasopharyngeal testing, the corresponding RR was 0.18 (95% CI: 0.06-0.55, P < 0.001) for protection against reinfection. • 10/15 symptoms were reported less frequently by participants who were seropositive at baseline. The difference was statistically significant only for impaired olfaction/taste (RR 0.33, 95% CI: 0.15–0.73, P = 0.004), chills (RR 0.59, 95% CI: 0.39–0.90, P = 0.01), and limb/muscle pain (RR 0.68 95% CI 0.49-0.95, P = 0.02) which were all less likely among reinfections.
Maier (2021) [19]	In this study, 2,338 individuals were followed to assess the	• Over the one year study period, 129 people tested positive by RT-PCR, an

new Prospective cohort Nicaragua Mar 2020-Mar 2021	incidence of SARS-CoV-2 infection and examine the degree of protection from repeat SARS-CoV-2 infection among seropositive individuals. Blood samples were collected in Mar 2020 or at enrollment, and mid-year samples were collected during Oct-Nov 2020. SARS-CoV-2 infections confirmed by RT-PCR were reported for the entire study period, and seropositive infections were reported for the period between blood samples. To examine the protection from symptomatic reinfection provided by anti–SARS-CoV-2 antibodies, the number of symptomatic RT-PCR–confirmed infections was compared by serostatus.	overall incidence of 5.3 infections per 100 person-years (95%CI: 4.4-6.3). • At mid-year, the overall seroprevalence was 56.7% (95%CI: 53.5%–60.1%). • Between the mid-year sample and end of Mar 2021, there were 12 symptomatic cases among 863 seronegative individuals (1.4%) and 1 symptomatic case among 1132 seropositive individuals (0.1%). Therefore being seropositive at mid-year was associated with 93.6% protection from symptomatic reinfection (95%CI: 51.1%–99.2%).
Finch (2021) [12] Preprint Prospective cohort US Apr 2020-Feb 2021	Analysed longitudinal PCR and IgG receptor-binding domain (RBD) serological testing data from a cohort of US SpaceX employees (n=4411) in four states. Reinfection was defined as a new positive PCR test more than 30 days after initial seropositive result. A multivariable logistic regression (Adjusted for race, ethnicity, state, job category and BMI) was conducted to investigate the association between baseline serological status and subsequent PCR test result. This required the authors to choose a cut-off week in order to define baseline seroprevalence and the subsequent observation period for PCR testing. A sensitivity analysis was conducted to identify the optimum cut-off date to define baseline	• Of 4411 individuals enrolled, 309 individuals tested seropositive during the study period for an overall adjusted seroprevalence of 8.2% (95% CI: 7.3-9.1). • Both serology and follow-up PCR testing data were available for 1800 individuals. • 14 possible reinfections were identified with a median time of 66.5 days between initial seropositive test and PCR positive test. • Estimated an adjusted odds ratio of 0.09 (95%CI 0.005-0.48) for reinfection, with the week of 26th July 2020 as the optimal baseline time point (this week fell after the first wave). Odds ratio estimates using cut-off weeks in between the two waves of infection (between mid-July and mid-September 2020) ranged from 0.09 (95%CI 0.005-0.48) to 0.25 (95%CI 0.037-1.01). • Overall, findings suggest that the presence of SARS-CoV-2 antibodies at baseline is associated with around

	seroprevalence. Follow-up was 6-10 months.	91% reduced odds of a subsequent PCR positive test, at least over a 6 month time period.
Krutikov (2021) [9] Prospective cohort UK Jun 2020-Feb 2021	Residents (n=682) and staff (n=1429) of 100 long term care facilities were tested for SARS-CoV-2 by RT-PCR monthly and weekly, respectively. Individuals who tested positive were not tested again for 90 days. Blood sampling was offered to all participants at three time points separated by 6-8 week intervals in June (baseline), August and October 2020 to determine antibody titers. All positive PCR tests after October 2020 were considered to indicate infection or reinfection. For reinfection cases, most participants had at least 90 days and all had two or more negative PCR tests between their baseline antibody test and PCR-positive test.	• Baseline antibodies were detected in 226 residents (33%) and 408 staff (29%). • In residents, a total of 93/456 antibody negative individuals had a PCR positive test at follow-up (0.054 per month at risk) compared to 4/226 antibody positive individuals (0.007 per month at risk). • In staff, a total of 111/1021 antibody negative individuals had a PCR positive test at follow up (0.042 per month at risk) compared to 10/408 antibody positive individuals (0.009 per month at risk). • In Cox regression analysis, the relative adjusted hazard ratios for PCR positive infection was 0.15 (95%CI 0.05-0.44, p=0.0006) for seropositive residents vs. seronegative residents and 0.39 (0.19-0.82, p=0.012) for seropositive staff vs. seronegative staff. • These results suggest that previous infection reduced the risk of reinfection by approximately 85% in residents and 60% in staff members, based on up to 10 months of follow-up. • Of the 12 reinfection for which symptom data was available, 11 were symptomatic. None were admitted to hospital or died as a result of their infection. • The median Ct value for reinfection cases was 36 (30.1-37.0). • There was no difference in quantitative antibody titres against spike or nucleocapsid proteins in reinfected individuals compared with uninfected individuals with baseline antibodies.
Wilkins (2021) [13] Prospective	HCWs were invited to participate in a cohort study of SARS-CoV-2 serology and COVID-19 risk. Participants	• In the 6194 participants who were seronegative at baseline, 519 (8.4%) had a positive PCR after baseline serology testing (rate = 4.25/10,000

cohort US May 2020-Jan 2021	were invited to undergo serology testing between May 26th and July 10th (baseline) and then between November 9th and January 8th, 2021 (6-month follow-up). Participants who were seropositive at baseline were considered to be at risk for possible reinfection 90 days after their antibody test until end of follow-up or to first positive PCR plus one 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. IRR analyses were adjusted for age, sex, race, and occupation.	person days). • In the 316 participants who were seropositive at baseline, 20 participants had positive PCR results during follow-up. Among those, 8 (2.5%) met the study criteria for possible reinfection, representing a possible reinfection rate of 1.27/10,000 days at risk (95% CI: 0.55 – 2.51). • Five of these eight cases of possible reinfection during follow-up were asymptomatic and no cases were severe. • The unadjusted and adjusted incidence rate ratios were 0.30 (95%CI 0.15 – 0.60) and 0.26 (95%CI: 0.13 – 0.53) for participants who were seropositive at baseline compared to those who were seronegative at baseline, respectively. • In a sensitivity analyses, in which seronegative participants were not eligible for inclusion in the infection analysis until 90 days or more following their serology result, the possible reinfection rate was 6.7%. The rate of infection per 10,000 days at risk was 3.72 (95%CI 3.39 – 4.08).
Ronchini (2021)[61] Preprint **new** Prospective cohort Italy Apr 2020-Jan 2021	Health-care, support staff, administrative and research personnel (n=1,493) at a cancer center in Milan were tested at baseline for SARS-CoV-2 infection by qPCR using the Allplex SARS-CoV-2 Assay and IgGs using an in-house ELISA assay. Participants were then followed up for up to 6-months to determine possible reinfection. Reinfection was defined as a participant with 2 positive PCR samples with a negative PCR in between and considering a positive PCR after 60 or more days.	• At baseline 266/1,493 (17.8%) infections were identified. • 8/266 (3%) possible reinfections were reported, of which 7/8 were IgG+ at enrollment. • 5 participants had reinfection at >60 days. • When considering only individuals who tested positive for more than one SARS-CoV-2 gene in the qPCR assay, the frequency of reinfections dropped to 2/266 (0.75%).

