Q&A: New vaccine recommendations for COVID-19

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A recent modeling study by Dr. Townsend and colleagues regarding

optimal timing for future COVID-19 vaccinations in preventing severe infection was cited by the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) in its briefing materials prior to its Jan. 26, 2023, meeting on vaccination recommendations.

What is the FDA's advisory panel recommending for future COVID-19 vaccinations and what is it considering in terms of the timing of those vaccines?

The FDA's advisory panel voted on Jan. 26 to "harmonize" the primary vaccine and boosters so that all COVID-19 vaccines will at least target currently circulating strains. They also plan to meet at later dates to ascertain which strains to target, likely planning to have boosters targeting a recent strain in the fall. An updated booster this fall could be administered concomitantly with the fall influenza campaign, which would simplify medical administration and may aid widespread uptake.

However, timing the production of the various vaccines so that they will be ready by autumn will be somewhat complicated. Because new variants of SARS-CoV-2 are constantly evolving, keeping as short a window between the selection of a strain and administration of the booster is advisable and will provide the greatest amount and durability of protection.

The two mRNA vaccine producers, Pfizer and Moderna, stated they needed 90 days to generate an updated booster, whereas Novavax stated that they needed nearly twice the advance notice to generate an updated booster. Novavax presented some data that they argued indicated that their platform yielded a vaccine conveying broader immunity; so perhaps that platform could match or better the performance of mRNA vaccines even with a less up-to-date target.

Another concern was that adopting only a once-per-year update may not serve some populations, such as the very young who have not yet been primed, the very old, and the immunocompromised. I would suggest that these two issues can partly be addressed by convening meetings selecting strains to target on dates that would suit both protein-based vaccine manufacturers 180 days prior to the fall administration and mRNA-based vaccine manufacturers 90 days prior to the fall administration. Such a plan would enable both manufacturers to produce the most up-to-date and effective vaccine, as well as provide targeting advice that could be applicable to the generation of more frequent mRNA vaccines for those who may need them.

Given the time constraints on making decisions this year, it seems most likely that the FDA will convene another meeting in May or June to select a strain for an updated monovalent or updated bivalent fall mRNA booster. Because the booster strain will, by necessity, be selected several months prior to administration, some years this booster may be more effective than other years, depending on the subsequent evolution of the virus. I would argue that in our "harmonization" of vaccines and boosters, it is time to exclude the "original" pandemic strain from our vaccine and booster formulations; it appears to continue to provide some efficacy at this time, but all the evidence argues it works less well than updated monovalent or updated bivalent vaccines, and it directs the human immune systems against antigens that haven't been seen for years.

In addition to its latest actions, the FDA should be vigilant and proactive in its consideration of new cutting-edge vaccines. For instance, vaccines that feature multiple and/or evolutionarily conserved portions of the externally expressed viral proteins could provide extended durability, as the virus would be unable to evolve ways to evade the immunity.

Another technology that deserves continued attention is the nascent nasal vaccine, which builds up immune defenses in mucosal tissue, where it

can better respond during the early stages of infection and might provide considerably increased protection against the respiratory exposures we have learned are essential to the transmission of SARS-CoV-2.

We mustn't miss the lesson from Operation Warp Speed, which is that back-end investment into vaccines can yield a diversity of outcomes for the same problem, some of which are likely to be game-changers. Vaccines are incredibly powerful tools for improving public health—much more impactful than treatments. They require public investment to make feasible the investigation of creative ideas with enormous potential.

What is the advantage of an annual vaccine over periodic booster shots?

A fall administration of the booster is sensible. It's been hard to know for sure what the seasonality of SARS-CoV-2 is because interventions, human behavior, and early variant evolution have all rendered it difficult for epidemiologists to directly ascertain its seasonality. However, we know that all other endemic coronaviruses tend to reach peak transmission in the winter when gatherings tend to be indoors in temperate regions, and indoor air is often poorly refreshed. It is unlikely that SARS-CoV-2, which is related to other human endemic coronaviruses, has evolved traits that would lead to a substantially divergent future endemic seasonality.

We also know that boosters provide especially strong protection shortly after administration, and that protection wanes. Consequently, timing administration to immediately precede the period believed to represent the greatest risk is highly appropriate. From a practical standpoint, it will be advantageous to medical administration and to population uptake to align the administration of the COVID-19 booster with the fall

administration of the annual influenza vaccination.

What did your research find in support of annual COVID-19 vaccinations?

It would be an understatement to say that there has been some public controversy about the COVID-19 vaccines and boosters. When the vaccines were first administered, there was no publicity about the likely durability of immunity conferred by previous infection or vaccination, and many people (including some voices in public health) thought that immunity would be long-term, like that achieved by many childhood vaccinations. One of our first studies on COVID-19 made use of short-term antibody waning data from SARS-CoV-2, SARS-CoV-1, MERS, and long-term antibody waning and reinfection data from the circulating endemic human-infecting coronaviruses. The study provided the first evidence that durability of immunity to reinfection would typically last just over a year, but also that in one in 20 cases might be as short as three months.

Our second study extended these findings to provide the first estimates of the durability of vaccine-mediated immunity and showed that mRNA vaccines such as those produced by Moderna or Pfizer conferred substantially higher durability of immunity than most other vaccines or natural infection. However, we also showed that protection still waned. Furthermore, protection depends on the vaccine strain not being too out-of-date compared to when it is administered. Unsurprisingly, boosters administered on an emergency-use basis that targeted the original pandemic strain provided successively less immunity and lower durability of immunity because of the mismatch between the vaccine strain and the substantially evolved strains circulating later in the pandemic. Even though these boosters were helpful in protecting from infection, this growing strain mismatch and underperformance in

protection versus infection, and empirical studies demonstrating the waning of protection, somewhat undermined the public conception of how useful booster vaccination was and could be.

Because of the lack of clarity regarding the future impact of boosters, in our most recent research, my coauthors and I set out to determine how effective regular uptake of boosters that target the currently circulating strains could be. Using data on the antibody response to boosting and the framework that we had developed for evaluating durability of infection- and vaccine-mediated immunity, we were able to project the efficacy of different frequencies of uptake of boosters targeting circulating strains.

Our analysis showed that three out of 10 people were likely to contract COVID-19 over six years if every year they received an annual, updated booster shot. That figure climbed to nine out of 10 for those that did not get a booster shot at all. Annual or biannual boosting performed much better than frequencies at intervals greater than a year.

Because of their connection to data on endemic human-infecting coronaviruses, those proportions likely to be infected are most applicable to the eventual endemic infection rates rather than pandemic COVID-19 infection rates. As we approach the lower levels of infection anticipated from endemic disease, the benefit of annual boosting should approach our prediction. But as you might imagine, adopting an effective annual booster schedule is even more important now, when COVID-19 is more prevalent than it likely will be in the future.

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