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should be considered when selecting new vaccine strains.

A key question is whether vaccination with an updated variant would induce de novo responses to that strain or if only recall responses against shared epitopes would be mounted. It has been observed, for example, with influenza virus, that the first exposures to antigen leave an immunological imprint—immune memory—that then skews responses to new but related strains toward epitopes that are shared between the initial strain and the new strain, with little de novo response specific for the new strain. For COVID-19 vaccines, serum antibody titers induced by bivalent vaccines consist of antibodies specific to the ancestral spike and antibodies that are cross-reactive between both spikes (*14*). However, BA.5-specific reactivity in serum samples of recipients of bivalent BA.5 vaccines was not detected (*14*). This suggests that the initial response to bivalent BA.5 vaccination is mostly a recall response focusing on shared epitopes (see the figure). Consistently, only 6 of 378 memory B cell–derived spike monoclonal antibodies (mAbs) that were isolated from individuals boosted with a monovalent BA.1 vaccine recognized the BA.1 spike protein, but not the ancestral one (*15*). All remaining mAbs identified both spike proteins. These data suggest that, although BA.1 or BA.5 spike sequence-specific reactivity is not detectible in serum after booster vaccination, the immune system is capable of inducing BA.1- and BA.5-specific B cells that become part of the memory B cell pool.

These findings are not necessarily bad news. Cross-reactive B cells may express neutralizing antibodies that already bind with high affinity to the new variant. Some may bind with low affinity but can undergo additional rounds of affinity maturation to enhance binding to the spike antigen. It makes sense that biochemical solutions for antibody–antigen interactions are reoptimized for an antigen that has changed, instead of finding new binding solutions. Notably, a potently neutralizing cross-reactive antibody is as good as a de novo strain-specific neutralizing antibody with the same potency if both are present at the same titer. Thus, cross-reactive neutralizing antibodies are likely to be as protective as strain-specific ones. In addition, the de novo response detected in the memory compartment, even if occurring at a very low frequency, could be expanded by an encounter with a variant virus related to Omicron. Overall, given the efficiency of engaging cross-reactive memory B cells by Omicron-derived spike antigens, the continued inclusion of the ancestral strain in booster immunizations is highly questionable.

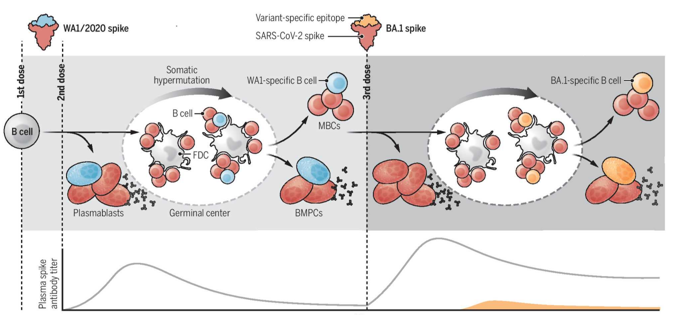
In the meantime, SARS-CoV-2 has not stopped evolving. The last dominant BA.5 descendant, BQ.1.1, has been outcompeted by recombinant BA.2 descendants of the XBB lineage, including EG.5, which is increasing in frequency and shows a stronger immune escape phenotype. A new BA.2-derived lineage, BA.2.86, has also recently been detected and is characterized by a large number of amino acid changes. The FDA, EMA, and World Health Organization (WHO) have recommended that COVID-19 vaccines should be updated again, for autumn 2023, and annual booster doses containing the newest variants may be recommended every year, similar to influenza virus vaccines. Which strain should be included? It is not useful to include the ancestral strain in updated booster doses in the autumn of 2023, and thus the recommendations of FDA, EMA, and WHO for updating to an XBB-based monovalent vaccine with a preference for XBB.1.5 make sense.

