

# COVID-19 fourth dose boosters and vaccine update with Peter Marks, MD

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On May 9, 2022, the AMA hosted episode 11 in the "COVID-19: What physicians need to know" webinar series.

Susan R. Bailey, MD, immediate past president, AMA, welcomes Peter Marks, MD, PhD, Director of the Center for Biologics Evaluation and Research at the Food and Drug Administration (FDA), to discuss a host of hot topics related to the fourth dose booster vaccine and updates on pediatric vaccine safety data. Hear the latest on who should receive the fourth dose—and when—and whether we'll be seeing a vaccine for younger children soon.

## Host

- Susan R. Bailey, MD, immediate past president, AMA

## Guest

- Peter Marks, MD, PhD, Director of the Center for Biologics Evaluation and Research at the Food and Drug Administration (FDA)

## Transcript

**Dr. Bailey:** Hello, and thank you for joining us this afternoon for the latest in our What Physicians Need to Know series about COVID-19 and other critical issues in health care. I'm Dr. Susan Bailey, immediate past president of the American Medical Association. And it is my pleasure to once again to serve as your host for this discussion about the latest in COVID-19 vaccinations.

Today, we'll be talking about second COVID-19 booster doses for those eligible to receive them and also look at where we are on the effort to vaccinate children under the age of five. Our goal as always is to provide you with the latest and most accurate information available so that you're better able to counsel your patients, address their questions and concerns, and ultimately to increase confidence in the available vaccines.

This afternoon, we are pleased to welcome again one of the leading voices on this topic to answer your questions and share his expertise on the effectiveness of booster doses and pediatric vaccines. Today marks our eleventh webinar focused on COVID-19 challenges and our response. Our previous sessions covered the FDA vaccine review process, vaccine development, vaccine safety and delivery, and the need to confront vaccine misinformation and disinformation.

Now, if you weren't able to join us for those sessions, they're still accessible on the AMA website. I'll share that link in the chat so that you can view them at a later time, or you can simply visit our main AMA page [ama-assn.org](https://www.ama-assn.org) and search for COVID-19 webinars.

We are in our third year of battling COVID-19, although it really seems much longer than that, doesn't it? Case counts are once more steadily rising in some areas of the country as we inch toward that once unthinkable figure of one million COVID related deaths in the United States. We know those who are unvaccinated remain at the greatest risk for contracting COVID-19 and are more likely to suffer severe illness and death as a result. About two thirds of eligible Americans are fully vaccinated and nearly 80% have received at least one dose, but only about 30% of those eligible to receive a booster dose have done so, which means we have some work to do here to educate the public on the importance of staying up to date on COVID-19 vaccinations.

As an immunologist, I can tell you that physicians play a vital role as vaccine ambassadors for our patients. To make sure that patients have their questions answered, we need to first make sure that we as physicians have a deep understanding of the vaccine and the booster development process, the scientific rigor involved and how their effectiveness helps combat COVID-19. That's the basis of our webinar today as we explore a range of topics related to a second booster dose, provide updates on pediatric vaccine safety and efficacy and discuss how soon a vaccine for our youngest children might be available.

Joining us today is our good friend, an AMA webinar regular, Dr. Peter Marks. He's the director of the Food and Drug Administration Center for Biologics Evaluation and Research. Dr. Marks is also the acting director of the FDA's Office of Vaccines Research and Review. He's board certified in internal medicine, hematology and medical oncology. Dr. Marks led the adult leukemia service at Yale University and served as chief clinical officer of Smilow Cancer Hospital in New Haven before joining the FDA in 2012 as the center's deputy director. In his current roles, Dr. Marks and his team are tasked with ensuring that COVID-19 vaccines are both safe and effective, and that they've undergone a rigorous evidence-based and transparent process.

We hope today's webinar not only provides a greater understanding of the science behind the process, but also gives you the information you need to talk with your patients about the safety and the reliability of boosters and pediatric vaccines. So now, please join me in welcoming Dr. Peter Marks.

