

INFECTIOUS DISEASE

Understanding protection from SARS-CoV-2 by studying reinfection

Understanding the risk of reinfection with SARS-CoV-2 in exposed cohorts provides an avenue to understanding the path to protection against SARS-CoV-2 for vaccine development.

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An underlying motivation for the current development of vaccines against the coronavirus SARS-CoV-2 is the premise that neutralizing antibodies will provide lasting protection from infection, drawn in part from experiences with other anti-viral vaccines. This desire to elicit neutralizing antibodies via a vaccine stems from the idea that antibodies should prevent infection if they block entry of the virus into the cell. One common benchmark for measuring vaccine efficiency is eliciting neutralizing antibody levels similar to those elicited by natural infection, on the basis of the assumption that infection induces responses that protect against reinfection. In the case of SARS-CoV-2, recent reports of reinfection, as indicated by viral sequence differences, clinical data and data on potential exposure, have raised critical questions about whether and how well a first infection protects against reinfection¹⁻³.

The idea that infection prevents reinfection was a long-held assumption for human immunodeficiency virus (HIV), until the first case reports of reinfection emerged about two decades into the pandemic. The first reports of HIV reinfection — often called ‘HIV superinfection’, because reinfection occurs while the first infection is still present — were documented through the use of both viral genetics and clinical and epidemiological evidence. For example, an early report was of a person infected with HIV who traveled to a region where there was a different circulating strain of HIV-1, and soon after his return, that regional strain was detected among his viral sequences⁴. Detecting viral reinfection using sequence studies of this type requires enough sequence difference between the strains to have confidence there was a new infection and not simply evolution of the virus in the person⁵. Evidence of risk strengthens the conclusions that can be drawn from sequencing data.

One of the recent case reports of a probable reinfection with SARS-CoV-2

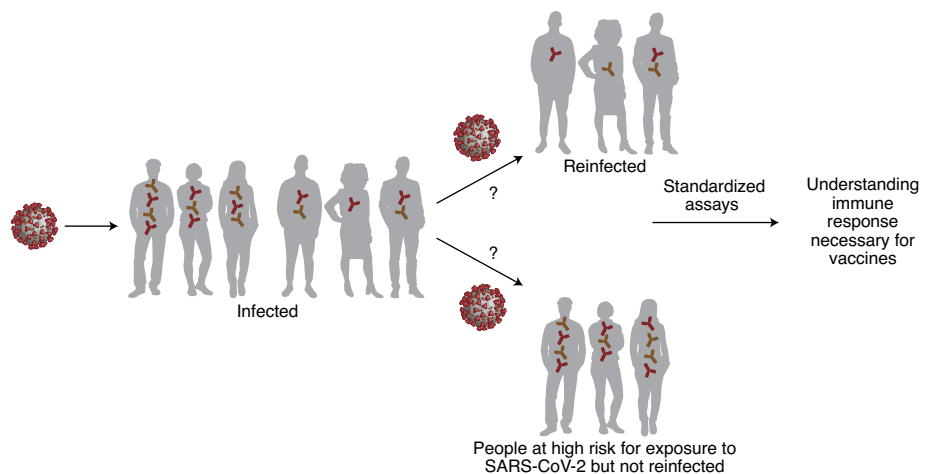


Fig. 1 | Studying exposure to SARS-CoV-2 and susceptibility to reinfection.

also deduced reinfection on the basis of the genetics of the infecting viruses and travel by the infected person¹. The second infection was detected about 4 months after the first infection resolved, as indicated by two negative RNA tests, and there was some clinical suggestion of a new acute infection in the person at that time. In this person, the two SARS-CoV-2 viruses with which they were infected differed at 24 nucleotide positions, which is more than expected for de novo evolution of SARS-CoV-2 within a person. Notably, the viral strain was from a clade different from that of the initially infecting strain, and the second strain resembled the viruses circulating in the time frame and region in which the person traveled — a story much like the first case report of HIV reinfection. In the other recently published cases, an interval of about two to four months between the detection of SARS-CoV-2 viral RNA and the sequence differences between the viruses support the proposal of reinfection^{2,3}. The fact that two cases were healthcare workers and were potentially continually exposed to the virus

adds to the likelihood that these were indeed cases of reinfection².

