Sandra Fryhofer, MD, discusses new "mix & match strategy" for boosters

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In today’s COVID-19 Update, AMA Chief Experience Officer Todd Unger discusses what physicians need to know about boosters for Moderna, J&J recipients and the newly approved mix-and-match strategy, with Sandra Fryhofer, MD, AMA’s liaison to the Advisory Committee on Immunization Practices (ACIP) and a member of ACIP’s COVID-19 Vaccine Workgroup.

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Speaker

- Sandra Fryhofer, MD, chair-elect, AMA Board of Trustees; AMA’s liaison to the Advisory Committee on Immunization Practices

Transcript

Unger: Hello, this is the American Medical Association's COVID-19 Update. Today we're discussing what physicians need to know about boosters for Moderna and Johnson & Johnson recipients, and the newly approved mix and match strategy. I'm joined today by Dr. Sandra Fryhofer, AMA's liaison to the Advisory Committee on Immunization Practices or ACIP and a member of ACIP's COVID-19 Vaccine Work Group. Dr. Fryhofer is also the chair-elect of the AMA Board of Trustees.
I'm Todd Unger, AMA's chief experience officer in Chicago. Dr. Fryhofer, we now have boosters for all three of our authorized COVID vaccines. That's good news. Can you start by reviewing these new recommendations? Let's first start with Moderna. Who needs a booster and when?

**Dr. Fryhofer:** Okay. Here's what's new. For Moderna, boosters only apply to certain adults at least six months after receiving a two-dose Moderna primary series. And you have to be 65 or have health issues or have a high exposure job or living conditions to qualify. Sound familiar? The booster recommendation for Moderna is the same as the one for Pfizer.

So in essence, the booster recommendations for both mRNA COVID vaccines have been harmonized. The same six-month time interval after the primary series applies to both mRNA vaccines but the size of the booster dose is different. For Pfizer boosters, it's a full 30 microgram dose. For Moderna boosters, 50 micrograms, that's half of a full Moderna dose is all that's needed.

**Unger:** So a little bit different for J&J's Janssen vaccine. Is the timeframe the same? Let's start with the particulars there.

**Dr. Fryhofer:** No, for adults who receive the Janssen vaccine, the timeframe's different. A booster's recommended at least two months after a single Janssen dose primary series. This applies to everyone 18 and older who received it. This broad eligibility is due to Janssen's lower vaccine effectiveness as compared to mRNA vaccines. The boost can help increase Janssen vaccine effectiveness. And to get a booster, it's still the honor system. If people say they're eligible, they can get it.

**Unger:** So that's who needs boosters and when but with the newly approved mix and match strategy, are the recommendations on which vaccine that people should get as a booster? Should they offer the same one as the primary series if it's available or try a different option?

**Dr. Fryhofer:** Well, this is where it gets really interesting. The language CDC uses in the recommendation for the kind of booster to give is neutral and vague. It's not specific. It doesn't specify what kind of booster to give and this is not an oversight. The bottom line, you can boost with any authorized COVID vaccine. The booster doesn't have to match the primary vaccine series type. This is called heterologous boosting. On the other hand, boosting with the same type of vaccine as the one you originally received is called homologous boosting. Either strategy is permitted.

**Unger:** New word for my vocabulary which I think just popped up last week, that is heterologous and homologous. How do we know this mixing and matching vaccine series and boosters will work?

**Dr. Fryhofer:** Well, it just so happens there's a really cool ongoing NIH study from NIAID, the National Institute of Allergy and Infectious Diseases. The official name of the study is the heterologous platform boost study AKA the mix and match study. It uses a non-randomized, open-label platform design.
Some early findings were presented to FDA and to ACIP. The initial study included about 450 people. They were divided into three main groups based on the kind of COVID vaccine they originally received.

The groups were then divided into subgroups about 50 people in each arm. Each subgroup was given a different kind of booster. The sample size was small so the study wasn't powered to compare vaccine booster responses. In the study, there was matched boosting, meaning the boost vaccine matched the original vaccine of the primary series. And there was mixed boosting in which the boost was different from the vaccine originally received. A full dose of all three vaccines was used.