**Dr. Marks:** Thanks so much. So I'll start by going over a relatively brief slide presentation for about 15 or 20 minutes and then I hope we'll have the majority of our time for questions and answers, which is usually the most useful thing at these sessions. So let me just go ahead and share my screen here.

So, I'll talk a little bit about a recent agency action that some may be aware of on the narrowing of one of the vaccine emergency use authorizations, talk a little bit about first and second booster doses, then talk just touch upon boosters for the 2022 2023 season, because I think that's something we're going to have to start to get our heads around. Talk about pediatric vaccines and then a little bit about our upcoming advisory committee meetings.

So this past week, the FDA undertook revision of the Janssen COVID-19 vaccine emergency use authorization based on the continued occurrence of the thrombosis with thrombocytopenia syndrome. For those who might not be familiar with this, this is a syndrome that was very rare, but quite striking with the Janssen vaccine. And it also occurs with other adenoviral vectored vaccines. It occurs with the AstraZeneca vaccine, which is not authorized in the United States, but it is basically usually blood clots in unusual locations, cerebral sinus vein, mesenteric veins that is associated with pretty significant thrombocytopenia. For all the world, it looks like heparin associated thrombocytopenia, but without the heparin. And so this is something that occurs roughly about ... we found it occurring about three and a quarter per million doses of vaccine given, which is pretty rare. Unfortunately, it's associated with about one death per two million doses, and those are pretty clearly attributable to the vaccination.

So what this led us to do is realize that in the setting of the United States, where we have the mRNA vaccines of which now hundreds of millions of doses have been given where we cannot identify any similar risk, that we felt it was appropriate to narrow this really to a vaccine for individuals who could not take one of the mRNA vaccines, because it was clinically not appropriate because of either allergic reactions or myocarditis or because they were unwilling to take an mRNA vaccine and the only way they would get vaccinated is to take a non-mRNA vaccine.

Just to put this in context, this a very useful vaccine still around the globe, because it does not require the types of cold storage that the mRNA vaccines require. However, where there's options like we have in the United States, we felt it was important for providers to know that ... I should just say that the major risk with this vaccine just has been in individuals 18 to 50 and mainly females, although that's not totally exclusively the case. So we'll see whether this additional work is done whether we can figure out the best population that might receive this vaccine, but this is the narrowing for now.

So I just want to move on to boosters for the general population. For the general population, it's pretty clear we know now that the vaccines wane over time, and that's particularly true in the setting of the SARS coronavirus 2 variants particularly as we've come to Omicron. And we now know pretty clearly that an additional vaccine dose can provide better immunity, preventing hospitalization and death, emergency department and urgent care visits, and potentially serious complications such as long COVID-19. And this last thing is something that perhaps a little bit more controversial is something that we may really have to deal with, because as additional data come out on the neurologic complications of COVID-19 and the potential impact on the brain, preventing long COVID-19 may be one of the important things that vaccination helps do in that we do know that people who are vaccinated, even if they do get COVID-19, tend to have a lower subsequent rate of long COVID.

Just to give you an idea of what the mRNA boosters have done during Omicron, we can see that in terms of emergency department visits, these are data from CDC, but there are other data that are similar from other sources and other countries. You can see that three doses of the vaccine, people who have had a third dose of the mRNA vaccines, have a relatively low rate of use of emergency department or urgent care visits. Two doses still protects reasonably, but not quite as well. And if you look for hospitalization, you see a very similar pattern for three doses. You have vaccine effectiveness of 82% here, and two doses given within the past six months, about 50%, 52%. And if given more than six months earlier, 38%. So again, showing this waning of protection. And it does appear that the third dose of these vaccines does provide a more mature immune response over just two doses. And that seems to continue out over time.

