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Previews

Omicron's message on vaccines: Boosting begets breadth

Duane R. Wesemann[1,2,*]
[1]Department of Medicine, Division of Allergy and Clinical Immunology, Division of Genetics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[2]Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA 02139, USA
*Correspondence: dwesemann@bwh.harvard.edu
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In this issue of *Cell*, three studies confirm that SARS-CoV-2 Omicron strongly evades a key immune defense—neutralizing antibodies. However, while one- or two-dose vaccine regimens fail to induce anti-Omicron neutralizing antibodies, a homologous third-dose booster rescues neutralization function in a way that highlights the adaptability of immune memory, where recalled immunity extends antibody reach across SARS-CoV-2 variants.

The SARS-CoV-2 Omicron variant hit a pandemic-weary world still groaning under the weight of the Delta wave. The strikingly high number of mutations in the Omicron spike protein, the virus's key for cell entry and principal target for infection-blocking (i.e., neutralizing) antibodies, worried scientists that vaccine immunity would be significantly weakened. In this issue of *Cell*, three papers by Dejnirattisai et al. (2022), Garcia-Beltran et al. (2021), and Hoffmann et al. (2021) demonstrate dramatic Omicron escape from vaccine-induced serum antibodies. However, the studies also agree on a hopeful prospect: a booster vaccine dose extends the reach of neutralizing antibody function to cover Omicron.

While there is no doubt that widespread vaccine-driven immunity is a path to maximize safe emergence from the SARS-CoV-2 pandemic, viral evolution-driven immune escape and waning human immunity conspire to complicate this process. In this light, a greater understanding of the immunological principles that regulate durability and breadth of immune responses is essential to inform vaccine strategies. For SARS-CoV-2 vaccines, there's room for improvement on both of these aspects—a vaccine that induces durable immunity including long-lasting antibody responses, such as the measles vaccine (Amanna et al., 2007), would be less effective if it is specific for one variant of an evolving virus like SARS-CoV-2. Conversely, a vaccine that is broadly protective across evolving variants, but does not last long, would also be a less practical solution.

The triplex back-to-back studies published in this issue of *Cell* shed some light on the breadth issue. Vaccination with the original parent SARS-CoV-2 spike provided robust neutralizing antibody activity to the parent SARS-CoV-2 strain but extremely poor activity against the Omicron variant. However, boosting with a third dose of the same vaccine several months later dramatically increased (20–30×) neutralizing antibodies to Omicron but only increased neutralization activity to the original parent strain modestly (1–4×) compared to the two-dose vaccine regimen (Garcia-Beltran et al., 2021; Dejnirattisai et al., 2022; Hoffmann et al., 2021). In other words, a third jab tended to equalize neutralization coverage of the highly mutated Omicron variant and the original parent strain.

How do these new findings help us understand relationships between vaccination and clinical disease? Omicron spreads like wildfire—with seemingly little deference to whether individuals have been vaccinated with a two-dose mRNA vaccine regimen (considered today as fully vaccinated) or not. In contrast, the same vaccine regimen is still 70% successful at preventing hospital admission from the disease (Collie et al., 2021). In this light, the insufficiency of two-dose mRNA vaccination to induce anti-Omicron neutralizing antibodies correlates well with Omicron breakthrough infections, consistent with the critical role neutralizing antibodies play in working upstream to prevent viral invasion into cells. However, other aspects of vaccine-induced immunity must account for severe disease prevention. Neutralizing antibodies are a part of a complex adaptive immune response that works collaboratively to protect against infectious disease. Other parts of adaptive immunity include other (non-neutralizing) antibody functions and T cell responses, which are in general more resistant to immune escape by evolving variants and are likely jointly responsible for vaccine-induced protection from severe disease.

With this in mind, to what degree can prevention of severe disease alone (the possible prospect without neutralizing antibodies) be sufficient to stem the tide of a pandemic in today's world? Regardless of the answer to this question, a solution to this and future pandemics would likely be much more feasible if it is possible to innovate improved vaccine strategies to induce broadly neutralizing antibodies. In this context, perhaps the most impactful revelation of the triptych published in this issue of *Cell* is the view of how a third dose of a homologous vaccine works much better to induce neutralizing activity to the very non-homologous Omicron variant. It's a noteworthy demonstration of the reach of adaptable antibody memory, and a better understanding of mechanisms responsible for this will help inform future vaccine strategy.

