COVID-19

Boosting immunity to COVID-19 vaccines

New studies highlight the immunological benefits of COVID-19 vaccine boosters, but questions remain over how to best make use of a limited global supply.

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The phenomenal speed of scientific development, clinical testing, manufacture and deployment of first-generation COVID-19 vaccines has been unprecedented. As early as the first quarter of 2021, countries such as Israel achieved high vaccine coverage. However, there are increasing signs that population-level immunity in such early vaccinated nations might be waning, and breakthrough infections are on the rise[1]. With questions raised about the durability of vaccine protection, the need for and nature of periodic booster immunizations is the subject of worldwide debate. In this edition of *Nature Medicine*, Articles by Choi et al.[2] and Shroff et al.[3] address two major considerations for the deployment of mRNA booster vaccines; first, the necessity to maintain protection against emerging variants of concern with immune evasion potential; and second, the need to increase vaccine effectiveness in vulnerable populations such as those with primary immunodeficiencies, those on immunosuppressive therapies, and the elderly.

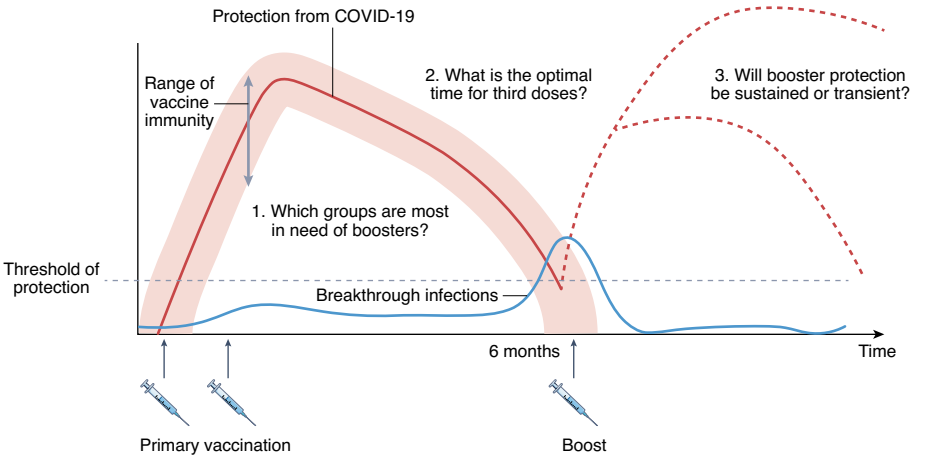

Fig. 1 | Impact of booster vaccines on protection from COVID-19. Primary two-dose vaccination results in the rapid establishment of immunity, providing protection against COVID-19. Vaccine immunogenicity and effectiveness at an individual level varies according to multiple factors, including age and immune competency (upper and lower bounds indicated by red shading). Over time, vaccine-associated protection wanes, and the incidence of breakthrough infections begins to increase (blue line). Immunization with a third dose rapidly boosts immune responses against SARS-CoV-2, but the long-term durability of such protection remains to be determined (dashed lines).

Choi et al.[2] monitored immune responses of people who were initially vaccinated with two doses of mRNA-1273 (Moderna) and who, six months later, received a third (booster) dose of the same vaccine, a vaccine reformulated to match the spike sequence of the Beta variant (B.1.351), or a multivalent vaccine containing both spike sequences. The boosters were deemed to be safe and effectively restored the serum neutralization activity that had waned after the initial two-dose vaccination. The study demonstrated the capacity of a third dose to broaden antibody-based immunity and boost protection against circulating variants of concern. However, it is interesting that neutralizing responses against the Beta variant, known to markedly escape vaccine-elicited antibody responses[4], were only fractionally better in those receiving a Beta-specific booster immunization. Although this phase 2 interim analysis was not large enough to clearly differentiate between vaccine formulations, the greatest neutralization breadth was observed in the multivalent booster group. Together, these results suggest that sufficient conserved neutralizing targets exist across the spike protein such that first-generation vaccines maintain recognition of current variants of concern. Nevertheless, this is likely to change in the future as the virus continues to evolve under an ever-increasing degree of vaccine-mediated selective immune pressure.

