Centers for Disease Control and Prevention

COVID-19

Science Brief: SARS-CoV-2 Infection-induced and Vaccine-induced Immunity

Updated Oct. 29, 2021

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This brief provides an overview of the current scientific evidence regarding infection-induced and vaccine-induced immunity, including both peer-reviewed and preprint publications, as well as unpublished CDC data. Although comprehensive, it is neither a formal systematic review nor meta-analysis. New data continue to emerge, and recommendations will be updated periodically, as needed.

Recovery from many viral infectious diseases is followed by a period of infection-induced immunologic protection against reinfection. This phenomenon is widely observed with many respiratory viral infections, including both influenza and the endemic coronaviruses, for which acquired immunity also wanes over time making individuals susceptible to reinfection.

CDC continues to recommend COVID-19 vaccination for all eligible persons, including those who have been previously infected with SARS-CoV-2.

Executive Summary

Key findings and considerations for this brief are as follows:

- Available evidence shows that fully vaccinated individuals and those previously infected with SARS-CoV-2 each have a low risk of subsequent infection for at least 6 months. Data are presently insufficient to determine an antibody titer threshold that indicates when an individual is protected from infection. At this time, there is no FDA-authorized or approved test that providers or the public can use to reliably determine whether a person is protected from infection.
  - The immunity provided by vaccine and prior infection are both high but not complete (i.e., not 100%).
  - Multiple studies have shown that antibody titers correlate with protection at a population level, but protective titers at the individual level remain unknown.

  - Whereas there is a wide range in antibody titers in response to infection with SARS-CoV-2, completion of a primary vaccine series, especially with mRNA vaccines, typically leads to a more consistent and higher-titer initial antibody response.
  - For certain populations, such as the elderly and immunocompromised, the levels of protection may be decreased following both vaccination and infection.
  - Current evidence indicates that the level of protection may not be the same for all viral variants.
  - The body of evidence for infection-induced immunity is more limited than that for vaccine-induced immunity in terms of the quality of evidence (e.g., probable bias towards symptomatic or medically-attended infections) and types of studies (e.g., observational cohort studies, mostly retrospective versus a mix of randomized controlled trials, case-control studies, and cohort studies for vaccine-induced immunity). There are insufficient data to extend the findings related to infection-induced immunity at this time to persons with very mild or asymptomatic infection or children.
- Substantial immunologic evidence and a growing body of epidemiologic evidence indicate that vaccination after infection significantly enhances protection and further reduces risk of reinfection, which lays the foundation for CDC recommendations.

Background

CDC recommends COVID-19 vaccination for all eligible persons, including those who have been previously infected with SARS-CoV-2 [1]. As of October 28, 2021, more than 45 million COVID-19 cases and over 740,000 deaths have been reported in the United States (US) [2]. Data from a seroprevalence survey that assessed for presence of antibodies and history of vaccination among US blood donors from January to August 2021 suggest that approximately half of previously infected adults in the US have not been vaccinated [3].

Both SARS-CoV-2 infection and COVID-19 vaccination induce an immune response that initially confers high levels of protection against symptomatic COVID-19 illness. This brief contains a review of evidence regarding vaccine-induced immunity and infection-induced immunity, including the initial immune response, antibody decay kinetics, protection from subsequent infection, impact of new variants, and effect of vaccinating previously infected individuals.

Separate overviews have been written on the types of assays used to assess the serologic response to SARS-CoV-2 (Interim Guidelines for COVID-19 Antibody Testing) and detailed evidence of the immunity provided specifically by vaccines (Science Brief: COVID-19 Vaccines and Vaccination).

Immune Response to Infection and Vaccination

Initial Immune Response to Infection

SARS-CoV-2 enters cells by binding to angiotensin converting enzyme-2 (ACE-2) receptors on the cell surface via the viral spike protein. As described in the Antibody Testing Guidelines, currently available serologic assays measure both overall production of antibodies against SARS-CoV-2 antigenic targets (binding antibodies) and functional ability to neutralize the SARS-CoV-2 virus via virus neutralization or pseudovirus neutralization tests (neutralizing antibodies). The antigenic targets most frequently assessed include those to the spike (S) protein, receptor binding domain (RBD) of the spike protein and nucleocapsid (N) core. IgM, IgA, and IgG isotypes may be developed against any of these antigens. As discussed below, serum binding antibodies to S and RBD and neutralizing antibodies have all been shown to correlate with protection against symptomatic SARS-CoV-2 infection.