Rivelli (2021) [23] Preprint **new** Prospective cohort study US Mar 2020-Jan 2021	HCWs (n=2,625) from Illinois and Wisconsin with a COVID-19 history, proven by the presence of SARS-CoV-2 antibodies and a previous RT-PCR, were recruited and followed for up to 10 months. COVID-19 reinfection was defined by current CDC guidelines (subsequent COVID-19 infection ≥ 90 days from prior infection). For those with more than two positive PCR results, the second documented infection that was closest to 90 or more days from the prior infection was included.	• Over the 10-month study period, 156/2,625 (5.94%) experienced reinfection. • The median days to reinfection were 126.5 (105.5-171.0), with the majority of reinfection occurring between 90-119 days (42.95%). • Incidence rate of COVID-19 reinfection was 0.35 cases per 1,000 person-days. Participants working in COVID-clinical and clinical units were 3.77 and 3.57 times at greater risk of reinfection compared to those working in non-clinical units, respectively.
Abo-Leyah (2021) [4] Prospective cohort Scotland May-Dec 2020	Health and social care workers (n=2063) were followed in this study. The Siemens SARS-CoV-2 total antibody assay was used to establish seroprevalence in this cohort. New infections post antibody testing were recorded to determine whether the presence of SARS-CoV-2 antibodies protects against reinfection.	• At enrolment, 300 HCWs (14.5%) had a positive antibody test. • There was one RT-PCR-positive reinfection among the HCWs (1/300, 0.33%). The presence of antibodies was associated with an 85% reduced risk of reinfection with SARS-CoV-2 (hazard ratio 0.15, 95% CI 0.06–0.35; p=0.026), over a follow-up period of up to 6 months. • This reinfection was in a symptomatic HCW who tested positive by RT-PCR 76 days after having detectable antibodies in their serum.
Dimeglio (2021) [8] LTE Prospective cohort France Jun-Dec 2020	Healthcare workers (n=8758) were screened for serum SARS-CoV-2 anti-spike antibodies and neutralizing antibody titers after the first wave of epidemic (June/July). Serology was investigated over time and new infections were identified during follow-up in Nov/Dec.	• The median follow-up was 167 days (IQR: 156-172). • Among the seropositive group, 1.8% (5/276) were positive at follow-up compared to 12.1% (1028/8482) of the seronegative group (p<0.01). • The five individuals who tested seropositive at baseline and then experienced infection during follow-up included two with low/undetectable neutralizing antibody titers after the first infection, and three with above-median titers. • The data indicate that previous

		infection provided protective immunity for at least 167 days.
Lumley (2020) [7] Prospective cohort UK Apr-Nov 2020	Followed asymptomatic and symptomatic staff (n=12,541) at Oxford University Hospitals for up to 31 weeks to estimate the relative incidence of PCR-positive test results and new symptomatic infection according to antibody status.	• Health care workers with positive SARS-CoV-2 anti spike IgG assays at baseline have lowers rates of PCR-positive tests at follow up than workers with negative baselines results (0.13 vs 1.09 per 10,000 days at risk). • The incidence of positive PCR tests was inversely associated with anti-spike antibody titers, suggesting previous infection resulting in antibodies to SARS-CoV-2 is associated with protection from reinfection for at least 6 months. • Of the three seropositive health care workers that had subsequent PCR-positive tests for SARS-CoV-2 infection, only one had previously tested positive for SARS-CoV-2, 190 days prior. This case was asymptomatic upon possible reinfection, with negative RT-PCR tests 2 and 4 days later and no subsequent rise in antibody titers • Reinfection results could be consistent with a re-exposure to SARS-CoV-2 that did not lead to symptoms but could also plausibly have been a false positive. Caution should be used when interpreting the results of this study.
Letizia (2021) [15] Prospective cohort US May-Nov 2020	This analysis was performed as part of the prospective COVID-19 Health Action Response for Marines study (CHARM) which includes predominately male US Marine recruits, young healthy adults. Baseline SARS-CoV-2 IgG seropositivity for RBD and spike proteins was assess during a 2 week quarantine period. PCR positivity was also assessed at 0, 1 and 2 weeks of the quarantine period and	• 3076 participants were followed-up during the study period after quarantine for 6 weeks. • 189 participants were seropositive at baseline, of which 19 (10%) had a subsequent positive PCR test during the 6-week follow-up (1.1 cases per person year). In contrast, 1079 (48%) of 2247 seronegative participants tested positive (6.2 cases per person-year). The incidence rate ratio for SARS-CoV-2 infection in the seropositive group was 0.18 (95% CI 0.11–0.28; p<0.001). Thus, presence

	individuals were excluded at this stage if they had a positive PCR test. Following quarantine, a closed cohort of 3076 recruits went on to basic training where three PCR tests were done at weeks 2, 4, and 6 in both seropositive and seronegative groups. SARS-CoV-2 was in circulation at the training site despite quarantines. Time from initial infection, prior to training is not reported. Only IgG titers at enrollment are available as an indication of the potential protection against reinfection for each participant.	of antibodies to SARS-CoV-2 conferred an 82% reduced incidence rate of SARS-CoV-2 infection. • After adjusting for the effects of race, age, and sex on the SARS-CoV-2 infections, the hazard ratio (HR) comparing seropositive participants and seronegative participants was 0·16 (95%CI 0.10–0.25, p<0.001). • Among seropositive recruits, infection was more likely in those that had lower baseline IgG titres than in those with higher baseline titres (hazard ratio 0.45, 95%CI 0.32-0.65, p<0.001). Seropositive cases who became infected were also more likely to lack detectable baseline neutralizing antibody activity compared to those that were uninfected (p<0·0001). • Infected seropositive participants had viral loads that were ~10-times lower than those of infected seronegative participants (p=0.004). • Symptomatic infection occurred in three (16%) of the baseline seropositive participants versus 347 (32%) of the baseline seronegative participants (p=0.13).
Papasavas (2021) [18] Prospective cohort US May-Nov 2020	Healthcare workers (n=6863) were tested for SARS-CoV-2 antibodies 3 times (baseline, after 2-4 weeks, and after 3-6 months). Abbott Architect i2000 platform was used for the qualitative detection of IgG antibodies to the nucleocapsid protein of SARS-CoV-2.	• At baseline, the prevalence of SARS-CoV-2 antibody among 6863 HCWs was 6.3% (95%CI 5.7–6.9%). • The incidence of reinfection was 0% in the seropositive group and the incidence of a positive PCR test was 1.2% in the seronegative group after a median follow-up of 5.5 months.
Cohen (2021) [49] Prospective cohort	Adults with end-stage kidney disease (ESKD) treated with in-center hemodialysis (ICHD) (n=2337) were assessed for the presence or absence of IgG against SARS-CoV-2 spike and	• 9.5% were anti-SARS-CoV-2 IgG positive at baseline; 3.6% had a known history of COVID-19. • Over 6679 patient-months of follow-up, 263 participants had evidence of