Maximizing COVID-19 vaccine protection in vulnerable subpopulations is of critical importance. In patients with solid tumors who are on active cytotoxic therapy, Shroff et al.[3] found that while canonical two-dose immunization with BNT162b2 (Pfizer/BioNTech) was generally immunogenic, T cell responses and serum titers of spike-binding or -neutralizing antibodies were diminished compared to those of healthy controls. Decreased responsiveness of patients with cancer to vaccination was potentially linked to the time since the last cytotoxic treatment. Encouragingly, while administration of a third vaccine dose failed to increase T-cell immunity, it did improve neutralizing antibody responses in most patients (16 of 20) to levels generally surpassing those estimated to be protective against COVID-19 (ref. [5]). Long-term follow-up of these and similar clinical cohorts will provide key information regarding the longevity of immune protection in vulnerable individuals.

These studies suggest that, in the clinic, third-dose vaccinations might work as expected to boost immunity, and there are growing indications that these clinical trial outcomes are mirrored in real-world settings. In July 2021, Israel became the first country in the world to deploy third doses of BNT162b2 in the general population aged 60 years and older. For people vaccinated at least five months earlier, a third dose resulted in a rise in serum neutralization titers (5–7-fold)[6], which was matched by a reduction (11.3-fold) in breakthrough infections[7]. Globally, however, there is little consensus on the appropriate roll-out of

vaccine boosters. Singapore has announced plans to offer third doses to individuals over the age of 60 years, and the US Food and Drug Administration (FDA) recently authorized booster doses of BNT162b2 for the same group in the United States. In other countries such as the United Kingdom, boosters were initially restricted to immunocompromised individuals before being expanded to the wider population over 50 years old, which reflects some uncertainty surrounding how best to target supplemental vaccine doses.

The science of booster vaccinations is moving fast, yet important questions remain (Fig. 1). Firstly, methods to accurately identify individuals most at risk of vaccine failure are lacking, as is data to support optimal timing for vaccine re-administration. While vaccine efficacy against symptomatic infection has been linked to neutralizing antibody titers in blood[5], protection against severe disease is almost certainly more complicated, with $CD8^+$ T-cell cytotoxicity[8] and antibody Fc-dependent functions probably contributing to control of viral replication[9]. Additional biomarkers of long-term vaccine protection might therefore be needed to inform the development of novel diagnostic tests or inclusion criteria to underpin booster recommendations.

Secondly, the durability of vaccine protection is likely to be influenced by the vaccine platform, dose and dosing intervals used in a given population. The extent to which immunity elicited by the various mRNA, viral or protein-based vaccine platforms differs in terms of long-term protection and disease outcomes following breakthrough infection is currently unknown. It is also unclear whether a single third-booster shot will dramatically extend the protective window, or if semi-regular boosters will eventually become a necessity for maintenance of population-level immunity. Further gains in protective durability might be possible by combining vaccine platforms (so-called 'mix-and-match' regimens); studies suggest this approach can significantly boost the magnitude of vaccine immunity[10], with potential benefits for long-term protection.

Finally, it is impossible to talk about vaccine boosters without touching upon the inherent ethical concerns. Somewhat ironically, the word 'boost' has dual meanings: (1) to help or encourage (something) to increase or improve; or (2) to steal (slang). In a global environment manifesting major inequities in vaccine availability, there exists an understandable concern about selected countries delivering third doses while the majority of low- and middle-income countries (LMIC) remain significantly under-vaccinated. Given the endemicity of SARS-CoV-2, waning vaccine protection and ongoing viral evolution driving emergence of new variants, effective COVID-19 vaccines will be a critical resource into the future. Urgent efforts are warranted to rapidly expand global vaccine access, potentially via patent and manufacturing support for LMIC. ❐

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Competing interests

The authors declare no competing interests.