

Protective immunity after recovery from SARS-CoV-2 infection



The SARS-CoV-2 pandemic is now better controlled in settings with access to fast and reliable testing and highly effective vaccination rollouts. Several studies have found that people who recovered from COVID-19 and tested seropositive for anti-SARS-CoV-2 antibodies have low rates of SARS-CoV-2 reinfection. There are still looming questions surrounding the strength and duration of such protection compared with that from vaccination.

We reviewed studies published in PubMed from inception to Sept 28, 2021, and found well conducted biological studies showing protective immunity after infection (panel). Furthermore, multiple epidemiological and clinical studies, including studies during the recent period of predominantly delta (B.1.617.2) variant transmission, found that the risk of repeat SARS-CoV-2 infection decreased by 80.5–100% among those who had had COVID-19 previously (panel). The reported studies were large and conducted throughout the world. Another **laboratory-based** study that analysed the test results of 9119 people with previous COVID-19 from Dec 1, 2019, to Nov 13, 2020, found that only 0.7% became reinfected.¹¹ In a study conducted at the Cleveland Clinic in Cleveland, OH, USA, those who had not previously been infected had a COVID-19 incidence rate of 4.3 per 100 people, whereas those who had previously been infected had a COVID-19 incidence rate of 0 per 100 people.⁶ Furthermore, a study conducted in Austria found that the frequency of hospitalisation due to a repeated infection was five per 14 840 (0.03%) people and the frequency of death due to a repeated infection was one per 14 840 (0.01%) people.⁴ Due to the strong association and biological basis for protection,¹² clinicians should consider counselling recovered patients on their risk for reinfection and document previous infection status in medical records.

Although those studies show that protection from reinfection is strong and persists for more than 10 months of follow-up,³ it is unknown how long protective immunity will truly last. Many systemic viral infections, such as measles, confer long-term, if not lifelong, immunity, whereas others, such as influenza, do not (due to changes in viral genetics).⁴ We are limited

by the length of current reported follow-up data to know with certainty the expected duration that previous infection will protect against COVID-19. Encouragingly, authors of a study conducted among recovered individuals who had experienced mild SARS-CoV-2 infection reported that mild infection induced a robust antigen-specific, long-lived humoral immune memory in humans.¹³

It important to note that antibodies are incomplete predictors of protection. After vaccination or infection, many mechanisms of immunity exist within an individual not only at the antibody level, but also at the level of cellular immunity.^{14–16} It is known that SARS-CoV-2 infection induces specific and durable T-cell

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Panel: Biological, epidemiological, and clinical evidence that previous COVID-19 infection reduces the risk for reinfection

Biological studies

- Dan et al (2021):¹ about 95% of participants tested retained immune memory at about 6 months after having COVID-19; more than 90% of participants had CD4⁺ T-cell memory at 1 month and 6–8 months after having COVID-19
- Wang et al (2021):² participants with a previous SARS-CoV-2 infection with an ancestral variant produce antibodies that cross-neutralise emerging variants of concern with high potency

Epidemiological studies

- Hansen et al (2021):³ in a population-level observational study, people who had had COVID-19 previously were around 80.5% protected against reinfection
- Pilz et al (2021):⁴ in a retrospective observational study using national Austrian SARS-CoV-2 infection data, people who had had COVID-19 previously were around 91% protected against reinfection
- Sheehan et al (2021):⁵ in a retrospective cohort study in the USA, people who had had COVID-19 previously were 81.8% protected against reinfection
- Shrestha et al (2021):⁶ in a retrospective cohort study in the USA, people who had had COVID-19 previously were 100% protected against reinfection
- Gazit et al (2021):⁷ in a retrospective observational study in Israel, SARS-CoV-2-naïve vaccinees had a 13.06-times increased risk for breakthrough infection with the delta (B.1.617.2) variant compared with those who had had COVID-19 previously; evidence of waning natural immunity was also shown
- Kojima et al (2021):⁸ in a retrospective observational cohort of laboratory staff routinely screened for SARS-CoV-2, people who had had COVID-19 previously were 100% protected against reinfection

Clinical studies

- Hall et al (2021):⁹ in a large, multicentre, prospective cohort study, having had COVID-19 previously was associated with an 84% decreased risk of infection
- Letizia et al (2021):¹⁰ in a prospective cohort of US Marines, seropositive young adults were 82% protected against reinfection

immunity, which has multiple SARS-CoV-2 spike protein targets (or epitopes) as well as other SARS-CoV-2 protein targets. The broad diversity of T-cell viral recognition serves to enhance protection to SARS-CoV-2 variants,¹⁵ with recognition of at least the alpha (B.1.1.7), beta (B.1.351), and gamma (P.1) variants of SARS-CoV-2.¹⁷ Researchers have also found that people who recovered from SARS-CoV infection in 2002–03 continue to have memory T cells that are reactive to SARS-CoV proteins 17 years after that outbreak.¹⁵ Additionally, a memory B-cell response to SARS-CoV-2 evolves between 1-3 and 6-2 months after infection, which is consistent with longer-term protection.¹⁸

Some people who have recovered from COVID-19 might not benefit from COVID-19 vaccination.^{6,19} In fact, one study found that previous COVID-19 was associated with increased adverse events following vaccination with the Comirnaty BNT162b2 mRNA vaccine (Pfizer–BioNTech).²⁰ In addition, there are rare reports of serious adverse events following COVID-19 vaccination.²¹ In Switzerland, residents who can prove they have recovered from a SARS-CoV-2 infection through a positive PCR or other test in the past 12 months are considered equally protected as those who have been fully vaccinated.²²

Although longer follow-up studies are needed, clinicians should remain optimistic regarding the protective effect of recovery from previous infection. Community immunity to control the SARS-CoV-2 epidemic can be reached with the acquired immunity due to either previous infection or vaccination. Acquired immunity from vaccination is certainly much safer and preferred. Given the evidence of immunity from previous SARS-CoV-2 infection, however, policy makers should consider recovery from previous SARS-CoV-2 infection equal to immunity from vaccination for purposes related to entry to public events, businesses, and the workplace, or travel requirements.

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