US Jul-Oct 2020	nucleocapsid proteins at baseline and then assessed ~90 days later, and 3 more times monthly, for SARS-CoV-2 infection detected by RT-PCR. Two outcomes were considered. First, any SARS-CoV-2 infection, whether detected during routine clinical surveillance or via a protocolized PCR test at Visits 3, 4, or 5. The second outcome was only those SARS-CoV-2 infections detected during routine clinical surveillance (termed clinically manifest COVID-19), because these represent symptomatic infections.	SARS-CoV-2 infection, 141 of which were captured via clinical surveillance (symptomatic). • Presence of SARS-CoV-2 antibodies at baseline was associated with a 45% lower risk of subsequent SARS-CoV-2 infection (incidence rate ratio 0.55, 95%CI 0.32-0.95) and a 79% lower risk of subsequent symptomatic SARS-CoV-2 infection (IRR 0.21, 95%CI 0.07-0.67).
Iversen (2021) [17] **new** Prospective cohort Denmark Apr-Oct 2020	Screening for antibodies against SARS-CoV-2 was offered 3 times during a 6 month period to HCWs in the Capital Region of Denmark. A total of 44,698 HCWs participated with 18,679 (42%) individuals participating in all 3 rounds. After each round, participants filled in an online survey and self-reported information about demographics, exposure to SARS-CoV-2, symptoms and SARS-CoV-2 PCR testing.	• The seroprevalence increased from 4.0% (1501/37,452) in round 1 to 5.8% (1722/29,862) in round 2, and 7.4% (2022/27,457) in round 3 (p<0.001). • 7/801 (0.87%) of those who were seropositive and 193/25,144 (0.77%) who were seronegative self-reported a positive PCR test between rounds 1 and 2 (RR 1.14, 95%CI: 0.54-2.41, p=0.68). • Between rounds 1 and 3, 5/760 (0.66%) of those who were seropositive and 389/20,894 (1.86%) who were seronegative self-reported having a positive PCR between the rounds (RR 0.35, 95%CI: 0.15-0.85, p=0.012). • Between rounds 2 and 3, 3/796 (0.38%) of those who were seropositive and 210/19,280 (1.09%) who were seronegative self-reported a positive PCR test between the rounds (RR 0.35, 95%CI: 0.11-1.08, p=0.051).
Rovida (2021) [16] Prospective	Healthcare workers (n=3810) were tested for previous SARS-CoV-2 infection according to serostatus determination (SARS-CoV-2 anti-S1 and anti-	• 336 subjects were seropositive and 3474 seronegative at baseline. • During the second pandemic wave, SARS-CoV-2 infection was detected in

cohort Italy Apr-Jun 2020	S2 IgG antibody). Nasopharyngeal swabs were collected and tested for SARS-CoV-2 RNA positivity in subjects with symptoms suggestive for SARS-CoV-2 infection or in case of contact with infected subjects.	9 seropositive and 225 seronegative subjects. The 3-months cumulative incidence of SARS-CoV-2 infection was 2.68% in seropositive vs 6.48% in seronegative subjects (p=0.006), with a hazard ratio of 0.41 (95%CI 0.26-0.61). The protective effect of the immunity elicited by natural infection was 59% (95% CI 39-74%). • Data on symptoms were available for 4 reinfection cases: one case developed mild symptoms and no patient required hospitalization.

Abbreviations: LTE, letter to editor; IRR, incidence rate ratio; RBD, receptor binding protein; RR, risk ratio

Table 2: Immune responses 12 or more months after SARS-CoV-2 infection (n=26)

Study	Method	Key Outcomes
Circulating Antibody, B-cell and T-cell Immune Responses (n=5)		
12 months post infection		
Lu (2021) [39] Prospective cohort US Mar 2020-Mar 2021	12 months post SARS-CoV-2 infection (n=29) this study investigated the function, phenotypes, and frequency of T-cells using intracellular cytokine staining and spectral flow cytometry. SARS-CoV-2 antibodies were also examined using CYTEK Aurora 5-laser spectral flow cytometer.	T-cells: • At 12 months there was evidence of polyfunctional and cytotoxic T cells responsive to SARS-CoV-2. • 75.9% (22/29) had CD4+ and CD8+ T-cells present identified using peptide pools of N, M and S SARS-CoV-2 proteins. • CD4 was more frequently identified than CD8 T-cells in peripheral blood. • Frequency of SARS-CoV-2 specific CD4 T cells and antibodies were higher among those that had severe COVID-19, but polyfunctional and cytotoxic T-cell responses were identified across a range of COVID-19 disease severities. Antibodies: • Antibodies against the S and N protein were present. • In mild cases anti-N protein antibodies were undetectable at 12 months.
Wang 2021 [38] Prospective cohort US Feb 2020-Mar 2021	A cohort of 63 recovered from PCR confirmed COVID-19 were assessed at 1.3, 6.2 and 12 months post infection. (At 12 months 26 had received at least one dose of mRNA-1273 (Moderna) or BNT162b2 (Pfizer) 2-82 days before follow-up and are excluded from this summary.) 10% were hospitalized during infection, 44% and 14% reported persistent long-COVID symptoms at 6 and 12 months	Immune responses among the unvaccinated (n=37) at 12 months post infection were as follows: Antibodies: • Antibody positivity was maintained for the anti-RBD IgM (103%), IgG (82%), and IgA (72%). • Anti-N antibody titers decreased significantly between 6-12 months. • Virus neutralizing activity against the original variant among the unvaccinated remained relatively stable between 6-12 months post