Now, one of the issues that was noted was even with third doses in Omicron, we still had symptomatic disease though not necessarily severe disease. And that's something that led to the look at additional doses. So, just to summarize to now, because of the data that I just showed you, we have boosters for the general population that were authorized and the entire population age 12 and up right now is eligible for boosters given the favorable benefit risk assessment. Really, just one footnote is that since the Pfizer-BioNTech vaccine is the only vaccine authorized for those 12 to 17 years old, that's the only booster that can be given in that age range. But otherwise, heterologous boosting is permitted for those 18 years and up. Some on the webinar may have heard that there is an application pending right now from Pfizer for boosting the five to 11 age range. And that will hopefully be acted on in the not too distant future. So stay tuned on that one for "coming attraction" from FDA.

But then there's the issue of the fact that with Omicron we saw waning against symptomatic disease, but it also was looked at in Israel in terms of whether there was waning against more serious forms of disease. Two studies that came out of Israel showed that both hospitalization and death was increased and the death rates and hospitalization could be reduced following Omicron with a fourth booster dose that was given at least four months after the third booster dose. And the data actually, when FDA reviewed, them were pretty compelling.

Now, the reduction in hospitalization was notable and persisted over time as well as the reduction in death. It is true that the reduction against symptomatic disease, more mild forms of disease against Omicron, starting somewhere about eight to 10 weeks after a booster dose does start to wane. But again, hospitalization and death were reduced. And the reduction of death in the Israeli study was pretty notable. Those over 60 and those at risk of complications from severe complications from COVID-19 who received a fourth dose had an 80% reduction in the risk of death after a fourth dose. So in a study that was considered to be well conducted that led us to authorize the fourth booster doses for individuals 50 years and up.

Now, you might have said 60 years and up for ... or you might have noted that the Israeli studies was an individual 60 years and up and in those at risk for severe outcomes from COVID-19. In the United States, we've had enough experience over what Dr. Bailey rightly note as it's been three very long years. And it's almost like living dog years each one of them feels like about seven years. We have developed some experience. And one of those pieces of experience is that it was very difficult for practitioners in offices to figure out when we said, "Well, give it to people at high risk." What that really meant is, is my patient in front of me who's 51 who has some mild reactive airway disease, are they at high risk? Those were the difficult ones.

The people who had terrible COPD, those weren't the hard ones, but there were a lot of people and questions about this. So it was felt that since on par CDC notes that about a third of Americans between the ages of 50 and 65 have some significant risk factor for severe COVID-19, should they get it? It was decided that we would just move the age down to 50 and make things simpler.

And I think that actually was wise because the first time when we tried to use that risk based approach, it created a lot of confusion. And if there's something I guess we have learned with maturation of living through this response is that the less confusion and the more clarity we can provide from FDA, the better it is for providers and for public health. So this is how we came out for the boosters.

I think the one thing I will just say is as much as good idea to get a fourth booster or a fourth dose. Sorry, I misspoke there. A second booster or a fourth dose, it's really important that we try to get the half or a little bit more than half of Americans who have only received two doses to get that third dose. That may make a difference moving forward here. And it may particularly make a difference now that we're coming into yet another wave of COVID-19. So good idea to just try to get people up to date on their vaccination.

We at FDA are realizing that we are in for probably new variants in the future. Hopefully, the next generation of COVID-19 vaccines that will come about in the next year or two will be better at getting the whole variety of SARS corona 2 variance for a more robust immune response that will protect us all year long or even longer against whatever variants may buffet us. But for right now, we have to deal with what comes along.

So we have guidance out at FDA about how we will develop these new vaccines and how we'll develop variant vaccines for the variants that have come along. Now, one of the issues here that makes things a little complicated is that the new variant such as Omicron may not provide the same immunity against some of the older variants that we've been through, like Beta or Delta. So as we move forward, we have to consider this. And that may mean that in the future, we may see multivalent vaccines to help both protect against what we have circulating now, which is Omicron, and Omicron is moving on as you're all well aware to evolve somewhat, and also to allow us to have protection in the event something else comes along. Because that's maybe the second piece of learning.

Besides having clear public health messaging, the second learning is these pandemics seem to do whatever they want and no matter how good we think we are at predicting things, we will almost always be wrong. So we have to be prepared to be wrong and have contingency plans.