For Moderna, the boost used in the study was 100 micrograms. Now understand that a half dose of Moderna, that's the 50 microgram dose has now been authorized by FDA for boosting. It's less reactogenic. This study was started before that authorization occurred. Researchers have now added an additional arm using a half dose Moderna booster but those results are not yet available. So researchers measured antibody levels. They're also looking at cell-mediated immunity but those results are still pending, but here's what we know so far.

Boosters of all three vaccines increased neutralizing antibody titers, irrespective of the kind of booster or the kind of primary vaccine series. Now, although the study isn't powered to compare boosters to determine which combination is best, their early findings are quite interesting. Moderna and Pfizer boosters did seem to do a better job at boosting and triggered stronger antibody responses than Janssen boosters.

Neutralizing activity against Delta and Beta variants are also increased substantially after boosting. Cellular immune responses were measured but are not yet available. They're still being analyzed. There were no new safety concerns. Reactogenicity and adverse events were similar across booster groups. So this is very reassuring.

**Unger:** That is great news. What about the side effects after boosters? Are any better or worse, about the same after a primary series?

**Dr. Fryhofer:** People should expect more of the same, pain at the injection, headache, fatigue, muscle aches, fever, chills. You can hope side effects will be less and they may be. They probably won't be worse with one exception, tender swollen lymph nodes under the vaccinated arm. Swollen lymph nodes were more common after boosters as compared to the primary series.

**Unger:** So we talked a little a bit about the mix and match strategies. Are there any other kind of considerations that come into play when deciding which booster to give?

**Dr. Fryhofer:** Well, any type of boost that's allowed but as per the NIH mix and match study, some may be better than others. Risk of vaccine-specific adverse reactions in certain age groups, as well as...
sex-based differences could be considered. For example, Janssen vaccine has been linked to TTS, thrombosis with thrombocytopenia syndrome in which rare types of blood clots and unusual places along with really low platelets. The TTS risk is higher females under 50 and this is why some ACIP members were concerned about young women receiving a second Janssen vaccine dose and push for the non-specific language for the kind of booster allowed.

On the other hand, mRNA vaccines have been linked to myocarditis. Risk is higher in males under 40, especially for young males age 18 to 25 particularly after the second dose. However, Israeli data have not shown an even higher risk of myocarditis with a third mRNA vaccine dose. Some studies have suggested that myocarditis risk is higher after Moderna as compared to Pfizer, some have not. Careful safety surveillance continues. And look for further CDC guidance for selecting the type of booster for particular patients in the Clinical Consideration Section on the CDC website.

**Unger:** Well, we kind of jumped into all the specifics around boosters but I think it might be worth just kind of taking a step back and talking about why these boosters are even needed in the first place. And talk a little bit about the science, about this issue around waning immunity. Is there something else that we need to be concerned about as we head into the winter months?

**Dr. Fryhofer:** We have three safe and highly effective COVID vaccines. COVID vaccines continue to maintain high protection against severe disease, hospitalization and death. However, we are seeing breakthrough infections. It's all about waning immunity with time and with the Delta variant, along with concern about vaccine effectiveness against future variants of concern. Studies presented to FDA and others reviewed by ACIP do show some waning of immunity with time.

For example, a recent study published in the September 28, MMWR looked at COVID vaccine effectiveness against hospitalization from mid-March through mid-August. VE, vaccine effectiveness was highest with Moderna at 93% as compared to Pfizer BioNTech vaccine at 88%. Pfizer vaccine effectiveness declined significantly from 91% down to 77% at more than four months after the second dose. Moderna vaccine effectiveness did not wane as much as Pfizer. VE for both mRNA vaccines was higher than Janssen. Janssen's single-dose vaccine had the lowest vaccine effectiveness at 71%.

Janssen protection is pretty stable. It doesn't wane as much but its vaccine effectiveness has never been up to par with mRNA vaccines. Janssen never made it up to mRNA vaccine standards when it came to vaccine effectiveness. So the booster recommendation for everyone who received Janssen should help enhance its protection. A company study from Janssen showed two doses of the Janssen vaccine given two months apart increased, VE from 70% up to 94%.