	respectively. Serum SARS-CoV-2 RBD specific antibody levels were measured by ELISA, memory B-cells specific to SARS-CoV-2 RBD were measured by FLOW cytometry. Virus neutralization activity in serum samples, against the original variant and VOCs was measured.	infection. • VOC neutralizing activity against Alpha, Iota, Beta and Gamma was generally lower than against the Wuhan strain; the greatest loss of activity was against Beta. Memory B-cells: • The number of circulating RBD-specific memory B-cells remained relatively stable, and was only 1.35 times lower at 12 months post infection compared to 6 months. • RBD memory B-cell clonality was expanded resulting in monoclonal antibodies with exceptional activity against a range of variants.
Rank (2021) [26] **new** Prospective cohort Germany Jul 2021*	Antibodies (Spike1 IgG/IgA), neutralizing antibodies, Interferon gamma (IFN-γ), interleukin-2 (IL-2), SARS-CoV-2-specific CD4+T- cells were measured in 83 convalescent plasma donors at 6 weeks, 6 months, and 12 months. IgG and IgA were analyzed with the Euroimmum ELISA assay. The ELISPOT Interferon-γ (IFNγ kit and IL-2 CoV-iSpot kit measure T-cell reaction against antigens based on secreted cytokines. The activation-induced marker (AIM) assay measured CD4+T-helper cells (THC, CD25hi CD134hi) through the upregulation surface activation induced markers.	Antibodies: • At 12 months anti-S1 IgA and IgG antibodies were detectable in 78% and 66% of participants, respectively. Median anti-S1 IgA levels were 1.9 (0.5–20.3) and anti-S1 IgG level were 1.7 (0.6–10.6) at 12 months, representing a ~50% within the first 6 months followed by a slow decline 6-12 months. • 48% (37/77) of participants had neutralizing antibody titers at 12 months however titers decreased from 1:5 (1:1–1:640) at 6 weeks to 1:1 (1:1–1:40) at 12 months. 6-week antibody and Nab levels were highly correlated with 12 month levels. T-cell: • At 12 months there were fewer detectable T-cell IFN-γ in 65% (48/76) and IL-2 in 43% (30/70) compared to the 6-month follow up (40/51 (78%) and 24/32 (75%), respectively). Stimulation indices also declined for IFN-γ and IL-2. • AIM assays found detectable specific T-helper cells (THC) in 80% (56/70) of

		participants at 12 months, of which 39% (8–64) were central specific T-cells and 58% (20–84) a effector memory T-cells. Correlative Analysis: • Older age and a longer duration of the acute phase of COVID-19 were associated with higher humoral and T-cell responses. • A longer acute phase of COVID-19 (median over 10 days) was associated higher anti-S1 IgG levels (3.3 (0.6–9.5) vs. 1.4 (0.6–10.6)), and significantly more double-positive T-cells (39%) vs. (8%).
Feng (2021) [31] **new** Prospective cohort China Jan 2020-Feb 2021	204 convalescent patients admitted to hospital were followed for up to 12 months (280- 360 days, n=50 completing all four sampling points). Plasma S-IgG. RBD-IgA, RBD-IgG were measured through the Kangrun Biotech electrochemiluminescence immunoassay kits in addition to miconeutralization assays and T-cell responses through IFN-y ELISPOT assays.	Antibodies: • RBD-IgG and S-IgG were stable and highly correlated between 6- 12 months with 12 month levels at 170 AU/ml and 290 AU/ml, respectively. • At the 12 month mark average RBD-IgA and RBD-IgM were negative. • Antibody level differences by severity of COVID-19 were not significant at 12 months. NAbs: • Microneutralization assays found stable neutralization capabilities from 6-12 months which were correlated with RBD-IgG. T-cell: • T-cell responses indicate IFN-γ to N, S1, S2 peptide pools decreased from baseline but remained stable between 6 and 12 months. • Severely infected patients had more IFN-γ secreting cells towards S1 and S2 peptide pools than those with moderate or mild disease at 12 months.
Zhang (2021) [27]	Antibodies (NAb, IgG, and IgM) and T-cell responses were measured in 101 convalescent	Antibodies: • 99% (95%CI 93-100) of cases had detectable NAbs at 12 months (95% at

new Prospective cohort China Jul 2020-Jan 2021	cases at 6 and 12 months after symptom onset. A total of 74 participants had results at the 12 month mark with 56 having results at both time points. NAbs and Spike RBD IgG and IgM was measured both through microparticle chemiluminescence and ELISA. IFN-γ, IL-2, TNFα T-cell responses were measured in PBMC (fresh and cultivated) with ELISpot assays with four peptide pools: S1, S2, M and N.	6 months). • 95% (95%CI 87-99) of cases were RBD-IgG positive on both assays and this was stable between 6-12 months. • 26% (95%CI 16-37) of the cases were RBD-IgM positive on both assays, RBD-IgG, RBD-IgM, and NAbs were all positively correlated to each other and with more severe disease. T-cells: • At 12 months positive T-cell responses were detected against SARS-CoV-2 (92%, 95%CI 83-97), S1 (78, 95%CI 67-87), S2 (68%, 95%CI 57-79), M (82%, 95%CI 71-90) and N (82% 95%CI 71-90). • T-cell responses at 12 months were linearly correlated with severity of COVID-19. • At 12 months, antibody responses were correlated with S protein directed T-cell responses. • CD4+ and CD8+ and the proportions secreting IFN-γ, IL-2, TNFα were stable between 6-12 months. These groups were mainly composed of effector memory T cells (CD45RA−CCR7−), as well as naïve (CD45RA+CCR7+), central memory (CD45RA−CCR7+), and effector (CD45RA+CCR7−) cells.
T-cell Immune Response (n=1)		
15 months post infection		
Patterson (2021)[40] Preprint Prospective cohort	The presence of SARS-CoV-2 S1 protein was measured in 46 convalescent individuals. T-cell, B-cell, and monocytic subsets in both severe COVID-19 patients and in patients Post COVID-19 condition were included in the analysis. Non-classical monocytes were sorted from post COVID-19 condition patients using flow	15 months post infection: • In patients with post COVID-19 condition the levels of both intermediate (CD14+, CD16+) and non-classical monocyte (CD14Lo, CD16+) were significantly increased compared with healthy controls (P=0.002 and P=0.01, respectively). • In convalescent cases that had severe COVID-19, neither the intermediate nor non-classical monocytes were

