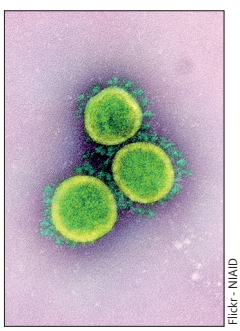
Imprinted hybrid immunity against XBB reinfection



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In the fourth year of the COVID-19 pandemic, the picture of population immunity has become increasingly complex and the certainties have become less certain.[1] Since the start of 2022, many countries have had sequential waves of infection with emerging subvariants of the SARS-CoV-2 omicron (B.1.1.529) variant. Clinical phenotypes associated with these waves in different settings have been diverse. In the USA and the UK, in which relatively high proportions of the population have received three or more doses of an mRNA vaccine, some large waves of breakthrough infections saw more than 8% of the population infected with SARS-CoV-2 (reported in weekly estimates of the rate of COVID-19 infections by the UK Office of National Statistics Coronavirus [COVID-19] Infection Survey), although sufficient protective immunity prevented a commensurate peak in deaths. However, in China, the consequences of the relaxation of physical distancing rules and poorer vaccine coverage reminded us that omicron subvariants can cause severe disease. Since the omicron variant was first detected, more than one year ago, the term omicron subvariant now encompasses considerable sequence diversity, with associated implications for differential transmission and immune evasion. In terms of sequence and epitope expression, the XBB omicron subvariant is now as distant from wild-type SARS-CoV-2 as SARS-CoV-2 is from SARS-CoV, such that XBB should probably be called SARS-CoV-3.[2,3] However, as virus sequencing surveillance has become less frequent and there are competing variants with different prevalence at any given moment in time, knowledge of which omicron subvariant is responsible for a given infection is usually not known with any confidence. In the UK, for example, the period since early 2022 has seen large, sequential waves of infection, each lasting a few months, caused by BA.1, BA.2, BA.4, BA.5, BQ1.1, and now XBB subvariants. Why do these details matter? Societal attempts to live with the virus have relied on hybrid immunity—the qualitative and quantitative boost to immunity that is imparted by a combination of infection and vaccination.[4-6] Analysis by Celine Tan and colleagues[7] of the national dataset during the XBB wave in Singapore provides a real-world picture of how well hybrid immunity holds up in this context. The answers are concerning with respect to protection from infection, although less so in terms of severe disease and death. This important study,[7] which assesses epidemiological data on breakthrough infections by BA.4, BA.5, and XBB subvariants, reminds us that the details of differential immune imprinting following different combinations of infection and vaccination matter. The first, key point of relevance is that hybrid immunity from the pre-2022, antigenically distant, pre-omicron variants did not confer protection against XBB reinfection. A new biomedical interface arose during the pandemic from the iterative rapid exchanges between real-world, national cohort epidemiology and laboratory, mechanistic immunology. The analysis by Tan and colleagues[7] includes epidemiological observations supporting the concept of differentially imprinted hybrid immunity conferred by previous infections during the period in which the omicron variant was dominant. For example, previous BA.2 infection provided hybrid immunity against subsequent BA.4 and BA.5 infection, but less protection against XBB infection. Differences were also seen in the imputed kinetics of immune waning, with accelerated waning of BA.2 hybrid immunity against XBB. Far from being nuanced footnotes in the pandemic response, these subvariant datasets provide great challenges to scientists, public health clinicians, policy makers, and vaccinologists. High prevalence of breakthrough infections are evidence of us failing in our war of attrition against the virus, measurable by increased caseload, hospitalisations and health-care provision, lost days from work, chronic disability from persistent symptoms, and an inability to simply return to normal life. Among the immunological challenges is the imperative to better define the rules underpinning the differential immune imprinting exemplified by these findings.[8,9] We now have a global population in which very diverse previous exposures to vaccines and SARS-CoV-2 infections—which shape antibody and T-cell-receptor repertoires—have imparted differential quantity and quality of protective immunity. This dataset from Singapore reminds us not only how far we are from understanding these imprinting rules but also how great would be the benefits of understanding them better. We are

arguably even further from decoding the details of differentially imprinted immune waning. Coming into the pandemic, immunity to reinfection by the human common cold coronaviruses was understood to be short-lived and fragile;[10] however, in the case of SARS-CoV-2, it was hoped that protection would be increased by highly effective vaccine platforms. If we now appreciate that even hybrid immunity to SARS-CoV-2 infection is (differentially, depending on previous immune experience) poorly durable[11] and annual debates on booster strategy are required, how should we move forward? The dataset from Singapore reminds us that suggesting the booster strategy will simply involve tweaking vaccines annually, as for influenza, seriously underestimates the complexity of the current challenge. The long-term strategy will require considerable effort towards the development of both next-generation vaccines (targeting neutralising epitopes that are truly conserved and disadvantageous for viral mutations) and vaccine platforms that provide durable, local protection in the nasal mucosa, thereby blocking viral transmission.[12]

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Rosemary J Boyton, Daniel M Altmann
r.boyton@imperial.ac.uk

Department of Infectious Disease (RJB) and Department of Immunology and Inflammation (DMA), Imperial College London, London W12 0NN, UK; Lung Division, Royal Brompton Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust, London, UK (RJB)

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