Sandra Fryhofer, MD, with latest on boosters and Delta variant

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In today’s COVID-19 Update, a discussion with Sandra Fryhofer, MD, chair-elect of the AMA Board of Trustees and the AMA's liaison to the Advisory Committee on Immunization Practices (ACIP), about if and when we'll need COVID-19 vaccine boosters, the role of the dangerous Delta variant and how this all affects immunocompromised individuals.

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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 the latest news from the Advisory Committee on Immunization Practices, or ACIP, on COVID-19 vaccine boosters, including if and when we'll need them.

I'm joined today by Dr. Sandra Fryhofer, AMA's liaison to the 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.

Well, Dr. Fryhofer, COVID vaccine boosters made headlines recently when Pfizer announced that it was time for a booster and would seek emergency use authorization for a third dose booster in August. Is that something that's still on track?

Dr. Fryhofer: Well, you're right, Todd, the booster club did make headlines. Pfizer said it's time for a

booster, FDA and CDC said not so fast. In a joint statement, they stressed fully vaccinated Americans do not need a booster shot at this time. FDA, CDC and NIH are engaged in a science-based rigorous process to consider whether and when a booster may be necessary. They promise to keep the public informed.

We have to follow the science. We can't base scientific policy on press releases. We need hard data to review and study. I look forward to the Pfizer study being available to FDA and to ACIP for review. If COVID stays around, and it looks like it will, we'll probably all need a booster eventually. The question is of what, and of course when, and who needs them first? But the reality is right now, we're not allowed to give booster doses. It's against federal regulations.

Unger: Will you talk a little bit more about that? Why can't someone just get an extra dose of the vaccine right now?

Dr. Fryhofer: Well, all three COVID vaccines are authorized under emergency use. None has yet received full licensing status. Full licensing requires submitting a BLA, a biologics license application. Pfizer and Moderna have done that. They've applied for full FDA approval but their BLA is still under FDA review and that takes time.

Those who administer COVID vaccines have to sign a federal provider agreement. And under those agreements, vaccine can only be administered under FDA's EUA, emergency use authorization. FDA's authorized a two-dose series for Pfizer and Moderna mRNA vaccines and a one-dose series for Janssen's viral vector vaccine. Administering additional vaccine doses outside the EUA is not permitted under current federal regulations.

This puts physicians in a challenging situation. The data's there that immunocompromised patients could be helped and could be better protected from COVID with a third vaccine dose. But third doses are not allowed unless FDA either amends the EUA or approves a BLA, which then would mean the vaccine is fully licensed. Once a COVID vaccine is fully licensed, physicians can then use their clinical judgment to decide on booster doses, even if it's an off-label recommendation. But to give a third dose now would be a violation of the agreement between HHS and the states. Third doses are not permitted under current regulations, even for those who might need it.

Unger: Well, should that change, what's the current thinking on who may need a booster and who will likely receive them first?

Dr. Fryhofer: Well, as you know, Todd, we now have three safe and highly effective COVID vaccines but none of them are 100% effective. Phase three trials showed Pfizer and Moderna two-dose mRNA vaccine series to be 94 to 95% effective, Janssen's phase three trial of its one dose and you're done viral vector vaccines showed a 66% effectiveness overall.

Immunity wanes with time, Pfizer and Moderna were authorized in mid-December, Janssen's

authorization came several months later at the end of February. So now we're at or close to the six-month mark for those vaccinated first. Residents of long-term care facilities, the elderly, health care personnel and immunocompromised persons. These are the populations that need close monitoring. And remember, immunocompromised persons were not included in phase three trials. Studies are now showing immunocompromised patients don't respond as robustly to the vaccine. They're at increased risk of poor outcomes from COVID-19. They don't develop as many antibodies after a primary vaccine series.

Unger: Well, I want to talk a little bit more in detail about that population you just mentioned, immunocompromised. Just for starters, can you give us a sense of scale about how many people are immunocompromised in the U.S. and how that relates in terms of kind of a subset of the population?

Dr. Fryhofer: Sure. Well, at least 2.7% of all U.S. adults are immunocompromised and that's about five to six million people. This includes those who've had organ transplants, stem cell transplants and cancer, as well as those with so-called primary immunodeficiency and those treated with immunosuppressive medications. Some people living with HIV are also immunocompromised.