US Jul 2021 (est)	cytometric sorting and the SARS-CoV-2 S1 protein was confirmed by mass spectrometry. PBMCs were screened for SARS-CoV-2 RNA using quantitative droplet digital PCR (ddPCR).	elevated. • A statistically significant number of non-classical monocytes (CD14lo, CD16+) contained SARS-CoV-2 S1 protein in both severe (91%, P=0.004) and post COVID-19 condition cases (73%, P=0.02) out to 15 months post infection. • 36% (4/11) and 4% (1/26) of convalescent severe COVID-19 cases and post COVID-19 condition cases respectively were ddPCR positive, these were confirmed to only be fragmented SARS-CoV-2 RNA. • These results show the patients developed an immune response to retained viral antigens (S1 of spike), which continues to be presented by CD16+ monocytes, eliciting an innate immune response characterized by elevated inflammatory markers including interferon , IL-6, IL-10, and IL-2, among others. This may indicate an innate inflammatory dysregulation due to persistent viral protein presentation, further work is needed.
Circulating Antibody Immune Responses (n=20)		
14-16 months post infection		
Yang (2021) [33] Preprint **new** Prospective cohort China Jan 2020-May	COVID-19 diagnosed patients were recruited between January and April 2020 (n=214) and followed as long as they were unvaccinated or were not reinfected, up to a maximum of 480 days (16 months). Viral inhibition was measured against variants (Alpha, Beta, Gamma, Delta and Lambda) in addition to the micro-neutralizations (NAbs) assay, the RBD and N protein IgG antibodies were measured by Sinobio.	• Samples collected between 11 to 16 months had detectable anti-RBD IgG (90.9% at 12, 13 and 16 months and -100.0% at 13 months positive rate), anti-N IgG (90.9% at 13 and 16 months and 100.0% at 12 months), and NAbs (72 % at 13 months and 87.5% at 12, 14-16 months). • Those with severe disease had higher anti-RBD IgG and NAb titers than those with mild or asymptomatic disease. At 15 months 14.29% of mild and ~50% asymptomatic cases did not have detectable NAbs. • Pseudotype virus neutralization assays found at 16 months, 8/14 had at least 50% inhibition against all variants:

2021		Alpha, Beta, Gamma, Delta, Lambda. Neutralization activities were decreased for Beta, Delta and Lambda.
Dehgani-Mobaraki (2021) [43] Preprint Prospective cohort Italy Mar 2020-Jun 2021	35 PCR confirmed COVID-19 cases were followed up at 14 months post infection. Anti-Spike-Receptor binding domain IgG CLIA was used for analysis. (Updated analysis to [36, 62] below.)	Antibodies at 14 months: • 96.8% (31/32) of cases were positive for anti-S-RBD IgG antibodies. • There was a significant association between anti-S-RBD IgG titers at 14 months and disease severity. • Cases that developed loss of taste and smell during acute disease had higher titers. • Cases that were anti-N protein at 10 months, were anti-S-RBD at 12-14 months.
11-13 months post infection		
Haveri (2021) [35] Preprint **new** Prospective cohort Finland Oct 2020-May 2021	2586 confirmed COVID-19 patients were identified and invited to provide serum samples 5.9-9.9 months after infection. Among the 652 subjects that were unvaccinated at 1 year 367 were randomly selected for another sample 11.7-14.3 months post infection. Neutralization was tested by micro-neutralization assays detected NAbs against the original variant and variants of concern (VOC). SARS-CoV-2 fluorescent multiplex immunoassay (FMIA) has been previously described on the MAGPIX system. Microspheres conjugated with SARS-CoV-2 N and spike full length (SFL) and RBD of the spike protein were used to detect IgG antibodies.	Antibodies: • S-IgG positivity did not appreciably decrease from 8-13 months with between 96-100% of participants positive at 13 months. • S-IgG positivity was lowest (96%, 117/122) among men >60 years old that had mild disease. • NAb positivity was 100% (n=47) among those with severe disease at 13 month. • NAb positivity for people with mild disease was 84% (99/1187) for men >60 years and 88% (151/171) among women >60 years and 93% (14/15) for men <60 years and 100% for women <60 years. • N-IgG was 67% for severe infections and 32% among those with mild disease at 13 months. • N-IgG titers were higher among those >60 years than <60 years with mild

		disease at 8 and 13 months. • RBD-IgG titers were higher among those with severe disease than in those with mild disease and among those >60 than those <60 years. VOCs: • Compared to the original variant at 13 months, there was a 77%, 69%, and 42% decrease in Beta, Delta, and Alpha Nabs, respectively.
Miyakawa (2021)[28] Preprint **new** Prospective cohort Japan Jan-Mar 2021	358 patients (over 20 years old) who had a positive COVID-19 result (RT-PCR, RT-LAMP, or antigen tests) were recruited to submit serum between 5-8 months and 11.5-14.5 months. N-IgG and RBD IgG were measured using the Tosoh immunoassay AIA-CL1200 while neutralizing activity was determined through pseudovirus and rapid qualitative neutralizing assays.	Antibodies: • 96% (344/358) had NAbs at 12 months. • Significant decreases for N-IgG, RBD-IgG, and NAbs. • NAbs were correlated with RBD-IgG titers, but not with N-IgG titers. • Significant differences were seen between those who experiences moderate or severe disease compared to mild disease in N-IgG, RBD-IgG and NAbs. • Multiple regression analysis of NAb titers at 12 months controlling for age, sex, BMI, and smoking found a significant association between higher disease severity and older age. VOCs: • At 12 months significant decreases were seen in neutralizing activities against Beta, Gamma, and Kappa. Neutralizing activity was maintained for Alpha and Delta. • RBD-IgG titers against Beta and Gamma were lower than for the original variant or Alpha strains. • Those with severe or moderate disease maintained high levels of NAb positivity (90-100%) at 12 months. • Nab positivity among those with mild disease varied more with original variant at 12 months (94%, 2%

		decrease from 6 months), Alpha (79%, 6% decrease), Beta (69%, no change), Gamma (76%, 5% decrease), Delta (75%, 4% decrease), and Kappa (69%, 6% decrease).
Dehgani-Mobaraki (2021) [36] Prospective cohort Italy Mar 2020-May 2021	35 PCR confirmed COVID-19 cases were followed up at 12 and 13 months post infection. Anti-Spike-Receptor binding domain IgG CLIA was used for analysis. (Updated analysis to [62] below.)	Antibodies at 12-13 months: • 97% (34/35) cases were positive for anti-SARS-CoV-2 RBD IgG. • Titers were higher in patients that had severe disease (19 AU/ml) compared to those with mild (6 AU/ml).
Shi (2021) [46] **new** Prospective cohort China Jan 2020-Feb 2021	102 COVID-19 recovered inpatients had blood drawn at 7, 14, 30 days post symptom onset (POS), and 1-2, 2-4, 4-7 and 7-13 months POS to measure serum antibodies (IgG, IgM, IgA) against S, N and RBD and nAbs. Antibodies were measured by quantum dot (QD)-labeled lateral flow immunochromatographic assay (LFIA), in vitro microneutralization assay, and immunofluorescence.	NAbs: • NAbs were detected in 95.2% of samples collected at the 7 to 13 m range and were stable with no significant decrease over long term follow-up. Antibodies at 7-13 months: • S2 or N IgM positivity was not maintained, but 7.1% were RBD-IgM positive. • 2.4% of participants had samples positive RBD-IgA and 9.5% of N-IgA were positive. • IgG positivity was more robust with 19% positivity for RBD-IgG, 52.4% for N-IgG, and 85.7% for S2-IgG. • Cumulative S2/N-IgG/IgA and RBD/S2/N-IgG/IgM/IgA positivity were both 88.1%.
Pradenas (2021) [58] **new**	Patients with asymptomatic to severe COVID-19 from three waves (March- June 2020, July - December 2020, January - June 2021) were recruited to determine longitudinal neutralizing antibody responses	Neutralizing antibodies: • Long-lasting neutralizing antibodies were observed in all cases at 12 months and the decay rate slope was flat (533 day half-life). For hospitalized cases the kinetics fit a two-phase exponential decay model with a steep