So we did recently have an Advisor Committee Meeting on April 6 to think about boosters moving forward. And really we are a little concerned about where we're headed with fall to winter 2022-2023. We'll see how wrong I am with this prediction. We suspect that this current bump we're having will probably reach some modest peak in the next month or so, and then we'll have a decline again. And then we'll have to deal with the fact that even though we may have a good late summer, relatively speaking, we're going to have to deal with the fact that we will have waning immunity over the coming months, that the virus is going to continue to evolve. There will be global circulation. It will be winter in places in the southern hemisphere. People will be indoors. The virus will have plenty of chance to become more problematic.

And then we ... next fall, usually in the November, December timeframe, depending on whether you're more north or more south will start to move indoors as well. And that combination makes us concerned that we could have a wave at some point next fall, winter. And for that reason, we're thinking about a booster campaign somewhat along the timing of our fall winter influenza campaign could be very timely and very convenient to have people in the October timeframe get both influenza and COVID-19 vaccinated. So we'll see how that works out.

There is one of the things that came from this Advisory Committee is that generally right now we have a variety of different vaccines, but we think that the composition of any boosters should be the same across those different vaccine platforms, if at all possible. Again, to allow that kind of practical heterologous boosting so we don't have to have providers so worried that if somebody got X vaccine, they have to get X booster.

Our next Booster Advisory Committee will be in late June. And at that point, we will review the data on the variant vaccines from various sources, including the manufacturers, the National Institutes of Health and the World Health Organization, and will be looking at both monovalent vaccine data and bivalent vaccine data. Again, it's a little bit of a challenge here because we don't know how much further the virus will evolve over the next few months, but we have no choice because if we want to

produce the hundreds of millions of doses that need to be available for a booster campaign, we have to start at risk in the early July timeframe or even somewhat sooner to get up to those kind of numbers. So this is where we will have to use our best guesses.

And that's why somehow the bivalence seem a little bit attractive here to be able to provide us with a little bit of wiggle room, but we'll see what the Advisory Committee says—whether we feel like there's a monovalent that can do the job or whether we need bivalence. And we also, at that Advisory Committee, there may be some discussion of whether this should be a general population recommendation or whether there will be appropriate target populations. .

And now to what probably people might want to hear most about. This is usually been the most popular topic recently, the pediatric data and when will we have it for the youngest children. The pediatric population for vaccine development has been divided into three major groups, the 12 to 17s, five or six to 11s, and the six months to five or sixes. And then the youngest age group study has been further divided out so that safety and immunogenicity in the six month to two-year-olds is kind of called out separately as well. These trials are focusing on safety and immunogenicity, but because we've had a fair amount of circulating virus, they've also captured vaccine efficacy whenever possible. And some of that is what created some of the challenges in the January timeframe as vaccine efficacy in the youngest children seemed to be quite off when truly it was probably just mirroring what a vaccine efficacy against Omicron was in terms of symptomatic disease. But that's a story for another day.

Just to remind people of the way these trials are done, in general, these are immuno bridging studies where we work our way down from an older population in the case of ... this is just using Pfizer as an example, the 12- to 15-year-old population. They considered 16- to 25-year-olds adults. So they immuno bridged using their adult dose. And you can see here the geometric mean titer ratio between the 12- to 15-year-olds and the 16- to 25-year-olds was excellent at 1.76. So clearly, they achieved non-inferiority. The ratio may have been as good as it was either by luck or by the fact that 12- to 15-year-olds overall may weigh less than 16- to 25-year-olds. It could have been a combination of both.

And you can see here bridging down to the five- to 11-year-olds. Similarly here, five- to 11-year-olds, where they reduced the dose by a third to 10 micrograms from 30 micrograms, had a GMT ratio of 1.04, pretty much right on the nose of where you'd want to immuno bridge. Efficacy in the adolescence, the 12- to 15-year-olds, we didn't have a lot of Delta around at that point. And they had excellent efficacy here with no cases of COVID-19 in the vaccinated individuals versus 16 in the placebo, about a thousand cases on each side of this equation. So it was a nice demonstration of clinical efficacy. In the era where we started to have Delta when the five- to 11-year-olds were vaccinated, this is now noting a two to one randomization here. So you have to do a little correcting in your head. Also, had quite reasonable vaccine efficacy.

