What we Know About Immunity to SARS-CoV-2

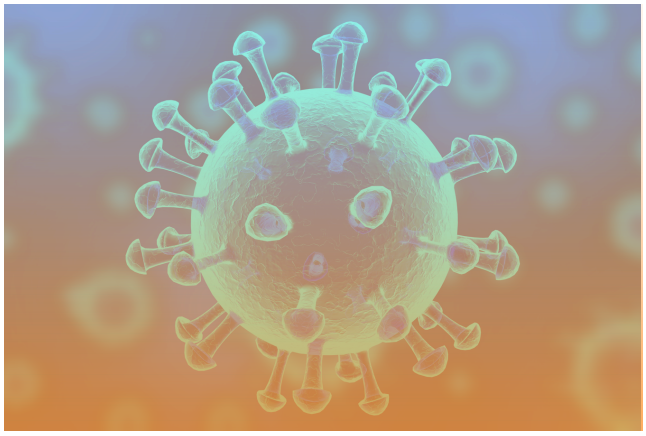
Immunity to SARS-CoV-2, whether acquired by infection, vaccination, or both (hybrid immunity), involves several components: circulating antibodies (which bind to the virus and neutralise it or activate other immune pathways), T cells (helper CD4+ T cells that support antibody production by B cells and cytotoxic CD8+T cells that destroy infected cells), and long-lived antibody-producing plasma cells (which reside in the bone marrow).

In case of natural infection with the virus, the immune response (both humoral and cellular) is directed mainly against the Spike (S) and the Nucleocapsid (N) proteins, whereas most COVID-19 vaccines are S-based and therefore elicit a response only to S (or a fragment of S). In addition, natural infection elicits systemic and local immune responses in the respiratory tract (mucosal immunity), while vaccination induces only systemic responses (1).

Predictors of immune protection

Neutralising activity and levels of binding **antibodies to S** in blood are strong correlates of protection (especially against infection) in both unvaccinated and vaccinated individuals (2,3). However, this correlation is less strong with recent SARS-CoV-2 variants, most likely due to immune escape mechanisms (4). Furthermore, low levels of anti-Spike antibodies do not imply a lack of protection against severe disease.

Virus-specific T cells (especially CD4+T cells) circulating in the blood have also been shown to correlate with protection against COVID-19 (5), but they are more difficult to measure in the laboratory.



Duration of immune protection

After several vaccination campaigns, we have learned that **protection against SARS-CoV-2 infections wanes fast** (within the first 6 months), especially in vaccinated people without prior infection. This is mainly due to the rapid waning of neutralising and binding antibodies in the serum and may be partly explained by the recent finding that COVID-19 mRNA vaccines do not generate long-lasting plasma cells in the bone marrow (6). Individuals with prior SARS-CoV-2 infection or with hybrid immunity (infection plus vaccination) are better protected against reinfection as compared to those vaccinated only, with hybrid immunity providing the most durable protection (7). The risk of reinfection is further reduced if the latest infection is recent (within the last 6 months) (3,8).

In contrast, **protection against severe disease remains relatively stable** over time, and across Omicron and pre-Omicron infections (9). This is because SARS-CoV-2 specific T cell responses, which play a key role in preventing severe disease (10,11) are maintained for at least three years following infection or vaccination. Furthermore, T cells provide good protection against emerging variants, as detailed below (12,13).

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Protection against new variants

Antibodies are sufficient to protect against infection and disease, but the virus has continuously evolved to counteract their action. Most of the mutations that have become fixed in the new variants are located in the S protein, significantly reducing the ability of antibodies to recognise the virus (14). This selective pressure, combined with the decline of antibody levels over time, makes the **humoral response highly susceptible to viral evolution**.

Despite significant antibody escape by emerging Omicron variants such as BA.2.86 (Pirola), **T-cell responses have largely remained preserved**, with only minor reductions in cross-recognition (12). This is because SARS-CoV-2 T-cell responses target multiple viral epitopes that are largely conserved across variants, including in the S, N, membrane, and non-structural proteins (15,16).

People with **hybrid immunity** have the **broadest T-cell responses** in terms of magnitude, breadth, and epitope diversity (17-19), especially if their first encounter with the virus was through infection and not through vaccination (12). Overall, these findings highlight the resilience of T-cell responses against emerging variants and make them attractive targets for broadly protective vaccines.

Open questions

Several important questions remain, including:

i) the possibility of developing a pan-coronavirus vaccine that provides cross-protection across coronaviruses

ii) developing a vaccine that induces mucosal immunity to better protect against infection

iii) whether other vaccine platforms (e.g. protein-based) protect longer against infection or disease

iv) the long-term implications of immune imprinting (whereby the immune response is skewed towards the first viral variant encountered) on future vaccine effectiveness.

Recommendations

- Given the ongoing evolution of SARS-CoV-2, updated vaccines to the dominant variants are recommended to sustain and enhance immunity, particularly in vulnerable populations that are at higher risk of severe COVID-19.
- People without recent previous infections (less than 6 months) should be prioritised for vaccination, especially when new variants arise.
- The development of broadly-protective vaccines targeting conserved viral antigens (in particular those recognised by T cells), as well as intranasal vaccines boosting mucosal responses, should be pursued.

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