Prospective cohort Spain Mar 2020-Jun 2021	with data on vaccination (not reported here) and VOCs. 139 unvaccinated individuals were followed up for a maximum of 458 days from symptom onset in the first wave. Neutralization Assays, pseudoviruses expressing SARS-CoV-2 S protein and Luciferase were generated against the original variant and variants of concern (VOC).	decline in the first phase (half-life 26 days) and a slower decrease in the second phase (half-life 533 days) whereas mild or asymptomatic convalescents had a steady slow decay slope. VOCs: Samples from 60 unvaccinated individuals with follow up beyond 300 days (>10 months) were used in neutralizing activity against variants. • 33% of participants had low neutralizing titers (neutralizing activity under 250) against the original variant and Alpha compared to 52% against Beta. Outpatients more frequently had low neutralizing titers than those were hospitalized.
Xiao (2021) [37] Prospective cohort China Jan 2020-Mar 2021	51 PCR confirmed COVID-19 cases were followed for 12 months after discharge. IgG and IgM were measured monthly by Antibody Detection Kit (magnetic particle chemiluminescence method) for Novel Coronavirus (2019-nCoV).	Antibodies: • IgG titers gradually decreased in the first 6 months and then remained stable to 12 months. • The more severe COVID-19 cases had higher IgG levels. • At 6 months 8% and at 12 months 11.8% were IgG negative. • At 6 months 50% and at 12 months 64.7% were IgM negative.
Masiá (2021) [30] Prospective cohort Spain Mar 2020-Apr 2021	From 80 PCR confirmed COVID-19 cases, sequential samples were collected at 1,2, 6 and 12 months post discharge. S and N IgG protein levels were measured.	Antibodies at 12 months: • 91.2% (71/80) were positive for S-IgG. • 43,8% (35/80) were positive for N-IgG • Logistic regression showed that seroreversion was inversely associated with peak IgG for both S and N.
Renk (2021) [41]	A group of 553 children and 726 adults from 328 households with	Antibodies at 12 months: • Between 4-12 months 3.78% of

Preprint Prospective cohort Germany May 2020-Jun 2021	exposure to SARS-CoV-2 were studied. Samples collected at approximately 4 months and 12 months. Neutralization in a surrogate assay was used to evaluate neutralization potential.	children and 17.11% of adults seroreverted. • Children's sera had higher neutralization compared to adult sera (p=0.02).
Chansaenroj (2021) [60] Preprint Prospective cohort Thailand Mar 2020-May 2021	A longitudinal cohort of 531 PCR confirmed COVID-19 cases was followed for 12 months with sampling points at 3, 6, 9 and 12 months. Only 229 provided multiple time point samples. Blood samples were tested for SARS-CoV-2 anti-N IgG by chemiluminescent microparticle immunoassay using the commercially available automated ARCHITECT system.	Anti-N protein antibodies: • 87.5% (328/375) at 3 months were seropositive • 38.6% (93/241) at 6 months • 23.7% (49/207) at 9 months • 26.6% (38/143) at 12 months
Zeng (2021) [47] Cross-sectional China Mar 2021	538 PCR confirmed COVID-19 cases were enrolled during their 1 year post COVID-19 follow-up in March 2021 in Wuhan. Blood samples were analysed using a CLIA for IgM and IgG antibodies to SARS-CoV-2.	Antibodies at 12 months: • 12.8% (69/538) were IgM seropositive • 82.9% (446/538) were IgG seropositive • No difference by sex • Analyzing IgG antibody levels by age showed younger cases were associated with lower IgG levels.
Gallais 2021 [10] Prospective cohort France	SARS-CoV-2 S protein and N protein antibodies were longitudinally measured in healthcare workers, including COVID-19 negative (n=916) and previously infected (n=393) individuals, using lateral flow assay and CLIA. Infected	Seropositivity rates differed widely depending on antibody isotypes (IgM or IgG), antibody specificity (N or S protein), assays and serum collection time points. Lateral flow assay results: 11-13 months post infection: significant reduction in sample seropositivity was

Apr 2020-May 2021	individuals were sampled at 1, 7-9, 11-13 month intervals.	observed (p<0.0001) for the following antibodies: • 51.8% S protein IgM vs. 1 month = 91.3% • 56.8% S protein IgG vs. 1 month = 83.7% • 20.1% N protein IgG vs. 1 month= 85% CLIA results : Serum S protein IgG antibody seropositivity in the sample remained approximately 97.1%, from one to eleven months post infection.
Petersen 2021 [45] Prospective cohort Faroe Islands Spring 2020, Fall 2020	Serum samples were collected longitudinally from Faroe Island residents with PCR confirmed COVID-19, at various time points between 1-12 months post infection, during the first and second infection waves in the region. Serum RBD specific IgG levels were measured by two ELISA assays.	IgG RBD antibodies: • 95% of the sample remained seropositive at all sample collection time points, via both assays. • IgG titers declined over time in both waves ($p < 0.001$). Pairwise comparison of samples found IgG levels rapidly declined significantly over time until 7 months post infection ($p < 0.001$) and remained fairly stable from 7-12 months after infection. • IgG titers followed a U-shaped curve by participant age, with higher antibody levels among the oldest (67+) and the youngest (0– 17) age groups compared to intermediate groups ($p < 0.001$).
Li (2021) [44] Prospective cohort China Feb 2020-Jan 2021	869 donors for convalescent plasma transfusion were recruited and sampled up to 12 months, all had confirmed COVID-19. CE-marked coronavirus IgG antibody detection kit was used to test the titer of RBD specific IgG.	RBD IgG positivity rates post diagnosis (titer cutoff <1:80): • 89.4% at 6-7 months • 81.4% at 11-12 months • 5.4% of convalescent plasma donors did not have detectable titers at any point. • After 9 months, the RBD-IgG titers began to stabilize at a GMT of ~200. The RBD-IgG titer 12 months was 70% lower than month 1 following diagnosis.