SARS-CoV-2 infection induces a robust humoral and cellular immune response [4-8]. SARS-CoV-2-specific IgA and IgG have been detected from both mucosal sites and the serum of infected individuals [8]. IgM, IgA, and IgG can be detected in the blood 5–15 days following symptom onset or a positive reverse transcriptase polymerase chain reaction (RT-PCR) test, with IgM typically appearing first [6, 9]. IgM antibodies peak within the first few weeks following symptom onset, then fall below detectable limits 2–3 months after infection [6, 9, 10]. IgA antibodies also decrease rapidly, with some studies noting a return to undetectable levels within the first 3 months following infection [9]. IgG antibodies are more durable, though waning is also noted as described below. SARS-CoV-2-specific memory B- and T-cells also begin to appear within the first month following infection [11].

The vast majority of persons with SARS-CoV-2 infection generate detectable anti-SARS-CoV-2 antibodies, with multiple studies reporting seroconversion rates of 90% or higher [10, 12]. One large population-based study reported a lower seroconversion rate of 76%, though, among those who did not seroconvert in this study, only 21% reported symptoms, and authors noted that only 34% had strong evidence of a true-positive PCR [13]. Among individuals who seroconvert following infection with SARS-CoV-2, substantial heterogeneity exists, with a 200-fold difference in peak antibody titers noted in some studies [11].

Multiple factors contribute to the degree of immune response mounted following infection. Both binding and neutralizing antibody titers rise faster and reach a higher peak in persons with more severe COVID-19 [9, 10, 14]. People with symptomatic SARS-CoV-2 infection tend to have higher antibody titers than people who are asymptomatic, and people who are hospitalized tend to have higher antibody titers than people managed as outpatients [9, 10, 15, 16]. Studies have also demonstrated a correlation between cycle threshold (Ct) value and antibody titer, with lower Ct values being associated with higher antibody titers at the population level [9, 13].

Most studies did not find a relationship between sex and level of peak binding or neutralizing antibody titer. Increasing age has been associated with decreased likelihood of seroconversion [13] but higher peak antibody titers among those who do seroconvert [10, 11, 13, 15]. Lower rates of seroconversion have also been reported in persons with hematologic malignancies or receiving certain immunosuppressive medications [17, 18]. Data on the impact of other medical conditions is more variable and often confounded by the increased risk of severe disease in persons with certain underlying medical conditions.

Initial Immune Response to Vaccination

As of October 28, 2021, approximately 92% of people who have been vaccinated in the United States received one of two FDA-approved or authorized mRNA vaccines (Pfizer/BNT1272b2 and Moderna/mRNA-1273), and 8% received an adenovirus vector vaccine (Janssen/Ad26.COV2.S) [2]. Both vaccine types are designed to elicit an immune response against the spike protein that is required for SARS-CoV-2 binding, fusion, and cell entry. Consequently, vaccination induces the production of anti-S and anti-RBD binding and neutralizing antibodies in the blood, but not anti-N antibodies. Similar to infection, vaccines result in early production of serum IgA, IgM, and IgG antibodies [19, 20], and also induce long-lasting memory B- and T-cell responses [19, 21-23].

In immunogenicity analyses completed during phase I/II vaccine trials, 100% of participants developed both binding and neutralizing antibodies following vaccination with Pfizer-BioNTech and Moderna vaccines, and 90% of participants developed binding and neutralizing antibodies following vaccination with the Janssen vaccine [24-26]. Whereas there is a wide range in antibody titers in response to infection with SARS-CoV-2, completion of a primary vaccine series, especially with mRNA vaccines, typically leads to a more consistent, and higher-titer initial antibody response [24, 26-29]. However, similar to infection, this immune response may be decreased in older and immunosuppressed persons. Decreased rates of vaccine-induced seroconversion have been reported among persons with a variety of immune suppressing conditions, including those on certain immunosuppressive medications, post-solid organ transplant, and with hematologic cancers [30-34]. Studies have also found that persons aged 65-80 years and above have significantly lower peak anti-S and neutralizing antibody titers following vaccination than persons less than 65 years [35-40]. This is of particular concern given the increased risk of severe disease in older and immunosuppressed populations [41, 42].

Correlation of Immune Response Metrics to Protection

Multiple correlate-of-protection studies have demonstrated that higher antibody titers are associated with decreased risk of subsequent symptomatic SARS-CoV-2 infection. Data from both the phase 3 AZD1222 and mRNA-1273 vaccine efficacy trials demonstrated that quantitative titers of anti-S IgG, anti-RBD IgG, and pseudovirus and SARS-CoV-2 neutralizing antibody tests all correlate with protection against symptomatic infection (though not asymptomatic infection), with neutralizing antibodies having the strongest correlation in both of these studies [43, 44].