And just to show you here, the vaccine safety here is always something that we care about very much. You can see here, the placebo versus the vaccinated 12- to 15-year-olds, and then the age 16 to 25

vaccinated individuals. And you see that the 30 microgram dose in 12- to 15-year-olds was very similar to the adults. Interestingly, with de-escalation of the dose by two thirds to 10 micrograms, although injection site pain was similar, the amount of fatigue, headache, muscle pain seemed to be somewhat less in the vaccinated individuals. Whether this is chance or not, it's possible, but it may well reflect the fact that the dose was backed off a little bit here.

So what about the youngest children? So really in children five years and less, we actually obviously have to further dose de-escalate. We have to make sure we have an adequate number of children, and we have to be careful about our benefit risk. I am not a pediatrician, but having covered for pediatric bone marrow transplant units and having been around kids growing up, high fevers in young children are not ideal because of the risk of febrile seizures occasionally. So we are very cognizant of worries about understanding the side effect profile in these vaccines, in the youngest children. There are completed trials from two sponsors in the process of submission and review, and we are moving as fast as we can to review these.

I fully expect that we'll have the data by June ready for review. And whichever of these gets there as quickly as they can, we'll get to the advisory committees as quickly as we can. There is a chance that we might have the two, the Pfizer and the Moderna vaccines, meet in the middle somewhere, but we're not going to hold anything back here because we hear very much from parents how desperate they are to have these vaccines. That said, we have to do it right because we need parents to feel confidence to get their kids vaccinated.

We're still suffering a challenge of vaccine confidence here. It's only about 25 to 30% of five- to 11-year-olds are vaccinated. I think that latest might have gone up as high as 30 to 35 now from just looking at some data from CDC this morning. But we want to make sure that people are confident that we have really looked at these vaccines closely and with our usual rigor. And so our reviewers will do that.

In terms of our upcoming Advisory Committees, we have an Advisory Committee at Meeting at the beginning of June on the Novavax COVID-19 vaccine. That is a protein based vaccine with a novel adjuvant. It will be nice to have an additional option. There are individuals who still are uncomfortable with the mRNA vaccines or who have contraindications to them. It will be nice to have a protein based vaccine for administration. There's actually even a second protein based vaccine following along a little bit behind it from Sanofi. So we can expect those hopefully. And we obviously have the review of the Moderna and Pfizer pediatric COVID-19 vaccine request, and then the vaccine composition selection.

So if anyone is running out of TV to watch over the month of June, you can certainly tune in to FDA TV as this will all be streamed from our Advisory Committee Meetings. So with that, I'll stop. And I might have gone on a little bit longer than I intended to, but I look forward to answering questions. Over to you, Dr. Bailey.

**Dr. Bailey:** Thanks so much for another amazing and informative presentation. We received well over 100 questions for this webinar. So it's really clear that physicians still have a lot on their minds and a lot that they need to sort out about COVID-19 vaccines, and of course the interest level is still very high. And of course, as with previous webinars, we've gotten some questions that were really good but were outside of the scope of this presentation. So we're going to focus only on COVID-19 vaccines today. We're not going to talk about therapeutics or other related issues.

First, I want to ask some questions about COVID-19 boosters or third, fourth doses in adults. Now, there's a lot of concern about the timing of boosters, especially if, as yours truly has experienced, had a breakthrough infection in the meantime. So if someone had their first booster, so their third dose of vaccine say four to five months ago and they got sick, so they had a breakthrough infection. Should they delay receiving the fourth booster another four to five months? Should that be after the last booster or after the breakthrough infection?

