Many people may wish to forget the level of societal and health care disruption, fear, and illness caused by SARS-CoV-2 before vaccines were available, when the only tools available to protect ourselves were incompatible with the lives we wished to lead. After effective vaccines became available, long lines formed in many countries of residents seeking their first and second doses, which protected the most vulnerable members of society from the most severe disease outcomes and thereby allowed social and professional activities to restart more freely without fear of those interactions causing unacceptable levels of societal harm. Subsequently, gradual reductions in observed vaccine-derived protection, particularly against milder end points of COVID-19, were observed approximately 5 to 6 months after the end of the vaccine primary series. In a bid to preserve effectiveness in the midst of emerging variants and waning immunity, third and even fourth “booster” dose vaccinations have been implemented in some countries. Booster doses restore protection against infection back to higher levels and incrementally improve protection against severe COVID-19, but frequent booster vaccinations are expensive, inconvenient, and possibly inefficient. The optimal timing of booster vaccinations is therefore a priority unanswered question for vaccine developers and policy makers alike, aiming to develop and implement vaccination programs that protect people most efficiently as we transition to endemic COVID-19.

Eliakim-Raz and colleagues report on a study that aims to help answer this question. Conducted in Israel, a country that has recommended fourth doses of the Pfizer-BioNTech BNT162b2 vaccine to all adults aged 60 years or older since January 2022, this observational study compared immune response—measured as anti–spike protein immunoglobulin G (IgG) antibody titers—before and after third and fourth vaccine doses, thereby providing information on the magnitude and duration of the immune boost. The results show a significant but transient increase in IgG titers after the third dose, decreasing approximately 10-fold after 5 months; titers were then restored immediately after a fourth dose. Sex, age, time since vaccination (which varied only minimally), and presence of comorbid conditions were not associated with postvaccination IgG titres, providing limited evidence that boosters are suitable for most people.

This study had some important limitations. It was observational, and the small sample of 48 participants was self-selected. Individuals with prior SARS-CoV-2 infection were excluded, limiting generalizability as the global prevalence of prior infection increases. Booster doses are thought to protect via mechanisms that include enhanced humoral responses but also through generation and expansion of T-cell memory, broadening epitope recognition and perhaps other immunologic parameters that were not measured. Decreasing antibody responses may be accompanied by the development of long-lived SARS-CoV-2–specific B cells or other cellular protective mechanisms that offer durable protection against more severe disease outcomes. Nonetheless, the magnitude and variation of IgG responses can provide some insights into vaccination strategies. The assay used in this study detects IgG antibodies, which may be especially important in protecting individuals from infection, as a first line of immune defense. A study of US military recruits found that the presence of antibodies was associated with an adjusted hazard ratio for SARS-CoV-2 infection of 0.16 (95% CI, 0.10-0.25); higher IgG levels appeared even more protective. Although we lack a full understanding of immune correlates of COVID-19 protection, the rapid decrease in IgG levels observed within 5 months of receiving a third dose would likely indicate that maximally protecting against even the mildest infections may require more frequent repeated booster vaccinations. Even if such a program were medically advisable, it would be expensive, and no comparable schedule exists in the adult
In any case, the priority of vaccination programs is normally to prevent severe and resource-intensive episodes that cause the most morbidity, suffering, and death. Early results from COVID-19 vaccine effectiveness studies suggest that protection against severe disease is maintained at high levels for many months after vaccination, in contrast to the rapidly decreasing humoral response observed by Eliakim-Raz and colleagues. For example, a retrospective cohort study from the US documented decreasing vaccine effectiveness against infection to approximately 50%, 7 months after the third dose, but vaccine effectiveness against hospital admission was approximately 90% and did not wane. COVID-19 booster vaccination planning, therefore, will need to carefully balance public health benefit, societal acceptance of SARS-CoV-2 transmission in the community, feasibility, and costs. Further research is urgently needed on the optimal timing of booster doses, particularly for the most vulnerable people in our communities.