Analysis of data across studies has been difficult due to a lack of standardization of serologic assays [45]. Two different studies used data from seven vaccine efficacy studies (standardized against mean convalescent plasma titers) and one convalescent plasma/reinfection study to model effectiveness as a function of antibody titer [46, 47]. These found a high degree of correlation between mean peak neutralizing antibody titers and anti-S IgG binding antibodies within a population, and overall decrease in risk of infection. One study estimated that neutralizing antibody titers amounting to only 20% of the mean convalescent plasma neutralizing antibody titer (54 international units/ml using the WHO standard) correlated with a 50% reduction in infection risk; this appeared robust in predicting the effectiveness of vaccines not included in the model [46, 48]. Of note, the

level of antibody associated with protection against severe disease was much lower than the level required to provide protection against infection, with only 3% of the mean convalescent antibody titer level correlating with 50% protection against severe disease [46].

Other immune mechanisms are also important in preventing SARS-CoV-2 infection and limiting COVID-19 illness severity, although their direct correlation with protection is less defined at this time. A study of rhesus macaques found that adaptive transfer of plasma with high titers of neutralizing antibodies was sufficient to protect from infection following a SARS-CoV-2 challenge. However, depleting CD8+ T cells compromised their ability to prevent infection once neutralizing antibodies had waned [49]. Analysis of antibody, B-cell and T-cell responses in acutely infected and convalescent humans has shown that protection depends on coordination of all three components of the immune response [50]. In the mRNA-1273 phase 3 clinical trial described above, investigators estimated that 68.5% (95% CI 58.5–78.4) of the protective effect of vaccination could be attributed to initial neutralization titers with some degree of protection occurring following vaccination, even when neutralization titers were not detected [43]. These, along with studies noted above, suggest that, while the magnitude of antibody response following infection or vaccination is correlated with protection and the absence of antibody with risk, antibody test results (particularly when not standardized nor quantitative) provide only a partial picture of an individual's immune response. At this time there is no specific antibody test or antibody threshold that can determine an individual's risk of subsequent infection.

Immune Response Kinetics and Duration of Protection

Immune Response Kinetics Following Infection

Antibody titers peak within 3-5 weeks following infection and then begin to wane in a manner that varies by individual, target antigen, antibody isotype, and assay used [6, 51]. Anti-N antibodies appear to wane fastest, followed by anti-RBD, then anti-S antibodies. Although at least 30% of persons may lose detectable anti-N antibodies within 10 months after infection, anti-S and overall SARS-CoV-2-specific IgG remain detectable in approximately 90% of persons who seroconvert up to 10 months to one year post-infection [16, 52]. Neutralizing antibodies appear to have a biphasic decline with an initial half-life of 2–3 months followed by a slower decline [11, 14, 15]. (**Table 1**)

For at least 2–3 months following infection, people with moderate-to-severe COVID-19 illness have higher titers of binding and neutralizing antibodies than people with mild illness [9, 14]; these differences may persist for 5–8 months following infection [11, 15].

B cells targeting SARS-CoV-2 increase in the first month and then remain at higher concentrations for at least 8 months post infection [11, 14, 53]. SARS-CoV-2-specific $CD4^+$ T cells increase then decline with a half-life of approximately 3-7 months; $CD8^+$ T cell measurements varied with at least one study reporting virtually no decline over the initial 4 months post-infection [11, 14]. (**Table 1**).

Protection from Reinfection in Cohort Studies

Multiple studies have compared the incidence of reinfection and primary infection during a specific time period to evaluate the level and duration of protection provided by initial infection with SARS-CoV-2. **Table 2** summarizes data from seven observational cohort studies from six countries, each with >10,000 participants, assessing the risk of reinfection over time. Five studies used RT-PCR positivity to define initial infection. In these studies, primary RT-PCR-confirmed SARS-CoV-2 infection decreased risk of subsequent infection by 80–93% for at least 6–9 months [54-58]. Studies specifically assessing persons seropositive with anti-N and anti-S antibodies following infection [16, 45] found slightly higher protective effects (89–93%). Most studies had a mean or median follow-up period of approximately 7 months; the longest reported follow-up was 12 months post-infection [58]. Three studies included sub-analysis to assess if the protection waned over time; none of these found a decline in protection within the follow-up period [54, 55, 57].