**Dr. Marks:** Really good question. And CDC is recommending that that be considered. From the data that we see, again, it may make sense. It's been said maybe to delay by about three months, that booster after an episode of Omicron, because we know that the immunity after Omicron, after a natural infection with Omicron tends to wane over that time. So whether it's three, four, five months you wait, it's perhaps a judgment call, but that is something that's been recommended and something that can be done. Now, I will say there's nothing ... the CDC will tell you just as I will that there's nothing wrong if somebody decides to go get vaccinated, it's just probably not going to help a whole lot over the natural infection at that point.

**Dr. Bailey:** Now, I was really intrigued with your comments on assessing the efficacy of the fourth booster and how that relates to ... language that's starting to sound like flu vaccine language, the 22-23 season, which variants we're going to be looking at and might be included. But I'm getting questions from my patients and I'm sure many of our audience are as well. If someone could be eligible to receive a fourth booster right now, I'm hearing patients ask, "Well, I'm thinking about waiting until fall to get that, so that I'll have better coverage for next winter." Is there any reason to consider postponing your fourth booster if you're due for one now?

**Dr. Marks:** So if you haven't had COVID recently or you don't know that you've had COVID because you haven't been symptomatic, I think the answer would be if you're eligible, there's probably no reason right now today to put it off, to getting that booster. Why? Because it's going to be four, five, six months before we get to when you get your next booster. So if you say May, June, July, August, September, October-ish, you're talking about having several months there at risk. So if it's been that long, you're probably putting yourself at additional risk during that time. There's no evidence that we have that we're getting immunosenescence with these mRNA vaccines here. So it seems to me that, especially for those older individuals who could be at risk of severe outcomes, that's one of the things that led us to authorize those fourth doses or second booster doses. So I wouldn't go crazy about that.

Now, if you haven't had ... I mean, there are people out there who are over 50 years old, who haven't had their third dose, those people rather than just being casual about it, I would urge them to try to get that third dose to ramp up the immunity, just because we do have plenty of circulating COVID-19, and there are some of us ... Again, this is not official U.S. government. This is just based on the experience of what we know probably is happening. That the numbers that we have right now for COVID cases probably are an underestimate because many of the mild cases are probably not being reported the same way they were at previously, because of all of the home testing, which means there's probably a fair amount of COVID-19 circulating. Again, mild case is not a big deal, but if you are a person at risk and you get one of them, that could be a problem for you.

**Dr. Bailey:** You mentioned immunosenescence. Another way of thinking about it is the point of diminishing returns on the boosters. Is there a concern that with booster after booster, especially if it's the same formulation, that we are going to reach the point of diminishing returns?

**Dr. Marks:** I think that is one of the reasons why perhaps it will ... I think that you'll hear that conversation come up in the June meeting about whether it probably makes sense to shift composition here to either to a different single variant or to a bivalent vaccine or multivalent vaccine, so that we shake up the immune system a little bit in this case. I mean, the good news is vaccines with four boosters are not unheard of, or three or four doses are not unheard of. So it's not like what we're doing here is totally pathbreaking here. It would be nice to have something that was more durable, because I'm less worried about this fatigue of our immune systems, which our immune systems are very kind to us. They just go and they take care of us day after day.

I'm worried more about our emotional and intellectual fatigue with getting vaccinated causing us a problem. And that's one of the reasons why I think you'll see a lot of work towards developing more robust vaccinations or vaccines that can lead us to have durable immunity, because we will not be able to. I'm the first to admit that I think that if we were to have to say that we're going to continue doing every five or six month vaccines for this infectious disease, we were going to have some real challenges here.

**Dr. Bailey:** I agree. My patients, I've certainly heard a lot of fatigue. I've been amazed at the number of patients that are eligible for boosters that just haven't even thought about getting one. And I think that we need to be thinking about, what is the definition of fully vaccinated? And is it two? Is it three? Is it four? Because there's a lot of confusion amongst I think the healthcare community as well as among patients. So bringing up the bivalent vaccines, that makes me wonder, is there an advantage of mixing and matching, if you will, boosters at this point in time. Does it give additional benefits or are there any additional risks?

