Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Protective immunity after recovery from SARS-CoV-2 infection

Published **Online** November 8, 2021 https://doi.org/10.1016/S1473-3099(21)00676-9

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.

***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-naive 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

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 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.

NK has received consulting fees from Curative. JDK serves as an independent medical director of Curative.

*Noah Kojima, Jeffrey D Klausner
nkojima@ucla.edu

Department of Medicine, University of California Los Angeles, Los Angeles, CA 90095, USA (NK); Departments of Population Health and Public Health Sciences and Medicine, Keck School of Medicine, University Southern California, Los Angeles, CA, USA (JDK)

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Serial antigen rapid testing in staff of a large acute hospital

Published **Online** December 6, 2021 https://doi.org/10.1016/S1473-3099(21)00723-4

Point-of-care (lateral flow) assays with an antigen rapid test (ART) for SARS-CoV-2 became commercially available in November 2020 worldwide, as a supplement to real-time PCR (rtPCR).[1] ARTs are self-administered and detect SARS-CoV-2 antigens from anterior nares swabs and return results within minutes. Depending on the kit, ART has a sensitivity of 40·2–74·1% and specificity 93·6–99·8% in asymptomatic individuals, which is inferior to that of rtPCR (86–92% and 99%, respectively).[2,3] However, ARTs are cheaper, easier to implement at scale, and give faster results than rtPCR testing.[3] Various institutions are using ARTs to detect and reduce the transmission of SARS-CoV-2.[4–6]

Singapore is a densely populated city state of 5·7 million residents. As of late July, 2021, the incidence of SARS-CoV-2 was 23·6 cases per million people per day, with a fully vaccinated rate of 60%. Mandatory mask wearing, limits on the size of social gatherings, thorough contact tracing, and supervised quarantine of all cases and contacts were already in place by this date. Since the start of the COVID-19 pandemic, The National University Hospital, a tertiary academic medical centre employing 8000 clinical staff with a capacity of over 1200 beds, had adhered to a national strategy of fortnightly rtPCR surveillance in all asymptomatic staff, 95% of whom were vaccinated. On July 30, 2021, serial ART was introduced as a more sustainable, less resource-intensive method of ensuring early identification of COVID-19-positive staff to mitigate transmission to patients at a time when community levels of COVID-19 were increasing.[7] In addition, symptomatic staff were asked to present immediately for testing. Universal mask wearing for staff had been in place since February, 2020.

Serial ART is an emerging testing strategy and few real-world examples of its use have been published. ARTs performed every 3 days can break chains of transmission of SARS-CoV-2.[8,9] Although a single ART is not as sensitive or specific as a single rtPCR test, serial testing two or three times a week can outperform a single weekly rtPCR test. The National University Hospital's implementation required all asymptomatic clinical staff to self-administer ART twice a week, routinely. Staff then submitted time-stamped photographs of their ARTs to a co-worker (their ART buddy), which could be reviewed by reporting officers on-demand. Any symptomatic staff were not to make use of this system; rather, they needed to promptly present to the occupational health clinic for rtPCR testing.

Staff read a simple guide based on manufacturer's instructions and electronically signed an acknowledgement stating that they would comply to twice weekly ARTs. Reports from ART buddies and spot audits suggested that staff were engaged and compliant. They

	Advantages	Disadvantages
Diagnostic performance	(1) Lower sensitivity and specificity than rtPCR, mitigated by a strategy of more frequent antigen rapid testing; (2) negative result can predict non-infectiousness; and (3) enables ad hoc quick screening of congregate, vulnerable settings (such as hospitals)	(1) More false positives and false negatives than rtPCR; (2) variable performance among kits; and (3) variable swabbing technique, reading of results among individuals, especially when self-administered
Implementation	(1) Self-administration does not require specially trained staff or rtPCR reagents or machines; (2) almost immediate results; (3) scalable depending on local prevalence and test availability; and (4) reduced barrier to testing as kits can be made easily available to staff for home use	(1) Test kits can be expensive; (2) large number of test kits are required, which might not be readily available in all settings; and (3) poor compliance could be an issue if testing is unsupervised and results are self-reported

rtPCR=real-time PCR.

Table: **Advantages and disadvantages of serial testing for SARS-CoV-2 with antigen rapid tests**