It is important to note that all of these studies were observational and all but two were retrospective. Low availability of testing early in the pandemic may have biased these studies toward populations that were more likely to have had symptomatic or medically attended primary infection. Most were unable to control for any potential differences in test- or healthcare-seeking behaviors between previously infected and naïve persons, though a large proportion of the reinfections reported across the studies were asymptomatic infections (**Table 2**). In one of the prospective cohort studies, over 25,000 healthcare workers were tested using RT-PCR testing every 2 weeks, allowing a more comprehensive ascertainment of

reinfections. This study found that a history of previous RT-PCR-confirmed infection provided 93% protection against a subsequent symptomatic infection, 52% protection against asymptomatic infection, and 84% protection against overall infection with SARS-CoV-2 [54].

Many of these studies were completed just as vaccination was being rolled out in their respective countries, which makes it challenging to follow up and determine when immunity after infection wanes and what markers best predict this waning. Based on the trajectory of antibody decline, researchers have predicted that the immune response following infection would continue to provide at least 50% protection against reinfection for 1–2 years following initial infection with SARS-CoV-2 or vaccination [13, 46]. This would be similar to what is observed with seasonal coronaviruses [59]. Further epidemiologic analyses are needed to confirm these hypotheses.

Of note, these studies occurred when the ancestral strain and Alpha variant were the predominantly circulating variants. There is evidence that protection may decrease in the setting of more transmissible variants of concern (VoC) and variants being monitored (VBM), as discussed below.

Immune Response Kinetics Following Vaccination

Anti-S, anti-RBD and neutralizing antibodies remain detectable at least 6–8 months following vaccination [21, 22, 60]. Neutralizing titers following vaccination with the mRNA-1273 vaccine are estimated to decay with a half-life of 68–202 days, whereas binding anti-RBD antibodies decline with a half-life of 52–109 days [60]. These rates of antibody decay overlap with those reported for convalescent individuals (as shown in Table 1), though at least one preprint study reported less rapid decay among people recovered from infection compared with those vaccinated with BNT162b2 [28]. As with infection, the protective effect of vaccine-induced immunity is also supported by longer-term components of the humoral response, including memory B cells [21, 23, 61]; vaccine-induced CD4+ and CD8+ T cells continue to be relatively stable up to 6–8 months following vaccination [21, 61].

Although some studies have reported a faster decay of antibodies in persons 65 years or older, as compared to persons less than 65 years, lower anti-S and neutralizing antibodies at 2–6 months post vaccination appear to be at least partially attributable to lower peak antibody titers in this population [39, 40]. Nursing home residents are a unique population given age, co-morbidity, and congregate-setting associated risks. One study reported that detectable pseudovirus neutralization fell from 84% to 30% among nursing home residents (median age: 76 years, age range: 48–100 years) between 2 weeks and 6 months following vaccination; this was significantly faster than the rate of decline reported among staff-member controls (median age: 48 years, age range: 26–76 years), 81% of whom continued to have detectable neutralization at 6 months post-vaccination [42].

Duration of Immune Protection from Vaccination

Evidence is still accruing regarding the duration of protection following vaccination. Using antibody kinetics, one model predicted that an initial vaccine effectiveness of 90% would likely decline to approximately 70% around 250 days post-vaccination [46], not accounting for other factors such as non-serologic components of the immune response or the impact of new circulating variants.

Both Pfizer-BioNTech and Moderna released data from their phase 3 trials reporting overall high efficacy of mRNA vaccines against laboratory confirmed SARS-CoV-2 infection 5-6 months following vaccination. Pfizer-BioNTech reported an overall vaccine efficacy of 91% against infection and 97% against severe disease 6 months after vaccination with BNT162b2, though also reported a gradual decline in efficacy against infection from 96% at 7 days–2 months to 84% at 4–6months [62]. Moderna reported 93% efficacy at a median of 5 months after vaccination with mRNA-1273, without further details on the rate of decline in efficacy over time [63].

As described in greater detail in CDC's COVID-19 Vaccine and Vaccination Science Brief and in a October 2021 Advisory Committee on Immunization Practices presentation , recent studies have demonstrated waning of both antibody titers and vaccine effectiveness against infection over time, especially among older populations [42, 64]. Decreased vaccine effectiveness may reflect a combination of waning antibody titers and decreased neutralizing capacity in the setting of widespread circulation of variants with partial immune escape. Notably, multiple studies have found that vaccine effectiveness against hospitalization and/or severe disease continues to be high, ranging from 84–96%, up to 6 months following vaccination [65-68].

Impact of Variants on Infection- and Vaccine-induced Immunity

Variants of SARS-CoV-2 have emerged with multiple mutations in the spike protein that can result in decreased neutralization by antibodies, including those induced by either prior infection or vaccination [19, 69].