Dobaño (2021) [32] Prospective cohort Spain Mar 2020-Apr 2021	Antibody levels and seropositivity was evaluated in a sample of primary health care workers (n=173), 149-270 days after symptom onset; serum samples were collected at 3 time points. A subset of unvaccinated HCWs were also tested at 322-379 days. Infections were confirmed by PCR. The majority of the sample was mild to moderate cases, and 14% were hospitalized. Levels of S protein and RBD IgM, IgA and IgG antibodies were measured by assay (not specified). Factors associated with higher levels of antibodies were identified by stepwise multivariable regression analyses.	Antibodies at 11.5–12.5 months: • Seropositivity was 96.9% (95.3% IgG, 82.8% IgA.) Antibodies at 5-9 months after symptom onset: • 92.5% (90.2 IgG, 76.3% IgA, 60.7% IgM) of participants were positive for at least one immunoglobulin isotype, indicative of highly stable and persistent immunity. • Factors associated with higher levels of antibodies at follow-up were hospital admission, fever, anosmia and/or hypogeusia, and previous allergies.
Violán (2021) [34] Preprint **new** Prospective cohort Spain Mar 2020-May 2021	Healthcare professionals (303 healthy, 72 asymptomatic, 367 mild-moderate, and 39 severe-critical) were recruited March 2020 with follow-up to May 15 2021. Repeat serological testing was carried out at 15, 30, 60, 90,180, 270, and 360 days after baseline visit. At the 360 day mark results were available for 109 individuals. Commercially available antiSARS-CoV-2 IgG and IgM anti-N ELISA kits were used but kit name is not reported. Anti-spike (S) IgG ELISA using DECOV190 allowed for the quantitative determination of IgG class antibodies.	Antibodies at 12 months: • Only anti-N IgG and IgM were tested and 67% and 43% were positive respectively. • Anti-N IgG and IgM at month 12 were higher among those who experienced severe-critical disease compared to those with mild-moderate or asymptomatic disease and there was no difference by sex. Antibodies at 9 months: • Anti-N IgG and IgM were tested and 67% and 46% were positive respectively. Anti-S IgG was 80%. • Those who were asymptomatic or had mild to moderate symptoms were below the threshold for positivity for IgM after 9 months. • Anti-S IgG was positive in most participants and those with more severe disease had higher levels of values.

Peng (2021) [42] LTE **new** Prospective cohort China Aug 2021(est)	85 recovered patients were recruited from the Yongchuan Hospital, China to measure long term humoral immunity with measurements at 1, 3, 8, and 12 months. Anti- S IgM, IgG, and IgA and NAbs were measured using Bioscience Magnetic Chemiluminescence Enzyme Immunoassay Kits.	Antibodies at 12 months: • 95.5% anti-S IgG and 93.2% NAbs (n=44) • IgM and IgA was below detection. • NAbs, IgG, IgM, and IgA decreased over the study period. • S-IgG and NAb was significantly and positively correlated across the study period. IgG decreased 82.8% from month 1 to month 12, IgM decreased 96.4% from month 1 to month 12, and IgA decreased 89.4% month 1 to month 12.
Zhan (2021) [29] **new** Prospective cohort China Jan 2020-Jan 2021	121 hospitalized COVID-19 patients were recruited to analyze antibody level one year after infection (10 – 12 months). Data on antibodies were also collected from prior clinical trials within 1 month, 1- 2, and 3-months. Antibody tests included Livzon Diagnostics immunochromatographic assays, InnoDx chemiluminescence microparticle immunoassay, and ELISA measuring RBD-IgG. Pseudovirus neutralization assays were conducted for neutralization activities.	Antibodies: • IgM positivity was 4% (95% CI, 2–10%). • IgG positivity was 62% (95% CI, 54–71%). Total RBD IgG was stable over the whole year period. • Total RBD had a log linear relationship with RBD-IgG and to a lesser degree N-IgG. • NAb titers were correlated to total RBD antibodies at 12 months. • It was predicted that 50% protection against the original variant infection at 12 months was 17% (95% CI, 11–24%) and 87% (95% CI, 80–92%) against severe infection for mild and severe cases respectively. • Generalized linear regression finds a positive association between total anti-RBD antibodies and age, having a severe disease, time from discharge and length of stay, and negatively associated with persistent symptoms and male sex. VOCs: 42 recovery phase serum and 23 convalescent sera with the highest titers

		were used to determine neutralization against VOCs. • At 10-12 months decreases in neutralizing activity was seen for Alpha and Beta (10-fold lower) variants compared to the original variant).

Abbreviations: AIM, activation induced marker; d.a.o, days post symptoms onset; ELISA, enzyme-linked immunosorbent assay; E protein, envelope; est, date study conducted is approximated using publication date; HCW, healthcare worker; ICS, intracellular cytokine staining; IFN, interferon; Ig, immunoglobulin antibodies; LIPS, luciferase immunoprecipitation system assay; LTE, letter; LTE, letter to the editor; M protein, membrane; MN, microneutralization assay; NAb, neutralizing antibodies; N protein, nucleocapsid; ORF, open reading frame; PBMC, peripheral blood mononuclear cells; RBD, receptor binding domain S, spike protein; Tcm, central memory T-cell; Tem, effector memory T-cell; THC, specific T-helper cells

Table 3: Systematic reviews and rapid reviews relevant to immunity (n=9)

Study	Method	Key Outcomes
Immunity from infection (n=6)		
Chivese (2021) [63] Preprint Systematic review NA Apr 2021 (est)	A systematic review of 6 databases was conducted with a search date of April 1, 2021. Risk of bias was conducted. Random-effects meta-analysis of proportions was conducted.	• 54 studies were included from 18 countries and >12 million observations. Follow-up was up to 8 months. 6-8 months post infection 90% of people had SARS-CoV-2 specific immunological memory: • IgG – 90.4% (95%CI 72.2-99.9, I^2=89.0%, 5 studies) • CD4+ - 91.7% (95%CI 78.2 – 97.1, one study) • memory B cells 80.6% (95%CI 65.0-90.2, one study) • The pooled prevalence of reinfection was 0.2% (95%CI 0.0 – 0.7, I^2 = 98.8, 9 studies). Individuals who recovered from COVID-19 had an 81% reduction in odds of a reinfection (OR 0.19, 95% CI 0.1 - 0.3, I^2 = 90.5%, 5 studies).
Chen (2021) [64] Systematic review NA Jul 2021 (est)	A systematic review of 6 databases was conducted with a search date of July 8, 2021. PROSPERO registration no. CRD42021256932. 50% neutralization titers were extracted. No risk of bias was conducted. Random-effects meta-analysis of GMTs was conducted.	• Included 106 studies, 65 and 10 were on previously infected with original variant and VOC participants respectively. 15 included vaccinated participants. • Neutralization was conducted in live virus neutralization assays (n=48 studies), lentivirus-vector pseudovirus neutralization assay (n=39) and VSV-vector pseudovirus neutralization assay (n=24). • They provide pooled GMT for original variants and VOCs showing 4.2 and 3.3 fold reductions in neutralization of Beta and Delta respectively. • Vaccine recipient titers are also presented with high heterogeneity