To understand possible underlying mechanisms of how a homologous

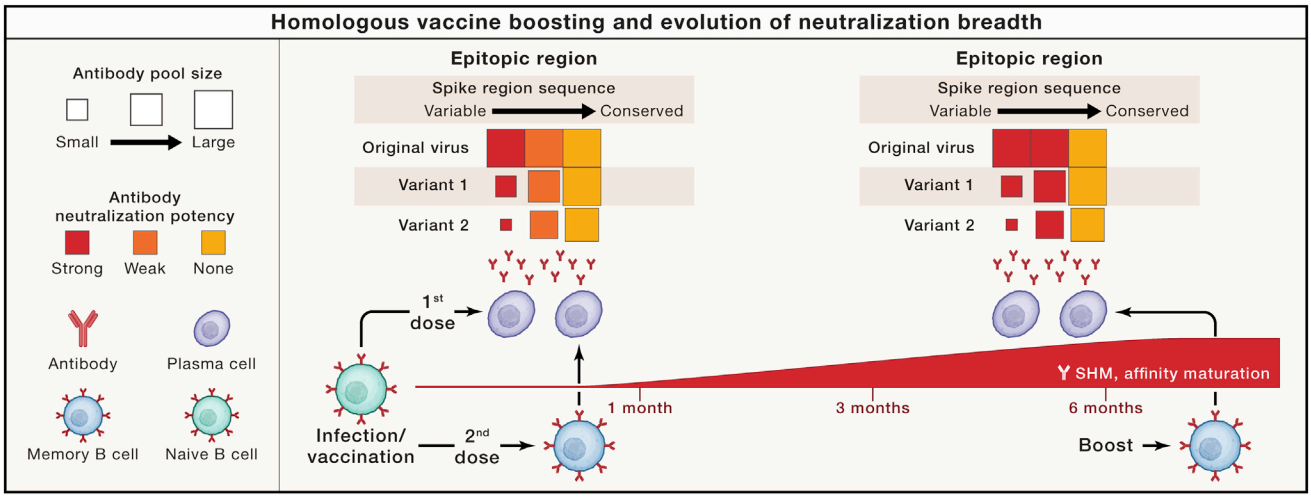

Figure 1. Homologous vaccine boosting and evolution of neutralizing breadth

Schematic diagram of a hypothesized contributing mechanism underlying findings from three studies published in this issue of *Cell* (Dejnirattisai et al., 2022; Garcia-Beltran et al., 2021; Hoffmann et al., 2021), suggesting that homologous vaccine boosting enhances cross-variant antibody neutralization breadth. Naive (green) and early memory (blue) B cells produce an antibody pool of low maturity upon a two-dose vaccine regimen spaced 3–4 weeks apart. The early pool includes antibodies available from the baseline repertoire with high neutralization potency (dark red) to more variable regions of the SARS-CoV-2 viral spike protein. Through viral mutation and selection, the antibody pool size able to recognize it shrinks as the virus evolves in part to evade neutralization by antibodies (indicated by shrinking squares). The early antibody pool also includes relatively abundant antibodies with weak (orange) or no (yellow) neutralization potency to epitopic regions that do not change as much throughout viral evolution (i.e., more conserved epitopes). Antibody pools recognizing more conserved epitopes do not shrink as much with respect to evolving virus (indicated by relative maintenance of square size with respect to viral variant spikes). Because antibody affinity maturation can continue to occur in memory B cells over many months, a booster vaccine dose at 6 months would result in the production of higher-affinity versions of antibodies from these memory B cells. This may result in higher-potency neutralization function to the relatively abundant and more conserved regions of the spike protein.

