COVID-19 natural immunity

Scientific brief

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World Health Organization

Key Messages:

- Within 4 weeks following infection, 90-99% of individuals infected with the SARS-CoV-2 virus develop detectable neutralizing antibodies.
- The strength and duration of the immune responses to SARS-CoV-2 are not completely understood and currently available data suggests that it varies by age and the severity of symptoms. Available scientific data suggests that in most people immune responses remain robust and protective against reinfection for at least 6-8 months after infection (the longest follow up with strong scientific evidence is currently approximately 8 months).
- Some variant SARS-CoV-2 viruses with key changes in the spike protein have a reduced susceptibility to neutralization by antibodies in the blood. While neutralizing antibodies mainly target the spike protein, cellular immunity elicited by natural infection also target other viral proteins, which tend to be more conserved across variants than the spike protein. The ability of emerging virus variants (variants of interest and variants of concern) to evade immune responses is under investigation by researchers around the world.
- There are many available serologic assays that measure the antibody response to SARS-CoV-2 infection, but at the present time, the correlates of protection are not well understood.

Objective of the scientific brief

This scientific brief replaces the WHO Scientific Brief entitled "'Immunity passports' in the context of COVID-19", published 24 April 2020.[1] This update is focused on what is currently understood about SARS-CoV-2 immunity from natural infection. More information about considerations on vaccine certificates or "passports"will be covered in an update of WHO interim guidance, as requested by the COVID-19 emergency committee.[2]

Methods

A rapid review on the subject was undertaken and scientific journals were regularly screened for articles on COVID-19 immunity to ensure to include all large and robust studies available in the literature at the time of writing.

COVID-19 immune responses to natural infection

Prior exposure to SARS-CoV-2 can be assessed by detecting the presence of virus-specific antibodies in serum. Functional neutralizing antibodies (NAb) are those able to neutralize the virus by blocking its entry into the cell.

Large cohort studies have reported that 90-99% of SARS-CoV-2 infected individuals develop neutralizing antibodies within 2-4 weeks after infection.[3–7] A small proportion of individuals do not develop NAb after SARS-CoV-2 infection for reasons that are unclear.[7] Individuals with mild or asymptomatic infection tend to have lower antibody levels than those with severe disease, and some studies have suggested that in some individuals waning of antibody levels occurs within several months after infection.[6–10] Studies aimed to detect immunological memory including the assessment of cellular immunity by testing for the presence of memory B cells, and $CD4^+$ and $CD8^+$ T cells, observed robust immunity at 6 months post-infection in 95% of subjects under study, which included individuals with asymptomatic, mild, moderate and severe infections.[11]

Correlates of protection against disease

How much cellular versus humoral immunity contributes to protection after natural infection is not fully understood. Studies point at NAb as a key element of immunoprotection, with cellular immunity likely to provide additional longer-term protection especially against severe disease and death.[12–15] How long overall protection may last remains unclear, and this may differ depending on the disease severity.[7] For other human coronaviruses (hCoV), hCoV-OC43, hCoV-229E, hCoV-NL63 and hCoV-HKU-1, which cause the common cold, antibodies last for at least a year after infection with significant inter-human variability,[16] while antibodies to more closely related MERS-CoV and SARS-CoV-1, which cause, respectively, middle east respiratory syndrome and severe acute respiratory syndrome, can be detected for years.[17–21]

Reinfection

Though rarely reported to date, reinfection with SARS-CoV-2 can occur. Four large studies from the United Kingdom, the United States of America and Denmark estimated that infection with SARS-CoV-2 provided 80-90% protection from reinfection up to 7 months, and up to 94% protection against symptomatic disease.[22–25] The level of protection against re-infection as assessed by PCR positivity was estimated to be 50% in people aged over 65 years old.[24]

SARS-CoV-2 variants and implications for immunity

The more the SARS-CoV-2 virus circulates, the more opportunities it has to change through natural evolution. The emergence of virus variants can pose new challenges. Currently, three virus variants, B.1.1.7, B.1.351 and P.1, with increased transmissibility or potential to partially escape immunity, are characterized as global Variants of Concern (VOC) by WHO and are circulating in many countries. Evidence of reduced susceptibility to neutralization by serum antibodies of some SARS-CoV-2 variants (*e.g.* P.1 and B.1.351) to natural (or vaccine-induced) neutralizing antibodies has been reported,[26–29] raising the concern that reinfection after natural infection (or breakthrough infection after vaccination) may increase in settings where these variants broadly circulate.[30] Of note, recent studies found that current global VOCs are unlikely to have an impact on $CD4^+$ and $CD8^+$ T cell reactivity in COVID-19 exposed donors and vaccinees, but how this observation applies to protection against reinfection or breakthrough infection after vaccination remains unclear.

Measuring immune responses

The immune response following infection with a virus can be measured by the detection of virus-specific antibodies such as IgA, IgM, IgG or total antibodies through immunoassays, as well as by the detection of sensitized memory B cells and/or CD4+ and CD8+ T cells, which require more complicated assays. The most commonly measured immune response is the presence of antibodies in serum. Serologic assays to detect the antibody response are usually based on enzyme immunoassays, which detect the presence of virus-specific antibodies in the blood or by live or pseudo-virus neutralization assays, which detect functional NAb. While serologic testing has limited use in clinical management because it does not capture active infection, it can be very useful in determining the extent of infection or estimating attack rates in given populations.

Interpreting the results of serologic testing, however, is complex: there are several antibody types and subtypes and multiple antigenic determinants/epitopes that can be used to target these antibodies, and the results may differ substantially depending on the combinations chosen. The results will also depend on the manufacturing specifics of the assay used. The most frequently used assays for detection of antibodies to SARS-CoV-2 are enzyme-linked immunosorbent tests, chemiluminescent tests, and lateral flow rapid diagnostic tests (RDTs). Advice on the use of RDTs for antibody detection is available on the WHO website.32

Conclusions

Current evidence points to most individuals developing strong protective immune responses following natural infection with SARS-CoV-2. However, inaccurate immunodiagnostic tests may falsely indicate infected individuals as naïve to the virus (not previously infected) or may falsely label non-infected people as positive for immune markers of recent infection.

To conclude, available tests and current knowledge do not tell us about the duration of immunity and protection against reinfection, but recent evidence suggests that natural infection may provide similar protection against symptomatic disease as vaccination, at least for the available follow up period.[33] The emergence of variants of concern poses challenges and their potential to evade immunity elicited by either natural infection or by vaccination, needs to be closely monitored.

Plans for updating

WHO continues to monitor the situation closely for any changes that may affect the information in this Scientific brief. Should any factors change, WHO will issue a further update. Otherwise, the validity of this brief will be reviewed 3 months after the date of publication.

Contributors

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