Factors that may decrease vaccine response among immunocompromised populations include older age, primary immune deficiency, lower lymphocyte counts, decreased kidney function, being on immunosuppressive drugs or high dose corticosteroids and also current or recent cancer treatment.

Immunocompromised people are more likely to get severely ill from COVID. They're more likely to transmit COVID to people they live with as well as other household contacts. They're also more likely to stay sick with COVID longer. Prolonged infection gives the virus more time to evolve and mutate and transform into new variants. Immunocompromised patients are also more susceptible to infection with COVID variants.

Unger: Well, what do the studies say about vaccines in immunocompromised patients?

Dr. Fryhofer: They don't work as well in immunocompromised patients. For example, a study looking at mRNA vaccine effectiveness in immunocompromised populations found 71% effectiveness against infection for immunocompromised people versus 90% overall. Another study showed two doses of mRNA vaccine were 80% effective in those with inflammatory bowel disease on various immunosuppressants. However, one vaccine dose was only 25% effective. Several studies have looked at breakthrough cases, meaning fully vaccinated people who test positive for COVID. A U.S. study showed 40% of hospitalized breakthrough cases were immunocompromised. An Israeli study found 40% of breakthrough cases were in immunocompromised patients.

Unger: Well, are there studies that are looking at booster doses for immunocompromised patients?

Dr. Fryhofer: Well, several recent studies have looked at giving a third COVID vaccine dose to immunosuppressed people who had a suboptimal response in the initial vaccine series. Giving an

additional vaccine dose increases the proportion who respond. The third vaccine dose can increase protection and seems to be well tolerated. Reactogenicity side effects and symptoms were mild and similar to prior doses and overall mild to moderate in severity. In a study of solid organ transplant patients who received three mRNA vaccine doses, no serious adverse events were reported. No acute rejection episodes occur. In a study of those immunosuppressed people with a suboptimal immune response, meaning low or no antibody response after initial mRNA vaccine series, 42 to 48% did develop an antibody response after an additional mRNA vaccine dose. So in summary, a third vaccine dose seems to improve immune response and is pretty well tolerated. We just can't do it right now, the EUA doesn't allow it.

Unger: But aren't they doing this in other countries already?

Dr. Fryhofer: Yes, in France they've been giving extra doses since April. And in France, they're routinely recommending a third dose for those severely immunocompromised. Patients that have had solid organ transplants, those who've had recent bone marrow transplant, patients on dialysis, those with autoimmune diseases and patients on strong immunosuppressive therapy. The United Kingdom has proposed plans for an additional dose for immunocompromised people starting in September. Israel has also announced it's offering third dose boosters to immunocompromised adults. In France, they're also doing quantitative spike antibody testing 30 days after the second and third vaccine doses.

Unger: Well, should physicians be checking antibody levels in immunocompromised patients?

Dr. Fryhofer: Well, CDC says no. Serological and cellular immune testing outside the context of research is not recommended in the U.S. at this time. Right now, there's no established correlated protection but ongoing research studies are monitoring the kinetics of antibody response. They're looking at both humoral and cellular immunity, neutralizing antibody titers, memory B cells and killer T cells. So far, overall, real-life effectiveness of available vaccines is looking pretty good. Vaccine effectiveness studies where variants are solid, so far, even for the Delta variant, for those who get a full vaccine series, you need both doses of a two-dose series. One mRNA vaccine dose may not be enough.

Unger: Well, it sounds like there's a lot of studies, research underway. Can you talk about what kind of boosters are being studied?

Dr. Fryhofer: Many kinds of booster studies are underway. Full dose and half doses of the original vaccines, boosters specific to the Delta variant. Also, half-and-half combination boosters, meaning half original and half variant specific vaccine. There are still many unanswered questions. And if you're going to get a booster, which formulation is best? Should you stick with your initial vaccine type or is it better to mix and match vaccine types? This is called heterologous boosting, getting a primary series of one type of vaccine followed by a booster with a different type of vaccine. We also need to figure out how long to wait before boosting. CDC and ACIP are collecting and reviewing available

data in real time. So they will be prepared and ready to go if and when an EUA is amended or full licensing granted. We may not all need boosters right now, but one thing is for sure, we all need to be vaccinated. More than 99% of recent COVID deaths in the U.S. are in unvaccinated people. New data shows rates of new COVID-19 cases are almost three times higher in states with low vaccination rates.