There is laboratory evidence that persons previously infected with the original lineage of SARS-CoV-2 have reduced neutralizing antibody titers against certain variants (i.e., Beta, Gamma, and Delta variants) [70-73]. One study found that among 367 unvaccinated persons assessed 12 months after infection, 98% had detectable anti-S IgG and 91% had neutralizing antibodies against wild-type virus. By comparison, among a subset of 78 persons assessed for neutralizing antibodies against particular variants, these were detectable in 84%, 68%, and 55% for Alpha, Delta, and Beta variants respectively [72]. Of note, absence of neutralization activity was higher among people reporting mild infection versus those with severe disease [72].

In studies examining neutralization from convalescent sera and vaccinated individuals together, the relative reduction in neutralization appears to be similar across both groups. A number of studies reported a 2- to 4-fold reduction in neutralization against Delta and a 6-fold (or higher) reduction in neutralization against Beta but minimal decreased neutralization against Alpha, as compared to the original SARS-CoV-2 lineage, for both convalescent and vaccinated individuals [70, 74, 75].

Decreased neutralization against Delta parallels reduced vaccine effectiveness against infection, but effectiveness remains high against hospitalization or severe disease [65, 66]. As highlighted in the COVID-19 Vaccine and Vaccination Science Brief, recent studies from the United States, United Kingdom, and Qatar have reported vaccine effectiveness of 54–85% against SARS-CoV-2 infection compared with 90–100% against hospitalization/severe disease during periods of widespread circulation of Delta [65, 76-78]

Comparison of Infection- and Vaccine-induced Immune Responses

A systematic review and meta-analysis including data from three vaccine efficacy trials and four observational studies from the US, Israel, and the United Kingdom, found no significant difference in the overall level of protection provided by infection as compared with protection provided by vaccination; this included studies from both prior to and during the period in which Delta was the predominant variant [79]. In this review, the randomized controlled trials appeared to show higher protection from mRNA vaccines whereas the observational studies appeared to show protection to be higher following infection.

A more recent analysis of data from a network of 187 hospitals in the United States found that, among more than 7,000 COVID-19–like illness hospitalizations whose prior infection or vaccination occurred 90–179 days beforehand, there was a 5.5 times higher odds of laboratory-confirmed COVID-19 among previously infected patients than among fully vaccinated patients [80]. This study included data on persons more recently infected and/or vaccinated than the studies in the systematic review, though the authors noted one limitation of the design was the potential of missing testing that may have occurred outside of the healthcare network.

The Office of National Statistics in the United Kingdom used data from a large-scale longitudinal community survey of COVID-19 to compare the risk of infection among fully vaccinated, partially vaccinated, unvaccinated/previously infected, and unvaccinated/uninfected persons during two different periods 1) when Alpha was the predominant variant (December 2020–May 2021) and 2) when Delta was the predominant variant (May–August 2021) [81]. Based on results that included over 26,000 RT-PCR positive tests, they found full vaccination to provide the greatest protection during the Alpha predominant period (79% vs. 65% reduction in risk), but equivalent protection from full vaccination and infection during the Delta predominant period (67% vs. 71% reduction in risk).

Vaccine-induced Immune Responses after Previous Infection

Although there appears to be varying evidence regarding the relative protection that occurs after surviving COVID-19 as compared with completing vaccination, there is substantial immunologic and increasing epidemiologic evidence that vaccination following infection further increases protection against subsequent illness among those who have been previously infected.

Immunologic Data on Vaccination Following Infection

There is clear evidence that neutralizing antibody and memory B cell response elicited by a single dose of mRNA vaccine following previous infection with SARS-CoV-2 results in an increased antibody titer that is approximately equivalent to a two-dose vaccine regimen in individuals who were not previously infected (**Table 3**) [22, 23, 82-89]. In one study of healthcare workers vaccinated 7–11 months after infection with SARS-CoV-2, antibody titers measured 6 days following their first vaccination dose were twice as high as the antibody titers measured the month after their initial infection, and were able to neutralize wild-type, Alpha, and Beta variants, irrespective of vaccine type, number of doses, or pre-vaccination antibody titers [90].

Risk of Reinfection in Unvaccinated vs. Vaccinated Individuals with a History of Infection

In studies directly comparing risk of reinfection among previously infected individuals who were never vaccinated versus individuals who were vaccinated after infection, most, but not all, studies show a benefit of vaccination. One retrospective cohort study described risk of reinfection from December 2020–May 2021 among 2,579 US-based healthcare users previously infected with SARS-CoV-2, about 47% of whom were vaccinated over the course of the study. Investigators did not detect any cases of reinfection, regardless of vaccination status during 5 months of observation and so could not detect a benefit of vaccination [91]. In contrast, a case-control study conducted among 738 residents of Kentucky with reported infection during March–December 2020 found that previously infected persons who were unvaccinated had 2.3 times greater odds of reinfection during May–June 2021 than previously infected but vaccinated individuals [92]. Both studies occurred before Delta became the dominant variant in the United States.