It is unclear whether annual SARS-CoV-2 vaccine updates are the best solution moving forward. It is also unknown if the mRNA vaccine platform is best suited for updated boosters or whether alternative platforms (such as recombinant protein–based vaccines or new technologies) or heterologous boosting will be more effective and better accepted by the population. Should an updated vaccine be administered once or twice? Vaccine equity is an important issue that emerged during the pandemic, and it remains unresolved how annual boosters, if needed, can be made available to the global population. Moreover, should the vaccine be offered to everyone or only to highly vulnerable populations? And which regimen would be ideal for SARS-CoV-2–naïve children? Practically, annual booster doses are easier to implement than ad hoc boosting whenever a new variant emerges. However, for healthy individuals, annual boosters may not be needed, and boosting only when a more virulent variant emerges may be more suitable. In this case, two doses given at a month's interval may enhance variant-specific responses. By contrast, for individuals with preexisting conditions that make them vulnerable to COVID-19, a regular annual booster will likely increase protection from severe disease regardless of the circulating variant.

Although similar systems have been in use for influenza vaccines, the "influenza model" may not be an optimal solution in the long term for SARS-CoV-2. Indeed, a new generation of influenza virus vaccines is being designed to give broader and longer-lasting protection independently of antigenic changes of the virus and to replace the current annual vaccinations. Similar broadly protective vaccines, potentially given mucosally (e.g., intranasally), are urgently needed for SARS-CoV-2. These vaccines will provide a much-needed advantage in the ongoing struggle against this virus's rapid evolution. ■

Dynamics of B cell and antibody responses to COVID-19 vaccines

Immunization based on the primary series of ancestral (WA1/2020 spike protein) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines followed by boosting with a variant-based vaccine (BA.1 spike) initially elicits a subset of spike-specific B cells, which rapidly proliferate and differentiate into antibody-secreting, short-lived plasmablasts. Some activated B cells form a germinal center reaction where responding B cell clones undergo iterative rounds of somatic hypermutation and affinity maturation of their B cell receptor against the inciting antigen that is presented by follicular dendritic cells (FDCs). Graduates of the germinal center differentiate into long-lived bone marrow plasma cells (BMPCs) and circulating memory B cells (MBCs). Cells that develop to recognize the ancestral spike protein may also cross-react to the new variant spike (red), whereas other cells may be variant-specific (blue and orange).



GRAPHIC: K. HOLOSKI/SCIENCE

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SUPPLEMENTARY MATERIALS

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The numbers of gray whales (*Eschrichtius robustus*) are fluctuating as a result of environmental changes.

PHOTO: GEMM LAB/MMI/OSU

ECOLOGY

The ecology of whales in a changing climate

Some whale populations are exhibiting unexpected cycles of boom and bust

By **Andrew J. Read**

The study of whale ecology did not begin until most populations had been depleted by commercial whaling. Some species still teeter on the edge of extinction, whereas others have shown encouraging signs of recovery. The Eastern Pacific population of gray whales (*Eschrichtius robustus*) was hunted to low levels in the 19th century but was protected from commercial harvest by the International Whaling Commission in 1947. The population then grew to almost 27,000 by 2016 (*1*), which is near the upper range of estimates of pre-whaling abundance (*2*). Most population models assume that after this recovery, gray whales would reach a relatively stable equilibrium. On page 207 of this issue, Stewart *et al.* (*3*) challenge this assumption by documenting boom-and-bust cycles in abundance, driven by surprisingly large and rapid changes in their food supply over the past three decades.

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Gray whales make one of the longest annual migrations of any mammal, from breeding grounds in Baja California, Mexico, to feeding grounds in the Bering and Chukchi seas, between Alaska and Russia. These whales feed by filtering crustacean prey using plates of baleen suspended from their upper jaws. Their near-shore migratory route has allowed researchers to collect a rich trove of data on abundance, reproduction, mortality, and body condition over the past 50 years; Stewart *et al.* used these datasets to construct a demographic model of the population. In their model outputs, carrying capacity—the number of whales that can be supported by the ecosystem—demonstrated a large degree of annual variation, caused by changes in prey availability and sea ice cover on the feeding grounds. In turn, these changes were driven by variation in the sub-Arctic climate. Large reductions in annual carrying capacity caused substantial mortality events in 1988, 1999, and 2019, which led to large decreases in gray whale abundance.

When population dynamic models were first applied to whales in the past century, few scientists could have imagined the