Unger: Well, of course, a lot of that is being driven by this Delta variant. Can you talk a little bit more about the role that variants play in the push for boosters right now?

Dr. Fryhofer: Well, India's B.1.617.2, aka the Delta variant, now causes as many as 83% of new COVID cases in the U.S. Delta is a super spreader. It's the most contagious variant we've seen yet. It's about 60% more transmissible than Alpha B.1.1.7, the so-called U.K. variant, but Delta has now overtaken Alpha and is now the dominant strain circulating in the U.K.

Variants are wildcards. Vaccine researchers understand this, and that's why Pfizer and Moderna are working on various specific boosters. Pfizer says it will seek FDA authorization for a Delta variant booster in August. Moderna's already working on a B.1.351 specific booster. When a variant specific booster is available, it will likely be under emergency use authorization pathway, at least initially.

We're in a race against time and the variants to get everyone vaccinated, especially with this new super contagious Delta variant on the scene. If the virus changes too much, protection from vaccination may no longer be protective and then we'll be back to square one with masks, quarantine, social distancing and everything shutting down. We don't want to go back there.

Unger: No, we do not want to go back there and getting that vaccine is so, so important. In terms of outside organizations, are we seeing kind of any feedback from the World Health Organization?

Dr. Fryhofer: Well, the WHO has gone on record that vulnerable populations like the elderly will likely need a yearly boost to protect against new COVID variants. The general population will likely need a booster every two years. Both Moderna and Pfizer, along with German partner, BioNTech, have been vocal in their view that the world will soon need boosters but to make that judgment, we need evidence, not just press releases. For Pfizer, we may have that data soon. We are so fortunate here in the U.S. to even be discussing getting a third dose booster. So many people around the world have not received even a first COVID vaccine dose. We need to get everyone in the world vaccinated.

Unger: Well, we talk a lot about emergency use authorization, do you think that the fact that our COVID vaccines were authorized under emergency use authorization and not yet fully licensed has contributed to vaccine hesitancy?

Dr. Fryhofer: Well, we may have that answer soon. As you said, right now, the COVID vaccines are authorized under emergency use, but both Pfizer and Moderna have turned in the data and have applied for full licensing so this could happen any day now. Some health care systems are already

requiring COVID vaccination for their employees and I also think more companies may make vaccination mandatory once the vaccines are fully licensed.

Unger: Well, in closing, any final thoughts?

Dr. Fryhofer: Todd, if and when boosters are recommended and available, I hope that physician offices will be welcomed as initial providers for booster outreach. To that end, I want to encourage all physician practices to think ahead and work now with your state and local health department. Get that red tape paperwork and training behind you so you're ready to go and can administer vaccine now, as well as booster doses later.

For now, a third dose is not permitted under current federal regulations, even if it's vaccine that would be otherwise be wasted and it breaks my heart to see vaccine thrown away. We're in a transition period but we may see some regulatory movement to address this problem soon. At our July 22 emergency ACIP meeting, ACIP's secretary said, CDC is actively looking at ways to provide access to third dose vaccines prior to changes in regulation, so stay tuned.

But for now, the best advice for these high-risk patients is to continue to wear a mask, avoid crowds and stay socially distanced as much as they can. Also, encourage all family members and anyone around them to get vaccinated to protect themselves and also to keep from spreading infection to immunocompromised family and friends who aren't able to respond as well to vaccination. Those of us who can need to be vaccinated to protect the young for whom vaccine is not yet available and to protect the vaccinated, but still vulnerable, including many immunocompromised patients, as well as the frail elderly. And remember, our patients trust us. Physician recommendation is one of the most effective motivators for vaccination.

Unger: Well, Dr. Fryhofer, thank you so much for being here today and sharing this news and your perspective. I hear from so many physicians and friends out there, how much they appreciate the clarity of your feedback and representing the science.

Well, that wraps up our COVID-19 Update for today. Thanks again, Dr. Fryhofer. We'll see you soon. For updated resources on COVID-19, visit ama-assn.org/COVID-19. Thanks for joining us. Please take care.

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