SARS-CoV-2: From herd immunity to hybrid immunity

David Goldblatt

Herd immunity, where a pathogen can no longer efficiently spread in a population, is achieved when a large proportion of the population becomes immune, making the spread of infection from person to person unlikely and protecting those without immunity. Despite the global spread of SARS-CoV-2, the failure of virus- and vaccine-induced immunity to prevent transmission, combined with the emergence of antigenically distinct variants, have made herd immunity to SARS-CoV-2 unachievable thus far. Where does this leave us?

Key to the development of herd immunity is an effective immune response that not only prevents infection and disease in an individual but also prevents transmission. With the relatively high reproductive number (R) of the ancestral strain of SARS-CoV-2 (R=2.0-4.0), and in the absence of highly effective vaccines, initial efforts to control the COVID-19 pandemic were focussed on identifying infected individuals and their contacts and isolating them. When viral transmission from asymptomatic individuals became apparent, population-wide strategies including social distancing and lockdown were required and proved to be effective in reducing the spread of infection.

Individuals with SARS-CoV-2 infection were found to produce neutralising antibodies that inhibit the interaction between the SARS-CoV-2 receptor binding domain (RBD) and the host cell surface-expressed angiotensin-converting enzyme 2 receptor (ACE2). Initial evidence that these antibodies persisted for months, coupled with the demonstration that a previous history of SARS-CoV-2 infection was associated with an 84% lower risk of infection, with a median protective effect observed for 7 months following primary infection[1], provided hope that herd immunity might be achievable.

For some epidemiologists and public health physicians, the negative impacts of societal lockdowns were as much of a concern as the SARS-CoV-2 infections, and they argued that the response to the pandemic should be focused on the protection of those most at risk, while allowing the 'build-up of immunity through natural infection' in others (The Great Barrington Declaration, October 2020; https://gbdeclaration.org). For this to be successful though, natural immunity needed to be robust, associated with reduced person-to-person spread, and persist over a long period of time. Moreover, it would need to be sustained in the face of potential viral antigenic evolution. Alternatively, immunity would need to be upheld through wide deployment of efficacious vaccines. With hindsight, such a declaration was premature.

In late 2020, several variants of concern (VOC) emerged, with increased viral fitness and transmissibility, denting hopes that natural infection or use of first-generation vaccines (containing antigen from the ancestral SARS-CoV-2 Wuhan strain) would result in widespread protective immunity. With the exception of the Alpha variant, these VOC were not neutralized as effectively by antibodies derived from previous SARS-CoV-2 infections or primary vaccination regimens. For example, the effectiveness of two doses of either BNT162b2 or ChAdOx1 against transmission of Delta and Alpha was modest (in the range of 31% - 42%)[2]. Subsequent reports on the reduction of vaccine efficacy against Omicron infection, most notably for primary vaccine-induced protection[3], emphasised the increasing complexity of trying to control SARS-CoV-2.

Third (and fourth) booster doses of vaccine have proven to be efficacious, in the short term, against symptomatic infection with VOC including Omicron. The mechanism behind this enhanced vaccine efficacy appears to be an expansion of the memory B cell clones present after primary immunisation as well as the stimulation of new clones with increased potency and breadth, targeting more conserved areas of the RBD. Moreover, it was shown that in a period dominated by Delta infection, protection was significantly greater in vaccinated (BNT162b2) individuals with evidence of prior infection than those without prior infection[4], and that protection with one or two doses of vaccine following natural infection was significantly greater than protection associated with natural infection alone[5].

It is clear that herd immunity is unachievable for a virus where natural infections or vaccines fail to induce sterilising immunity and where antigenically novel variants evade immunity. Nevertheless, the finding that prior natural infection can enhance the activity of vaccines may still be important for informing global vaccine strategies. In Africa for example, where only 15% of the population have completed primary vaccination, approximately 75% of the population have antibodies to SARS-CoV-2, although seroprevalence as high as 97% has been reported in a South African community following the Omicron

wave. In a household study conducted in South Africa, prior infection with Beta and Delta was 93% (95% CI 85 – 96%) protective against reinfection for the first 3 months and decreased only marginally to 87% (95% CI 79 – 93%) after 9 months[6]. Omicron, however, was subsequently shown to have a much higher propensity for reinfection than any previous VOC[7] indicating that infection alone will not produce robust, enduring pan-variant immunity.

In communities with high seroprevalence, vaccines will augment natural immunity by boosting antibody titres and broadening immunity. Whether one or two doses of vaccine administered on the background of previous infection have equivalent vaccine efficacy is unclear at the moment and will depend on whether prevention of infection or severe disease is being evaluated, the nature of the variant circulating following boosting and the length of follow up, as persistence of immunity may vary by dose. High-risk individuals, irrespective of their serostatus, are likely to require at least two doses.

Relatively little is known about differences in natural immunity induced by primary infection with the different variants. What is clear is that asymptomatic infection is associated with lower subsequent virus-specific IgG concentrations compared to those with symptomatic infections and this variation in the magnitude of the immune response to natural priming, as well as the variant causing the infection, may be relevant to subsequent vaccine responses and influence vaccine efficacy. In vaccinated individuals, breakthrough infection with Omicron appears to induce less neutralising antibody than Delta and this may be true for primary infection too. Prior vaccination has also been shown to imprint serological responses towards the Wuhan strain contained in the vaccine[8], although the biological relevance of these differences in variant-specific antibody levels in the absence of robust correlates of protection is unclear.

The discussion around herd immunity and the reduction of viral transmission has understandably focussed on neutralising antibodies with their potential to prevent viral entry into human cells and stop infection. Although T cells have been described that can abort infection, they appear to be rare in the general population[9]. T cells are thought to have an important role in mediating protection against severe disease rather than infection, while also providing help to B cells to make antibodies. These separate but related functions of the humoral and cellular immune systems are reinforced by the observation that the decline of vaccine effectiveness parallels the drop in serum neutralising antibody titres. In contrast, the relative persistence of peripheral SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells[10] is consistent with a slower decline in protection against severe COVID-19 and may contribute to modifying disease severity following reinfection with VOC. T cells may retain the ability to protect against VOC disease by virtue of the fact that mutations in the variants appear to largely spare T cell epitopes. T cell immunity may explain the low mortality following Omicron infection in communities with high seroprevalence and/or high vaccine coverage compared to the high mortality rates seen in settings where both vaccine coverage and natural immunity, due to stringent lockdowns, are low.

Generating robust immunity to SARS-CoV-2 in the future is a priority in case new VOC emerge. In the short term, this is likely to involve harnessing the power of 'hybrid immunity', that is, intelligently augmenting widespread natural immunity with the rational use of existing vaccines. This could include optimising the use of existing vaccines by adopting heterologous schedules utilising vaccines from different platforms to maximise the breadth of vaccine-induced immunity. In the future, this may involve novel vaccines, perhaps with antigens from multiple variants or a pan-sarbecovirus 'variant proof' vaccine, possibly delivered mucosally to optimally interrupt transmission.

The global death toll of 6.15 million attributed to SARS-CoV-2 could have been much higher were it not for efficacious vaccines. With 491 million global cases, it could have been much lower if herd immunity had been achievable. Sadly, thus far it hasn't been.

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[1]*Affiliations: Professor of Vaccinology and Immunology, Great Ormond Street Institute of Child Health, University College London*
**e-mail: d.goldblatt@ucl.ac.uk*

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