More recent observational cohort studies including over 700,000 health system users in Israel and over 11,000 healthcare workers in India reported that history of prior infection provided greater protection from subsequent infection than vaccination alone, but overall risk of infection was lowest among those that were vaccinated following infection during periods of Delta predominance [93, 94]. In the systematic review described above, a pooled analysis across seven studies showed a modest but significant increase in protection from infection when previously infected individuals were vaccinated [79].

Limitations

This review summarizes characteristics of infection- and vaccine-induced immune responses, evidence regarding duration of immunity, and the potential impact of circulating variants. The approach was limited in scope focusing primarily on articles that were published in high-impact journals or novel in their findings; therefore, this does not represent a systematic review of all the scientific literature on SARS-CoV-2 infection-induced immunity. Particular biases related to observational study designs have been discussed above. The majority of studies included in this review came from a small number of countries, often with limited diversity in participants. Many of the immunologic studies did not include detailed demographic data. More consistent inclusion of descriptive data about demographics of participating populations (e.g., race/ethnicity, socioeconomic status, educational attainment) and conscious efforts to improve the racial, ethnic, and social diversity of participants in studies would be of great benefit in ensuring that related policies address the needs of all populations.

Conclusions

Multiple studies in different settings have consistently shown that infection with SARS-CoV-2 and vaccination each result in a low risk of subsequent infection with antigenically similar variants for at least 6 months. Numerous immunologic studies and a growing number of epidemiologic studies have shown that vaccinating previously infected individuals significantly enhances their immune response and effectively reduces the risk of subsequent infection, including in the setting of increased circulation of more infectious variants.

Although the Delta variant and some other variants have shown increased resistance to neutralization by both post-infection and post-vaccination sera in laboratory studies, observed reduction in effectiveness has been modest, with continued strong protection against hospitalization, severe disease, and death.

Multiple studies have shown that antibody titers correlate with protection at a population level; however, data are presently insufficient to determine an antibody titer threshold that indicates if an individual is protected from infection. At this time, there is no FDA-authorized or approved test that providers or the public can use to reliably determine whether a person is

protected from infection.

CDC will continue to follow and evaluate evolving scientific evidence in these areas and update recommendations accordingly.

Table 1: Duration of various immune markers after infection, multiple studies

Immune marker	Half-life/Duration	Citation
Anti-nucleocapsid IgG	63–85 days	[11, 14, 15, 53]
Anti-spike IgG	126–229 days	[11, 13-15, 52, 53]
Anti-receptor binding domain	83–126 days	[11, 14, 53]
Neutralizing Abs	55 days (at <70 days post infection), then 519 days 150 days (at >42 days), then 254 days (at>120 days post symptom onset)	[14] [53]
Pseudovirus neutralization	90–114 days	[11]
Memory B Cells	Increased over initial 4 months, then sustained	[11] [53]
CD4+ T Cells	Increased over first month then declined with half-life of 94–207 days	[11, 14, 53]
CD8+ T-Cells	Increased over first month then declined with half-life of 125–690 days	[11, 14, 53]

TTable 2: Summary of cohort studies with N>10,000 and population-level observational studies on reinfection, multiple locations

Study Design/ Location	Population/Sample Size	Definition of initial infection	Follow-up period	Definition of reinfection	Key Findings	Citation

Study Design/ Location	Population/Sample Size	Definition of initial infection	Follow-up period	Definition of reinfection	Key Findings	Citation
Multicenter prospective cohort (SIREN) with routine RT-PCR and antibody testing every 2-4 weeks United Kingdom	Healthcare workers (HCWs) Median age: 46 yrs (Range: 18–84yrs) (N = 25,661)	RT-PCR or antibody positive (n = 8278)	Enrolled: Jun–Dec 2020 Data extracted Feb 2021	RT-PCR positive >90 days following previous positive RT-PCR or >4 weeks following prior positive antibody test (further classified as confirmed, probable, or possible from clinical review)	Incidence of reinfections: 7.6 per 100,000 person-days compared to 57.3 for per 100,000 person-days for primary infections SARS-CoV-2 infection offered 84% protection against infection (93% against symptomatic infection) at 7-months following primary infection Mean interval to reinfection was 200 days 50% of cases were symptomatic	[54]
National-level observational study Denmark	Individuals tested nationally during 1st wave (N = 525,339)	RT-PCR positive during the 1st wave (Mar–May 2020) (n = 11,068)	Assessed for reinfections during 2nd wave (Sep–Dec 2020	RT-PCR positive during the 1st and 2nd wave (or subsequent positive >90 days later in alternative analysis)	Protection against repeat infection was 80.5% overall; 47.1% in persons >65years (in alternate analysis) No difference found when comparing 3-6 months to >7 months of follow-up	[55]