Reinfection suggests that the immune response to the first infection was not adequate to provide protection against reinfection, and its occurrence challenges the assumptions that the levels and/or qualities of antibodies in natural infection should be the goal of a vaccine. However, a few case reports do not mean that protection cannot be achieved but instead provide a chance to thoroughly investigate whether there are immunological deficits in these patients. It is critical to remember that the conclusions that can be drawn from a small collection of case reports are limited. A larger collection of reinfection cases represents the opportunity to more clearly define the benchmark needed for protection by identifying what fails to provide protection.

Studies of HIV reinfection may be informative here. After the first case reports of superinfection, several groups with longitudinal follow-up of populations at high risk of HIV exposure began to

examine viral sequence dynamics in their cohorts and found that reinfection was more common than expected, at about half of the incidence of first infections, which means that first infections were not highly protective⁵. Several studies suggested that while reinfection could occur any time after a first infection, the risk was highest soon after the first infection, potentially suggesting that the main risk was before the antibody response to the virus fully matured, which takes months for HIV⁶. But even now, there is little clear evidence for deficits in the antibody responses in those who became superinfected with HIV⁶; one contributing factor to this may be the lack of large cohorts and/or coordinated efforts to approach this question.

The HIV field may thus serve as a guide for considering the importance of reinfection and how to study this for SARS-CoV-2. For example, understanding the timing of reinfection may be informative, including whether the window of protection is soon after a first infection, with more-limited protection over time, and whether responses decay during this period, as reported for endemic coronaviruses⁷. Current data suggest that antibodies to SARS-CoV-2 are induced to peak levels within weeks of infection, but there are variable data on how quickly they wane over time^{8–10}, and longer follow-up will be needed for full understanding of the antibody dynamics for this new viral infection and how this affects reinfection risk.

There are numerous additional points that should be understood about reinfection with SARS-CoV-2. Is such reinfection a rare phenomenon that occurs in people with notably weak immune responses? If so, what is limited about these responses? Is there evidence that neutralizing antibodies are especially poor in these patients, and can cases of reinfection shed light on the titer of antibody and/or other immune measures that are no longer protective? Do people who are reinfected have little disease and are

their viral loads lower than those typical of first infections? This would suggest that even though the immune response to infection is not adequate to provide sterilizing immunity, it may provide therapeutic benefit, which could still be useful for a vaccine approach, at least initially, until better vaccine concepts emerge.

Answering these questions and determining if a first infection does anything to protect from infection critically requires the follow-up of well-characterized longitudinal cohorts. These cohorts should include people who unavoidably are at continued risk of exposure, due to occupation or other factors, because the studies of reinfection, like vaccine studies, require exposure for the measurement of efficacy. It is also important that the groups that study populations at risk of reinfection cooperate with each other, because if there is protection, cases of reinfection will be at a lower rate than first infections and therefore this will require the study of large numbers of previously infected people. It is critical that cases are examined in parallel with large numbers of controls with similar levels of exposure (Fig. 1).

Lab assays comparing reinfection cases and controls should be comprehensive and as biologically relevant as possible and should be standardized. For example, the same neutralization assay should be used, because introducing variation through the use of different assays will make it more difficult to define a threshold of activity that distinguishes cases of reinfection. The most relevant would be measuring neutralization of replicating SARS-CoV-2 in cells that are natural targets of the virus; if there are limitations in handling infectious virus, then the assay used should be one that has been shown to correlate well with an assay of replicating virus. Even more powerful than simply using the same assays across studies would be conducting them in a single lab, although the logistics of this would be prohibitive.

The study of reinfection with SARS-CoV-2 is critical because if neutralizing antibody responses are robust in people who are reinfected, this suggests that the vaccine concepts need to be diversified. This could include considering diverse antibody epitopes, both neutralizing and non-neutralizing, and optimizing the effector function of antibodies and enhancing cellular responses. It is critical to understand how infection with SARS-CoV-2 affects reinfection risk and to use these studies of naturally exposed populations, working in concert with vaccine efforts, to understand correlates of immunity. Studies of naturally HIV-exposed populations and vaccine trials have also taught that researchers need to look beyond neutralizing antibodies and consider other measures of antibody function^{11,12}, and such a broad approach to studies of reinfection seems equally prudent for SARS-CoV-2. □

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Competing interests

The author declares no competing interests.