booster vaccine stretches antibody memory toward variants, we need to take a deeper look under the hood of the immune system. As a balance to viral evolution, the mammalian antibody system is equipped with its own rapid evolution-based system to resist viral immune escape by expanding the functional breadth of its immune memory banks. Antibodies are expressed from a vast diversity of immunoglobulin (Ig) gene segments assembled during B cell ontogeny. Ig variable region exons encoding antibodies that initially engage antigen during an immune response, clonally expand and contribute to the memory B cell pool. They can also differentiate into antibody-secreting plasma cells. Some activated B cells enter germinal centers where their Ig genes undergo somatic hypermutation (SHM) over time. Mutated antibody variants that bind with higher affinity are selected to expand further and can also contribute to the memory B cell pool and become plasma cells. The frequency of broadly neutralizing antibodies in an antibody response can vary. Because not all antibodies that bind a pathogen can neutralize it, an important factor that influences neutralization capability is where on the antigen the binding occurs.

In this light, the most potent neutralizing antibodies recognize the RBD roughly in the same region recognized by ACE2 (epitopic region RBD-2) (Tong et al., 2021), the receptor used by SARS-CoV-2 for cell entry. A likely contributing factor to early vaccine success was that the baseline (pre-SHM) human antibody repertoire tends to harbor very potent neutralizing antibodies to this region, which are available without the need for extensive maturation in germinal center reactions. This is also the region targeted by most FDA-approved monoclonal therapeutic antibodies. The downside is that many of Omicron's spike mutations are concentrated on or near this binding surface, resulting in loss of neutralization potency by immune serum and most therapeutic antibodies while retaining similar affinity for ACE2 (Dejnirattisai et al., 2022; Hoffmann et al., 2021). A silver lining is that the lone therapeutic mAb that retains reasonably good neutralization potency—namely, S309/sotrovimab (Dejnirattisai et al., 2022; Hoffmann et al., 2021)—belongs to a class of antibodies (RBD-1) that are relatively abundant in the human repertoire and bind to a relatively conserved region of the RBD. Many antibodies in the RBD-1 class can neutralize viral invasion, albeit with weak potency on average (Tong et al., 2021). However, because antibody improvement through SHM and affinity maturation continues to occur in the memory B cell population for several months after infection (Gaebler et al., 2021; Chen et al., 2020) and vaccination (Cho et al., 2021), continued months-long evolution of the memory B cell pool may allow for affinity enhancement of antibodies that initially had weak affinity to very high affinity (Figure 1).

So how is this relevant to neutralizing antibody breadth enhancement through a homologous vaccine booster shot? Since memory B cells are called upon for rapid plasma cell differentiation and antibody production in the setting of a repeat exposure, a booster shot several months after initial vaccination would call upon a memory B cell pool that has

had the benefit of months-long accumulation of more somatically mutated and affinity-matured versions of antibodies encoded in the the original pool. Since antibody affinity of neutralizing antibodies is positively correlated with neutralization potency (Bates et al., 2013), recalled immunity from initially low-potency but now affinity-matured neutralizing antibodies to conserved RBD regions in the memory B cell pool would be expected to enhance cross-variant neutralizing breadth (Figure 1). In this light, the interval between vaccine jabs may matter as much as the number of them.

How far can this immune flexibility work to allow the current version of spike in vaccines to induce neutralizing antibodies to future variants? Unfortunately, it is likely only a matter of time before neutralizing antibodies induced by current vaccines will become ineffective to a future SARS-CoV-2 variant. Cousins of SARS-CoV-2 include common cold coronaviruses endemic in humans. Immune responses to these coronaviruses have been traced over decades to show that continued coronavirus evolution can completely evade immunity induced by earlier versions of the same virus (Kistler and Bedford, 2021; Eguia et al., 2021). This suggests that a reason that endemic coronaviruses infect humans repeatedly is at least in part due to continued immune evasion driven by ongoing viral antigenic evolution.

On the bright side, despite what appears to be continued endemic coronavirus evolution and immune evasion, there does not appear to be any known cases of endemic coronavirus dramatically increasing virulence due to these mutations. So far in known history, coronaviruses with the most devastating mortality rates have been through recent zoonotic transmissions. Time will tell whether SARS-CoV-2, whose membership in the endemic coronavirus club seems inevitable, will retain its virulence or drift into a nuisance of the upper respiratory tract.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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