Study Design/ Location	Population/Sample Size	Definition of initial infection	Follow-up period	Definition of reinfection	Key Findings	Citation
Retrospective observational study (national reporting system) Austria	Compared “COVID-19 survivors” from first wave to general population (N~8.9 million)	Positive RT-PCR during 1st wave (Feb to April 2020) excluding deaths (n = 14,840)	Assessed for reinfections during 2nd wave (Sep–Nov 2020)	RT-PCR positive during 1st and 2nd wave (did not track infections that occurred from May to Aug 2020)	Odds ratio (OR) for reinfection amongst COVID-19 survivors compared to general population was .09 Mean time to reinfection was 212 days Noted 5 hospitalizations and one death amongst 40 “tentative” reinfections, though death was thought to be unrelated	[56]
Retrospective cohort study (health system) United States	Healthcare users tested for COVID-19 from Mar to Aug 2020 Mean age: 51 years (SD: 22 years) (N = 150,325)	RT-PCR positive prior to Aug 30, 2020 (n=8,845)	Initial testing: Mar–Aug 2020 Follow-up through Feb 2021	RT-PCR positive ≥90 days after initial positive test	Protection against repeat infection was 81.8% overall and 84.5% against symptomatic infection Average time to reinfection was 139 days; protection increased over time 50% of possible reinfections were symptomatic	[57]

Study Design/ Location	Population/Sample Size	Definition of initial infection	Follow-up period	Definition of reinfection	Key Findings	Citation
Population-level observational study (using laboratory-system) Italy	Healthcare users Median age: 59 years (Range: 0-108 years) (N = 15,078)	RT-PCR positive during 1st wave (Feb–Jul 2020) (n = 1579)	Mean follow-up: 280 days	RT-PCR positive test >90 days after resolution of first infection (with at least 2 consecutive negative tests in-between)	Incidence of reinfections: 1.0 per 100,000 person days compared to 15.1 per 100,000 person days for primary infections Incidence rate ratio (IRR) 0.07 (93% reduction in risk) Mean interval between primary infection and reinfection was >230 days Of 5 reinfections, 1 required hospitalization	[58]
National-level observational study (using national laboratory) Qatar	Individuals with testing data in centralized national database, from April to Dec 2020 Median age: 35-38 years (N = 192,967)	Antibody positive from Apr–Dec 2020 (n = 43,044)	Median follow-up: 16.3 weeks (range: 0–34 weeks)	RT-PCR-positive >14 days after infection, assessed clinically for evidence of reinfection and then adjusted for proportion that were able to be confirmed as genetically distinct in paired genomic sequencing	Calculated incidence rate of reinfection as 0.66 per 10,000 person-weeks compared to 13.69 per 10,000 person weeks for primary infection Amongst antibody-positive individuals, protection was estimated at 95.2% for up to 7 months of follow-up Incidence of reinfections did not increase with time Reinfections were less severe than primary infections (none were critical or fatal)	[95]

Study Design/ Location	Population/Sample Size	Definition of initial infection	Follow-up period	Definition of reinfection	Key Findings	Citation
Prospective Cohort United Kingdom	HCWs at four Oxford University teaching hospitals Median age: 38 years (Range: 18-86 years) (N = 12,541)	Anti-S IgG positive (n = 1265)	Initial testing: Mar 2020 Follow-up until Nov 2020 (31 weeks)	RT-PCR positive 60 days or more after their first positive antibody test or RT-PCR test	Incidence of reinfection: 0.13 per 10,000 days at risk compared to 1.09 per 10,000 days at risk for seronegative participants aIRR of 0.11 (89% reduction in risk) All reinfections were asymptomatic	[96]

Table 3: Selected studies evaluating the immune response to a 1st and 2nd dose of mRNA vaccine following previous infection