**Dr. Marks:** So I don't know that there are any additional risks that we see, and there are data that suggests that even mixing and matching ... clearly mixing and matching the mRNA and the adenoviral vector vaccines appear to have some ... there may be some benefit there, but there's even a

suggestion from some publications. And again, we have not reviewed them internally at FDA in terms of the actual data so I can't comment for sure. But at least on face value, they seem to suggest that even mixing and matching the mRNA vaccines, the Pfizer and the Moderna, there might be somewhat of a more robust response in doing so, in terms of expanding the spectrum of the immune response. So that's why generally what I've told people is don't think a lot about which of these you've gotten. Really, if it makes you feel more comfortable to get the same thing every time, probably go ahead and do it. If they don't have the same thing, it's totally good, maybe you'll get a somewhat better immune response. I think probably the differences though are probably small. And the good news is we have not seen any evidence that there's an adverse effect of mixing and matching.

**Dr. Bailey:** Great. Now, given the fact that antibody levels seem to have a fairly rapid drop off after immunization, do we have any long-term data on T-cell responses?

**Dr. Marks:** So we're starting to gather more of those data. And I think that you've probably read papers on T-cell mediated immunity in COVID-19. It's coming more to the fore here. The challenge has always been with assays for T-cell responses are much more challenging to do than the assays for antibody mediated responses in terms of automating them, et cetera. But there are now some automated ways to do these. And I suspect that over the coming months, we'll start to hear more and more about T-cell mediated immunity, because really importantly, as we start to look at next generation vaccines, the antibody responses will be important as a starter to get started on the work. But understanding the T-cell responses are going to be critical to understanding whether they're really generating a more robust response that might be more durable compared to the current generation of vaccines. So we have to do the work here.

And I think what happened was initially we went with what was most convenient. It wasn't for lack of trying even, but what came out as immune correlates or potential immune correlates were mostly antibody responses, but I think continued work will hopefully elucidate what T-cells are actually doing here.

**Dr. Bailey:** A couple more questions about the boosters, and then I'm going to move on to talk about safety updates and pediatric vaccines. First of all, what about pregnant women? What are the recommendations for boosters and pregnant women?

**Dr. Marks:** Yeah ... we would do exactly what we would do for the rest of the population. Pregnant women should just basically as if you were not pregnant.

**Dr. Bailey:** So, should they get fourth doses or are they still considered at high risk? I think they are.

**Dr. Marks:** I see what you're saying. A pregnant woman would be eligible for up to three doses at this point, unless they had some other immuno compromising condition. And if they had an immunocompromising condition, then you would potentially have eligibility for what would be a fourth

dose. But honestly, at that point, it's actually three primary doses and a booster dose, but we could go for that. It gets to a more complicated situation because we did actually authorize up to two booster doses for those who were immunocompromised. So immunocompromised individual would be a different issue, but we don't consider your average healthy pregnant woman to be an immunocompromised person.

**Dr. Bailey:** What about fourth doses for health care professionals?

**Dr. Marks:** Yeah. Interesting, interesting. So there again, the feeling was the way the study was done was not in health care providers, but in individuals at high risk of complications from COVID-19 or people over the age ... in Israel, it was over 60. We obviously modified that to 50 and over. I think, Dr. Bailey, this goes to your issue of the fact that our T-cells, the T-cells in your health care workers, they're doing us right. And the risk there is probably of mild ... in what we see in younger individuals of mild to moderate COVID, which does not result in hospitalization. And so provided they've had their first booster, three doses total of the mRNA, a younger health care provider is probably okay.

**Dr. Bailey:** So that kind of leads me into my last booster question. Is anyone looking at boosters in healthy adults under the age of 50?

**Dr. Marks:** In other words, another dose, a fourth dose in that population?

**Dr. Bailey:** Right.

**Dr. Marks:** Good question. They're looking at them in terms of some of the variant vaccines, but not for deployment broadly at this point, to my knowledge. And I may be missing ... I apologize if someone's aware of a study that I'm not at this point.

