COVID-19
LITERATURE REPOSITORY

# Can we tell who is "immune" to COVID-19?

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## Discussion

A large number of commercial and in-house antibody tests have been developed to assess the humoral immune response to SARS-CoV-2 infection (the virus that causes COVID-19). These tests detect the presence of different antibody classes (immunoglobulin [Ig]G, IgM or IgA) that recognise various viral antigens. These tests have fairly high specificity (around 98%) to detect SARS-CoV-2-specific antibodies, but low and variable sensitivity depending on the timing of the sample collection(1). Most detect the presence of antibodies without providing any information on their function, which require more complex virus neutralisation assays. Antibodies targeting either the whole, or specific subdomains of the spike protein (in particular subdomain 1 and the receptor binding protein) have the strongest correlation with neutralisation activity, more so than antibodies binding to the nucleocapsid protein(2-6). There is some evidence from animal models that neutralising antibodies (nAbs) provide protection from severe disease, at least in the short term(3), i.e. their presence confers protective immunity. However, it is still not clear what level of antibody is associated with immune protection in humans, i.e. there is no validated correlate of protection.

The durability of the immune response to SARS-CoV-2 is also unknown. At present there are limited data on the longevity of antibody responses beyond 40 days from symptom onset(7). One recent study (in pre-print form) has shown that although IgG levels are maintained in the majority of infected individuals for up to 90 days, nAb titres start to wane after 60 days(2). In contrast, evidence from other closely related human coronaviruses such as SARS-CoV-1 (the virus that caused severe acute respiratory syndrome; SARS) and MERS-CoV (which causes Middle East respiratory syndrome; MERS) suggests that the humoral immune response may persist for 2-3 years in many individuals. Among 176 SARS patients, SARS-CoV-1-specific IgG was maintained for an average of 2 years, but declined significantly in the third year(8). Serum neutralising activity seems to persist for longer (up to 36 months) than detectable SARS-CoV-1-specific IgG(9). Similarly, nAbs following infection with MERS-CoV have

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been shown to persist for up to 34 months in recovered patients(10); again longer than persistence of measurable IgG(11).

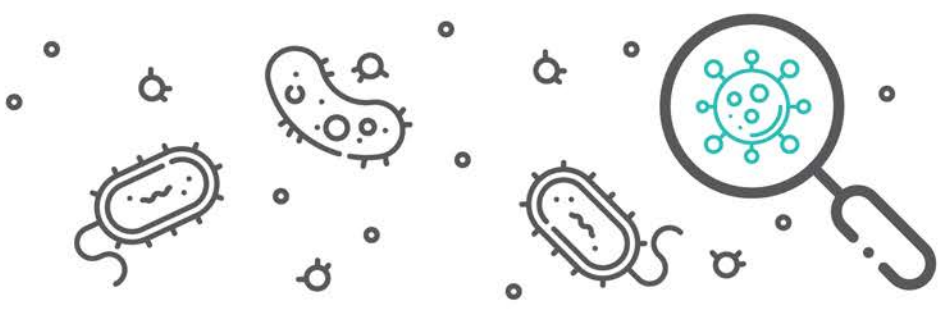
SARS has not re-emerged since 2004, and MERS remains sporadic with mostly self-contained outbreaks. However, limited human-to-human transmissibility of these related coronaviruses makes it difficult to comment on the durability of immune protection. Animal challenge/rechallenge studies have demonstrated protection from re-infection following primary infection with SARS-CoV-2, with evidence of an anamnestic (booster) antibody responses(12, 13). Thus it is likely that development of a robust memory B-cell response(14) will contribute to ongoing protection from severe COVID-19 disease, in the absence of circulating antibody. To date, no human reinfections with SARS-CoV-2 have been confirmed. Re-infections can occur with at least 3 of the other 4 common human coronaviruses—specifically, 229E, NL63, and OC43, all of which generally cause mild respiratory illnesses. It is likely that these re-infections are due to short-lived protective immunity and re-exposure to genetically distinct forms of the same virus. It remains to be seen with SARS-CoV-2 if, and how much, these factors play a role in long-term susceptibility to re-infection and disease progression. Eight months into the pandemic there is evidence of genetic evolution of the spike protein of SARS-CoV-2(15).

Furthermore, it is not clear how the severity of COVID-19 disease influences the development and the longevity of the immune response. In particular, concerns have been raised as to whether mild or asymptomatic SARS-CoV-2 infection will elicit durable protective immunity. After mild or asymptomatic MERS-CoV infections, antibody responses were either limited or rapidly declined(11, 16). This has implications beyond individual immunity. It may be premature to assume that the results of sero-epidemiological surveys, that document in some places high rates of “sero-positivity” for SARS-CoV-2-specific antibodies among the general population (up to 19%)(17), can be used to infer population immunity.

Finally, although most of the scientific literature, and media and public attention, have been focused on antibody responses, it is important to also consider the role of cellular immune responses. Two individuals with X-linked agammaglobulinaemia developed COVID-19 pneumonia but were able to clear the virus despite being unable to produce antibodies(18). Among 23 patients infected with SARS-CoV-1, 60% were shown to have virus-specific memory T-cell responses six years after their acute infection, despite the absence of detectable IgG(19). Similarly, circulating SARS-CoV-2-specific CD8+ and CD4+ T-cells have been identified amongst convalescent COVID-19 patients(20). The contribution of circulating and memory T-cells in protective immunity to SARS-CoV-2 requires further study.

**Conclusions**

1. There are currently no validated correlates of immune protection for COVID-19 and protective immunity cannot necessarily be inferred from standard antibody assays.



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2. The longevity (beyond 3 months) of measurable and/or functional neutralising antibodies that appear following SARS-CoV-2 infection remains unknown.

3. The role of cellular immune responses in long-term immune protection against SARS-CoV-2 requires further study.

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