

Immunity to SARS-CoV-2 and the concept of an Immunity Certificate.

Background

As SARS-CoV-2 continues to circulate, we approach a time when a significant number of people who have been infected in early pandemic waves may have some 'immunity' that protects them during subsequent exposure.

In addition, results from clinical trials of novel vaccines expressing or containing SARS-CoV-2 antigens suggest that a high degree of immunity to COVID-19 disease can be obtained, at least in the short-term.

This new context leads us to re-examine the concept that those who have recovered from SARS-CoV-2 infection or have been given an effective vaccine might be given, for a period, an exemption from current non-pharmaceutical interventions designed to control the spread of SARS-CoV-2.

Current evidence is that:

1. SARS-CoV-2 antibodies can be detected in at least 90% people after infection, and with new assays this figure approaches 100%. Antibodies can be measured within about a week after onset of symptoms, peaking at about one month; they then decline to a quite stable level which shows little evidence of further decline over 5 or 6 months. (High confidence).
2. The type of antibodies most closely associated with protection are neutralising antibodies which correlate with antibody to the receptor binding domain (RBD) of the spike protein. Currently available commercial tests do not measure *neutralising* antibody.
3. High levels of neutralizing antibodies that target the RBD of SARS CoV2 Spike protein confer protection against infection. This may even be 'sterilizing' immunity that protects from both disease and infection. People who have high neutralizing antibody levels at the time of re-exposure are unlikely to serve as permissive hosts for the virus and are unlikely to contribute to community transmission. (Moderate confidence).
4. In the face of intermediate, low or absent levels of neutralizing antibody, other immune parameters including B cell memory, tissue resident CD4 and CD8 T cells might confer protection from disease. This type of immunity is likely to modify viral load but might not prevent initial infection. Emerging evidence suggests that such immune parameters may be maintained for 5 months or more after natural infection. However, measurement of cell mediated immunity is not currently possible in routine laboratories and is not currently suitable to guide certification (High confidence)
5. Reinfection upon re-exposure to SARS CoV2 does occur, but seems rare. Most reported reinfections are mild, but some are severe; these require further investigation. UK based surveillance studies in Health Care Workers are well placed to detect and investigate reinfections. The SIREN study reports a low number of confirmed reinfections to date suggesting that natural immunity is sustained in most cases; evidence is still emerging. The Oxford HCW study has reported 89 PCR-confirmed symptomatic infections in seronegative individuals (0.46 cases per 10,000 days at risk) and no symptomatic infections in those with prior anti-spike antibodies. This suggests previous infection confers good protection against symptomatic re-infection. However, 3 (0.21/10,000 days at risk) anti-spike IgG seropositive

individuals had PCR-positive tests in asymptomatic screening compared to 76 (0.40/10,000 days at risk) seronegative individuals suggesting the presence of anti-spike IgG does not provide full protection against asymptomatic re-infection. There are also a number of care home studies (eg Vivaldi) in which the serostatus of individuals is known and where attack rates could be compared. The SIREN interval analysis due in December, and other evidence concerning attack rates in seropositive vs seronegative individuals in available cohorts are critical to confirm whether seropositivity confers immunity (Low confidence).

6. In Non-Human Primate (NHP) challenge studies, disease was averted but viral load in the nose was not affected by vaccination. This opens the possibility that individuals with some immunity could become silently infected and still contribute to onward transmission of virus. How relevant the NHP challenge is to virus acquisition through normal transmission events is not clear, given the very high dose of virus used in challenge. (Moderate confidence).
7. Current data from clinical vaccine trials demonstrates protection from disease but there is currently no information on the effects on viral load or impact on transmission. During vaccine roll-out, there is an important opportunity to gather immunological and viral load data to assess the impact of vaccination on transmission in settings such as care homes. This would enable us to establish better correlates on sterilizing and disease modifying immunity and increase confidence in the concept of a vaccine based immunity certificate.
8. The length of immunity conferred by natural infection or vaccination is currently not known. Waning immunity is believed to partly underlie the propensity for other coronaviruses to reinfect after 1-2 years. Studies on MERS-CoV and SARS-CoV found waning antibody levels over this time period. Reinfections with seasonal coronaviruses occurs frequently at 12 months, sometimes as early as 6 months but not within three months. Therefore, based on the variability in the data and differential responses in the population we conservatively estimate that a protective immune response after SARS-CoV-2 infection or vaccination may last for 90 days (moderate confidence).

Based on this information, we conclude that:

Within one month of natural infection, a high proportion of people will develop immunity which is protective against disease caused by reinfection (high confidence). This protection is likely to persist for at least three months (moderate confidence). The level of protection against subclinical re-infection (as opposed to disease) is uncertain.

28 days after the first dose with an effective vaccine, a high proportion of people develop immunity which is protective against disease caused by reinfection (high confidence). The duration of protection is not yet known. The level of protection against subclinical infection is uncertain and we need to see secondary endpoint data from the vaccine trials that assess infection.

Some individuals will *not* develop immunity following either natural infection or vaccination (high confidence). The proportion is unknown but it likely to be small (moderate confidence).

Some form of COVID-19 immunity certification is likely to be possible but further data and considerations are needed before a recommendation can be made.

Key uncertainties:

The level of sterilising immunity provided by natural infection or immunisation is not yet fully understood. Data on the level of sterilising immunity provided by natural infection should be available from the SIREN study and the Oxford Health Care Worker study before the end of the year. Data on the level of sterilising immunity provided by immunisation should be available from some vaccine studies before the end of the year.

The duration of natural or vaccine induced immunity is not yet fully understood.

Recent citations that support our conclusions:

Immunological memory to SARS-CoV-2 assessed for greater than six months after infection
<https://www.biorxiv.org/content/10.1101/2020.11.15.383323v1.full.pdf>

ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques
<https://www.nature.com/articles/s41586-020-2608-y>

<https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine>