FDA has not verified this data. There were also concerns that there were not enough data in older patients or against the Delta variant. We also see greater declines in vaccine effectiveness in older patients and that's why boosters are recommended for everyone 65 and older, as well as for younger adults with underlying medical conditions that put them at increased risk of severe COVID. With the
Delta variant on the scene and with potential concerns about new variants emerging, it's important to keep antibody levels high.

Unger: So when the Janssen vaccine was initially authorized, obviously we talked about it as a single-dose vaccine. Is it now considered a two-dose vaccine?

Dr. Fryhofer: No. A Janssen vaccine series is still a single-dose of vaccine. That's designated in Janssen's emergency use authorization from FDA. However, a COVID booster is now recommended for those who received a single Janssen dose. Some experts say Janssen should have been a two-dose vaccine from the beginning. When and if Janssen receives full FDA approval, the one-dose recommendation could change and possibly become two but that has not happened yet and it may not. It will be interesting to see what happens.

Unger: So just to clarify for everybody out there, what is the most number of COVID vaccine doses a person can receive?

Dr. Fryhofer: Todd, this question actually came up at our ACIP meeting and there's some nuances to consider. For those who receive Janssen’s one-dose vaccine series, a booster’s now recommended, meaning a total of two COVID vaccine doses. For immunocompetent people who received a two-dose mRNA vaccine series and who now qualify for a booster, the total number of doses would be three.

However, for immunocompromised patients, the additional mRNA vaccine dose is not a booster. It's part of an augmented primary series because the regular primary series was not protective. An FDA representative clarified immunocompromised patients would be eligible for a booster six months after completing their augmented primary series, which would be six months after their third mRNA vaccine dose making a total of four doses for them.

Now we're not there yet in the timeline. The additional dose for immunocompromised patients was authorized on August 12. So the earliest six-month booster recommendation would kick in for these immunocompromised patients would be February 2022 and a lot can happen between now and then. I am very concerned about my immunocompromised patients and I was relieved that at least, for now, a booster for them is planned.

Unger: That is good news. And this mix and match strategy, it does seem that that is going to help our overall vaccine efforts. Can you talk about why that is?

Dr. Fryhofer: Being able to and match greatly increases flexibility. You can choose the boost vaccine depending on the vaccine available and the potential vaccine reactions. It also gives patients and physicians more input in the process. There are no additional safety concerns with mixing and matching and they're not bad choices. Regardless of what boost you give, you still get a good response. In summary, this mix and match option gives us a flexibility we need for efficient and

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effective vaccination programs.

**Unger:** And we talked about upfront about who was eligible to get the boosters and there is a difference between those that received the J&J shot initially versus kind of select groups for Moderna and Pfizer for that matter. Do we expect the FDA or the CDC to eventually expand the eligibility to younger Americans who are not deemed at this point to be at high risk and when would we expect that to happen?

**Dr. Fryhofer:** Well, news reports say that FDA is considering authorizing boosters starting at age 40 for everyone but these are just news reports. There’s nothing official yet from FDA. And this is based on booster data from Israel showing boosters can prevent serious illness in younger adults. ACIP will continue to follow the science and the evidence but we should have a Pfizer kiddie dose for those five to 11 soon.

**Unger:** And that is good news and big news. We’ll cover that as the news developed. Any final thoughts before we close for today?

**Dr. Fryhofer:** Vaccination is clearly the safest and most effective way to prevent COVID. We now have three safe and highly effective COVID vaccines. COVID vaccines can be co-administered with other vaccines so you can get your vaccine and your flu shot at the same time, and you do need both.

This discussion comes at a time when many people around the world have not received even a single vaccine. We must get everyone in the world vaccinated. This conversation is focused on boosters for those already fully vaccinated but our greatest effort should and must be vaccinating those still not vaccinated. Vaccines don’t save lives, vaccinations do.

**Unger:** It’s an excellent point. Boy, if we were to think about all this good news where we are right now as we headed into winter last year, it’s almost unbelievable the progress we’ve made. Dr. Fryhofer, thank you so much for joining us today and sharing this latest update. For resources on COVID-19, visit ama-assn.org/COVID-19. Thanks for joining us. Please take care.

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