Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Why hybrid immunity is so triggering

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It is becoming clear that hybrid immunity, that is immunity provided by a combination of infection and vaccination, provides better protection against subsequent COVID-19 than either vaccination or infection alone – higher antibody levels, less frequent and less severe infection. However, the picture is complex due to a chequered pattern of immunity in the population. People differ not only in their history of infection timing and infecting variant, but also in the type of vaccine they received, how many doses and finally, how well their immune system responded.

Immunologically, it makes sense that hybrid immunity provides better protection. Irrespective of whether an antigen is introduced as a vaccine or due to pathogen replication, repeated exposure stimulates B cell responses and antibody production. Most people with hybrid immunity will have encountered SARS-CoV-2 antigens more often than people who were only vaccinated or only infected. Additionally, the quality of the immune responses differs. Infection exposes the body to a whole range of antigens coming from different parts of the virus; mRNA and virus-vectored vaccines express only spike, which is the most important vaccine target on the virus surface and exposed to secreted antibodies. However, other antigens are also important for T cell responses.

Furthermore, most vaccines given so far target the ancestral spike from SARS-CoV-2 circulating early during the pandemic. Currently circulating variants have accumulated spike changes that enable them to evade antibody recognition. Infection with one of these newer variants stimulates B cells with antigenically divergent spikes, broadening the immune response. The balance between recall of 'ancestral' immune responses and development of 'novel' responses is not entirely clear yet. There is some evidence of imprinting, that is, preferential recall of old responses; however, the superiority of hybrid immunity tempers concerns somewhat, as the strength of hybrid immunity tends to depend on how closely the first infecting variant matches the subsequent one (although results are complex to interpret due to waning of immune responses).

Finally, injection of antigens will provoke a qualitatively different immune response than infection of respiratory epithelial cells. Innate immune responses and inflammatory stimuli 'orchestrate' the following adaptive immune response, although most viruses can dampen this response. The site of exposure also influences the quality of responses. While SARS-CoV-2 infection of the upper respiratory tract induces mucosal IgA, current COVID-19 vaccines induce systemic IgG. Systemic IgG is also produced after infection and it is effective at targeting virus in the lung, but generally much less so in the upper respiratory tract.

Immunologically it makes sense to favour hybrid immunity, however, we would like to strongly caution against the conclusion that hybrid immunity should be a public health measure and people should not protect themselves from infection or even be encouraged to acquire infection to gain superior hybrid immunity. Infection comes with risks, both during the acute phase and long-term, such as an increased cardiovascular risk or Long Covid. Unfortunately, the concept of hybrid immunity has become highly polarised, with some groups using it to argue against non-pharmaceutical interventions, such as mask wearing or isolation during active COVID-19. Such conclusions are misleading and risky, in particular, for people at high risk due to age or co-morbidities. Importantly, it also alienates the large group of people in low- and middle-income countries who have no access to any vaccines yet.

So, where do we go from here? Chequered immunity patterns in the population, waning of immune responses and the rise of immune-evasive variants such as BQ.1.1 or XBB, which might threaten protection afforded by hybrid immunity, require a multi-layered approached. First, we need an agile, scalable and fast infrastructure to develop and approve new vaccines that either target newly emerging variants, are pan-variant, and/or provide mucosal protection. However, we do not have the same will and funding as earlier during the pandemic for new vaccines, nor to track the variant landscape. While these are urgent needs, we should not forget non-pharmaceutical interventions, which can be adapted to the current local risk level. Although these interventions can have societal and economic consequences, a wildfire of COVID-19 will cost us too, causing disruption, disability, and death. If one must make any political arguments with hybrid immunity, it should be that people who had no access to vaccines yet must urgently get them. ■ *The Lancet Infectious Diseases*