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New boosters are here! Who should receive them and when?

The FDA has authorised bivalent booster vaccines containing mRNA for the ancestral SARS-CoV-2 variant as well as B.1.1.529.4 (BA.4) and B.1.1.529.5 (BA.5), the latter being the most prevalent omicron subvariant circulating now.

The US CDC recommends everyone 12 years and older receive these bivalent boosters at least 2 months after their last vaccine dose, regardless of number of previous boosters.

Is this the best strategy based on what we know from boosters with the ancestral spike? The Qatar results demonstrate strong protective effects of a single booster against severe disease with omicron subvariants B.1.1.529.1 (BA.1) and B.1.1.529.2 (BA.2).¹ In a Singapore study, a single booster provided additional protection against severe disease for at least 6 months.² A study in Israel of the effectiveness of nirmatrelvir showed that, in an age-stratified immune population during the omicron era, risk of hospitalisation was low in people aged 40–64 years (approximately 15 hospitalisations per 100 000 person-days regardless of nirmatrelvir treatment), although the risk in those aged 65 years or older was significantly lowered by administering nirmatrelvir (58.9 hospitalisations per 100 000 person-days without treatment compared with 14.7 hospitalisations per 100 000 person-days with treatment).³ Finally, a recent study among 30 million individuals in the UK demonstrates that boosters reduced severe disease after two vaccine doses in the following risk groups: aged 80 years or older, and having five or more comorbidities, being on immunosuppressants, or having chronic kidney disease. This study allows us to understand who will likely need ongoing boosting for COVID-19.⁴

Given all of the data showing strong protection of boosters with the previous mRNA vaccines against severe disease, we believe that upcoming human data will probably show that the bivalent boosters have efficacy similar to or better than the original booster (given the improved antigen match with currently circulating strains). Therefore, we recommend this omicron-specific booster for people 65 years and older, those who are immunocompromised, and those with multiple comorbidities. Because B cells typically take 2–4 days to start making neutralising antibodies,⁵ people who are more susceptible to severe disease need the earlier protection afforded by high antibody levels.

Although the CDC has opted for a simple message across all age groups, data-driven recommendations will increase trust, especially given that only 71% of the population in the USA older than 65 years had received a single booster as of Oct 12, 2022.⁶ If we clarify the goals of our booster strategy to prevent severe disease⁷ (as recommended by WHO), the annual booster campaign that the FDA has stated is the new strategy going forward will probably only be needed for people who are at highest risk (as defined by age, comorbidities, and whether they are immunocompromised). In fact, once a year might not be enough for some risk groups.

As for timing, we agree with the Canadian National Advisory Committee on Immunization to recommend the updated vaccine at an interval of 6 months after previous vaccination or infection. Antibody levels stabilise 6–9 months after vaccination for individuals with and those without previous infection.⁸ Giving a booster too soon (within 60 days) after a recent infection interferes with effective B-cell responses,⁹ and extended intervals between vaccine doses increase both neutralising antibodies and memory B cells.⁸ If one of the aims of omicron-specific boosters is to increase antibodies and prevent even mild

infections, the antibody level plateau at the 6-month mark would signal an ideal time to boost with a variant-focused vaccine.⁸

We are excited about the ability of the mRNA vaccines to be updated as new variants emerge. However, focusing our booster recommendations on those most clinically vulnerable to severe disease first, and timing vaccine administration to optimise the immune response, is a good public health strategy.

We declare no competing interests.

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- Butt AA, Dargham SR, Coyle P, et al. COVID-19 disease severity in persons infected with omicron BA.1 and BA.2 sublineages and association with vaccination status. *JAMA Intern Med* 2022; **182**: 1097–99.
- Ng OT, Marimuthu K, Lim N, et al. Analysis of COVID-19 incidence and severity among adults vaccinated with 2-dose mRNA COVID-19 or inactivated SARS-CoV-2 vaccines with and without boosters in Singapore. *JAMA Netw Open* 2022; **5**: e2228900.
- Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir use and severe Covid-19 outcomes during the omicron surge. *N Engl J Med* 2022; **387**: 790–98.
- Agrawal U, Bedston S, McCowan C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. *Lancet* 2022; **400**: 1305–20.
- Palm AE, Henry C. Remembrance of things past: long-term B cell memory after infection and vaccination. *Front Immunol* 2019; **10**: 1787.
- US Centers for Disease Control and Prevention. CDC COVID data tracker. 2022. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-additional-dose-totalpop (accessed Sept 26, 2022).
- Barouch DH. Covid-19 vaccines—immunity, variants, boosters. *N Engl J Med* 2022; **387**: 1011–20.
- Goel RR, Painter MM, Lundgreen KA, et al. Efficient recall of omicron-reactive B cell memory after a third dose of SARS-CoV-2 mRNA vaccine. *Cell* 2022; **185**: 1875–87.e8.
- Buckner CM, Kardava L, El Merhebi O, et al. Interval between prior SARS-CoV-2 infection and booster vaccination impacts magnitude and quality of antibody and B cell responses. *Cell* 2022 published online Sept 27. <https://doi.org/10.1016/j.cell.2022.09.032>.



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