Not Everyone Needs a Second COVID Booster

— Fourth doses should target those at risk for severe breakthrough infections

by Amesh Adalja, MD
March 21, 2022

Last week, both Pfizer and Moderna applied for emergency use authorization (EUA) of additional booster doses -- in essence, fourth doses -- of their COVID-19 vaccines. The companies cite waning protection and believe fourth doses are needed. While Pfizer has asked for an EUA focused on those above 65 years old, Moderna is seeking one applicable to all adults. It is critical, as we debate COVID-19 vaccine clinical guidance, to be explicit about the goals we are trying to achieve.

A few weeks ago, the Biden administration articulated a goal, with which I completely agree, of preventing severe disease from COVID-19. We should not be focusing on total case numbers. SARS-CoV-2 is an ineradicable, ineliminable efficiently spreading respiratory virus that is destined for endemicity alongside four of its other viral family members. Making SARS-CoV-2 a manageable virus, similar to how we manage influenza and respiratory syncytial virus (RSV), reflects this microbiological fact. Shifting the spectrum of illness to the mild side, to the outpatient side, has become an achievable goal with the medical countermeasures -- antivirals, monoclonal antibodies, and vaccines -- we now have on hand.

With this endpoint in mind, it becomes clear that COVID-19 vaccine booster doses should be targeted to protect those at risk for severe breakthrough infections.

First and second doses of the mRNA COVID-19 vaccines prevent severe disease for the vast majority of the population. Only those with advanced age or high-risk conditions benefit from additional doses of vaccine in terms of severe illness, hospitalization, and death. This is because erosion of protection against hospitalization was almost exclusively evident in those with high-risk conditions (including advanced age) as time passed since their second dose. Meanwhile, hospital capacity was primarily compromised by unvaccinated individuals. Therefore, a targeted approach to boosters -- emphasizing their essential nature in those with high-risk conditions in which a breakthrough infection might not be mild -- was always the best policy.

Some have argued that boosters for healthy people prevent infection and spread -- an important public health goal. In the pre-Omicron era they did, albeit transiently. But with Omicron, the protection from breakthrough infection has become even more transient and breakthroughs are, essentially, inevitable. Thus, with the first-generation vaccines currently in use, protection against severe disease is the primary aim. In healthy individuals, without any high-risk conditions, third and fourth doses do not provide additional protection against severe disease.

In fact, I refrained from getting a booster dose of the COVID-19 vaccine until one particular hospital where I am on staff changed their policy and required goggles and N95s at all times for those who were not boosted (in an attempt to minimize healthcare worker quarantine post-exposure and to remain consistent with CDC guidance). I was willing to get the booster -- as it's safe and effective -- but as a young, healthy person, it likely didn't afford me *added protection* against severe illness.

While it may seem attractive to public health authorities, especially in a crisis, to have a one-sized-fits-all policy, precision-guided recommendations are optimal. Not only does precision medicine more exactly fit the scientific evidence, it also recalibrates in the minds of the public what these vaccines were intended to do: tame the virus and decouple cases from hospitalizations. We have the tools and data to be precision-guided at this stage of the pandemic.

There may be a time when second generation, variant-specific, or universal coronavirus vaccines might durably prevent more than severe disease, meriting reconsideration of vaccine policy. With current vaccines, however, recommendations for additional doses should be evidence-based and directed towards those who meaningfully benefit. We should continue to focus efforts on vaccinating the unvaccinated and boosting those at high-risk for severe disease.

It is biologically probable that fourth doses of the mRNA COVID-19 vaccine will be beneficial in those whose immunity may have waned to the point that renders them susceptible to a severe breakthrough infection (the prophylactic, and underutilized, monoclonal antibody tixagevimab/cilgavimab (Evusheld) is also indicated for many in this population). However, universal booster recommendations for the entire vaccinated population are far from warranted. Hopefully, the FDA and CDC advisory panels will convene, engage in robust discussion about the data, integrate the data with overarching COVID-19 goals, and endorse an evidence-based, precision-guided booster policy.

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