		across studies and reduced neutralization for Beta and Delta. Potency of immunity depended on the vaccine platform. • For vaccinated individuals that had previously been infected, neutralization was significantly higher than for uninfected vaccinated individuals. • Data is not analysed for changes in neutralization titers over time.
Arkhipova-Jenkins (2021) [3] Living rapid review NA Mar 2021 (est)	A rapid review that aims to synthesize evidence on the prevalence, levels, and durability of detectable antibodies after SARS-CoV-2 infection to determine if antibodies to SARS-CoV-2 confer natural immunity. Relevant literature between Jan 1 and Dec 15, 2020 was included in the review. 444 observational studies were included in the review.	• Evidence suggests most adults develop detectable levels of antibodies (i.e. IgM, IgG, and NAb) that peak between 20-30 days post symptom onset. • The estimated duration was IgM 115, IgG 120, and IgA 140 days. • Most adults generated neutralizing antibodies (99% NAb, 95% IgG and 80% for IgM), which persisted for several months after infection. • Age, disease severity, and the presence of symptoms may be associated with higher antibody levels (low level of evidence). • Some adults did not develop antibodies after SARS-CoV-2 infection, for reasons unclear. • The summarized evidence was assessed to be low to moderate in quality.
Poland (2020) [1] Review NA Oct 2020 (est)	This review discusses what was known about human humoral and cellular immune responses to SARS-CoV-2 as of the search date Sept 24, 2020.	• The article reviews humoral and cellular immunity and presents some data on kinetics and durability of antibody response and correlation with T-cell response. Many inconsistencies were noted in the initial research. • Knowledge gaps include high-quality studies on duration of protection by neutralizing antibodies and a good understanding of how the

		immunological measures being used correlate to protection.
Post (2020) [52] Systematic review NA Jun 2020 (est)	A systematic review on antibody response to SARS-CoV-2 with a search date of June 26, 2020. 150 papers were included. Inclusion criteria included follow-up of greater than 28 days and measured antibody titres. High variability across includes studies and study designs was reported by the author. See appendix 2 for a figure on antibody kinetics over time.	• Inconsistency in antibody correlates were seen across the literature. • IgM (seroconversion 4-14d, peak 2-5 weeks and declining to undetectable levels around 6 weeks) was consistently detected before IgG. • IgG (seroconversion 12-15 d, peak 3-7 weeks, plateaued until at least 8 weeks with longest follow-up of 12 weeks still detecting antibodies). • IgA infrequently studied showed seroconversion between 4-11 days, with outliers reporting 24 days. • Neutralizing antibodies detected 7-15 days after symptom onset, peaking 14-22 days and then declining over 6 weeks. AT 39 days one study had 79% of participants with low neutralizing antibody titres, 3% with high titres. Mild cases had lower neutralizing antibodies. • Animal studies show promising initial results for protective immunity; however studies were small and short in duration. There are studies that have demonstrated correlations with disease severity. An inverse relationship with viral load has been inconsistently reported and no association with re-detection was reported. Studies cannot speak to lasting immunity.
Shrotri (2021) [65] Systematic review NA	A systematic review that critically evaluates and synthesises published and pre-print literature from Jan 2020-Jun 26 2020 on T-cell mediated immunity post SARS-CoV-2 infection. 61 publications included in the review.	• Symptomatic adult cases consistently show a reduction in peripheral T cell counts in the acute infection phase, which positively correlates with increased disease severity, duration of RNA positivity, and non-survival. The observed relative reductions in CD4+ and CD8+ T cell were variable. • Asymptomatic and paediatric cases

Jun 2020 (est)		display preserved T-cell counts. • Severe or critical COVID-19 cases developed more robust, virus-specific T-cell responses. Elevated levels of pro-inflammatory cytokines, interleukin-6 (IL-6), to lesser degree, interleukin-10 (IL-10), and tumour necrosis factor alpha (TNF-α) were identified in severe cases. • Longitudinal follow-up (14-44 days post infection) suggested recovery of T-cell subset counts alongside clinical recovery and viral clearance. • T-cell memory and effector function in early convalescents (up to approximately 3 months post onset) was demonstrated against viral antigens S, M and N proteins. T cell response breath and magnitude were generally enhanced among individuals recovering from sever infections. Cytokine producing activity of CD 8+ T cells specific to M and N proteins displayed wider functionality than those targeting S proteins among individuals with mild disease. CD3+ T cells were reduced in severe infections. • Cross-reactive T-cells among unexposed or individuals previously exposed to other coronaviruses (e.g., pre-pandemic seasonal corona virus strains, SARS-CoV-1) were often identified and appear long-term; in some cases maintained up to 17 years post infection. Cross-reactive T-cells targeting viral S protein and N proteins were the identified cross-reactive immune cells. The impact of cross-reactivity on SARS-CoV-2 infections remains largely unclear, but assumed to be low due to variability in coronavirus epitopes.
Reinfection (n=3)		

Shenai (2021) [66] Systematic Review NA Aug 2021 (est)	A systematic review of studies reporting on the rate of infection among recovered and vaccinated individuals. Search was Aug 31, 2021 and included published and preprint papers. Risk of bias was New Castle Ottawa Scale.	• 9 studies included, 3 RCTs, 4 retrospective cohorts, 1 prospective cohort and 1 case control. • 4 studies looked at vaccinated vs. infection immunity, RR was 1.86 [95% CI 0.77-4.51, P=0.17] was not significant for superior protection of vaccination over infection immunity. • Vaccination immunity among individuals that had COVID-19 was significant RR of 1.82 [1.21-2.73, P=.004], compared to those that recovered and did not get vaccinated. • The analysis does not include data on time since vaccination or infection and waning immunity which may in future provide more clear benefit of COVID-19 vaccinations to those previously infected.
Kojima (2021) [67] Systematic Review NA Aug 2021 (est)	A systematic review of studies reporting on reinfections. Search was Aug 18, 2021 and included published and preprint papers. Risk of bias was not conducted.	• 10 studies were included in the review with observation periods of 1-10.3 months. • The weighted risk reduction against reinfection was 90.7% (SD 7.7%). • This review cannot establish the longer term protection from reinfection and does not include studies on high risk groups.
Lo Muzio (2021) [24] Systematic Review NA Jul 2021 (est)	A systematic review of studies reporting on reinfections. Search was Jul 31, 2021 and included published and preprint papers. Risk of bias was not conducted. A quality of reporting and risk of bias checklist was used.	• 117 articles were included with 260 confirmed cases of reinfection. (only 14 studies met all risk of bias criteria) • 92/ 260 had severe COVID-19 and 14 died of the reinfection. • Different clades or lineages were confirmed between infections in 52/260 cases.

Abbrevition: est, search date or publication date when search date was not available was used

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