Participants	Effect of 1st dose if previously infected vs. 2nd dose if SARS-CoV-2 naïve	Effect of if previously infected, 2nd dose vs. 1st dose	Notes	Citation
SARS-CoV-2 naïve (n=33) or previously infected (n=11; 65–275d prior); similar age and sex distribution who received two doses of Pfizer-BioNTech or Moderna vaccine	Antibody and memory B cell responses 2 weeks after 1st dose similar to SARS-CoV-2 naïve participants 1 week after 2nd dose	No increase in overall or neutralizing antibodies, or spike-specific memory B cells	Included assessment of response to B.1.351 variant	[22]
Study within cohort of participants who were SARS-CoV-2 naïve (n=490 post dose 1, n=228 post dose 2) or previously infected (n=35 post dose 1, n=11 post dose 2)	Anti-RBD IgG no difference ≤21d post 1st dose than for SARS-CoV-2 naïve participants ≤21d after 2nd dose (10.0 [9.2–10.4] vs. 9.9 [9.4-10.3)	No difference in Anti-RBD IgG (10.2[8.4–10.5] vs. 9.9 [9.4–10.3])	Sensitivity analysis including participants with data at all time points found similar results. Timing of previous infections not specified.	[86]
Study within cohort of participants who were SARS-CoV-2 naïve (n=67 post dose 1, n=36 post dose 2) with previously infected (n=43 post dose 1, n=19 post dose 2)	Median anti-spike IgG 6-fold higher after 2nd dose than SARS-CoV-2 naïve participants after 1st dose	No increase in antibody titers after 2nd dose	Assay measured by area under the curve; antibody levels 10–45 times higher at baseline if previous infection. Timing was soon after 2nd dose but was unspecified; timing of prior infection is also unknown.	[88]

Group receiving 2 doses of Pfizer-BioNTech vaccine, either previously infected (n=6, 2–7 months post-infection) or SARS-CoV-2 naïve (n=9)	Neutralizing anti-RBD IgG at day 7 post 1st vaccine dose in previously infected group no different to day 7 post 2nd dose in uninfected group (GMT, 95% CI: 906, 552–1348 vs. 670, 364–1228, p = NS)	Results chart indicates no difference between antibody titers after 1st vs. 2nd dose (numbers not provided)		[87]
Healthcare workers infected a median of 2 months previously (n=18), 9 months previously (n=19) or SARS-CoV-2 naïve (n=73) who received 2 doses of Pfizer-BioNTech vaccine.	(not assessed)	No substantial difference in binding assay (0.92-fold) or neutralizing titers (1.17-fold) between 21d after 1st dose and 28 days after 2nd dose	Similar antibody responses after vaccine by whether previous infection was ~2 months or ~9 months previously	[82]
Cohort of recipients of Pfizer-BioNTech vaccine previously infected (n=51; 25 in 1st wave, 26 in 2nd wave) or SARS-CoV-2 naïve (n=50)	Irrespective of time since infection, previously infected recipients had higher spike-specific IgG and pseudovirus neutralization than previously uninfected after 2nd dose.	Neutralization did not increase between 1st and 2nd doses.	This study noted similar trends for IgA, IgM, and IgG. There is limited information on timing of tests after vaccine doses.	[85]
Group of recipients of Pfizer-BioNTech vaccine previously infected (n=23; 1–9 months after infection) or uninfected (n=23)	Higher IFN-gamma 20 d after 1st dose if previous infection than 20d after 2nd if no previous infection	IFN-gamma declines after 2nd dose (but boosted after 1st dose)	IFN-gamma from CD4+ T cells assessed to SARS-CoV-2 spike and peptide pools. Note that a separate analysis indicates natural infection drives IFN-gamma responses more than vaccine-induced immunity.	[84]
Recipients of Pfizer-BioNTech vaccine, 1 dose if previously infected (n=43; 17 with severe illness 12 months prior; 17 with mild illness 12 months prior; 9 with mild illness 6 months prior); or 2 doses if SARS-CoV-2 naïve * (n=25)	Two months after 2nd dose without previous infection, similar antibody levels but lower neutralization against variants, lower proportion of anti-spike B cells that were anti-RBD, and less diverse responses. Neutralizing B-cell clones were present but less common without infection.	(Not assessed)	Stable IgG and memory B-cells 6 to 12 months after infection.	[23]
Recipients of Pfizer-BioNTech or Moderna vaccine, anti-nucleocapsid negative (n=148) or positive (n=20; mostly by RT-PCR)	Similar titers of anti-spike antibody if previously infected ~21 days post dose 1 compared with ~66 days after dose 2 if SARS-CoV-2 naïve.	No increase in median anti-spike or anti-RBD titers. However, no. post infection with neutralizing antibodies increased from 10/15 to 12/15 and varied by individual.	Timing of RT-PCR positive tests is unclear.	[89]

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