**Dr. Bailey:** I trust your judgment and your memory better than mine. So in terms of safety updates, is there any update on the incidence of myocarditis from the vaccine? Not only in adolescents and young adult males, but really across the spectrum in women. In my personal experience, the fear of myocarditis has been a major issue in talking to parents of my patients about their children getting vaccinated. And how does the incidence of myocarditis compare with the incidence of myocarditis with COVID-19 infection itself?

**Dr. Marks:** Well, let's start with the easiest one. The incidence of myocarditis with COVID infection is several fold higher than with vaccination with the mRNA vaccines, even the second dose of the mRNA vaccines, which is where the risk of myocarditis is highest. So getting COVID-19 is a bad thing to do for myocarditis. So good to be vaccinated to help prevent that. What we have seen now, we're understanding the risk of myocarditis better. We now understand that good news for those parents of five- to 11-year-olds, we really don't see myocarditis. I mean, it's very rare in younger children, okay? Less than less than 12 years old.

We start to see it come up somewhat in adolescents. The risk of myocarditis probably peaks somewhere between about 16 and 24 years of age. And in fact, there's some indication it might peak even highest around the 16 to 18 year age range, and then it starts to come downward. And then it tails off between age 30 to 40. You don't really see again, older individuals, very uncommon. Mostly males, not exclusively, but mostly males. And the risk after the first dose is lowest after the ... it appears to be the highest after the second of the doses given either three or four weeks after. And then it tends to be somewhere intermediate between the first and second doses for the booster dose.

And you may have noted that in CDC guidance, they have suggested that it's not unreasonable if you're concerned. If the choice is not to get vaccinated or to get vaccinated and to put eight weeks between the first and second dose, better to get vaccinated and have the additional time, because there's some data from a Canadian study that suggests that putting that additional four or five weeks between the first and second doses seems to reduce the risk of myocarditis.

Now, I'm not sure in the middle of a pandemic that it's always the best thing to do, but if the choice is not getting vaccinated versus getting vaccinated because you feel like you're more comfortable getting a dose two months after the first, better to get vaccinated. So I think, although it might sound a little loosey-goosey compared to our normal vaccine schedules, which are very prescribed, if this helps get more people vaccinated, it's a good thing.

**Dr. Bailey:** Shifting gears a little bit, talking about flu vaccines. What is the status of a combination influenza and COVID vaccinations? I know that there's being some work done on that.

**Dr. Marks:** Yeah. I think this is a coming attraction possibly for the 2023-2024 season. It's just that it's not together yet for this coming season. And I can explain to you why. Influenza vaccine manufacture is something that is ... the bulk of our influenza vaccine, about 80% of it is made by a relatively old technology embryonated chicken eggs, and that manufacturing process for this year's flu vaccine started at risk last February. Well, this past February. And the problem is that the ability to make some novel vaccine that would have both the COVID-19 vaccine and the flu vaccine in it so it was a combi vaccine just was not there for this year.

Hopefully next year, there will be more of a possibility of that both because we'll have the background of knowing what we're going to do for strain selection in place earlier on and the manufacturers will have had time potentially to generate better COVID-19 vaccines that when combined will be confident will give long lasting protection. Because part of what we're doing here by waiting for production of the COVID-19 vaccines is trying to get the best match we possibly can. We take our chances with influenza vaccines because we do that year to year. And I think we'd like to try to maintain the best efficacy that we can with our COVID-19 vaccines.

Remember, the COVID-19 vaccines have a different level of effectiveness generally compared to influenza vaccines. Influenza vaccines, even on a good year are less than perfect. They're basically

efficacy effectiveness of 50% is considered a good thing for a flu vaccine against one of the circulating strains. So we've been lucky with the COVID-19 vaccines. And hopefully as we come into the 23-24 season, we'll be able to have a tuned up bunch of COVID-19 vaccines, so that when we have to combine them late on in the process, it will be something that will allow us to vaccinate with confidence in the September October timeframe.

The one thing we're lucky about is that although production begins for influenza vaccines in February, as they make the bulk vaccines, which they then, and since we typically have four different two As and two Bs in our multivalent flu vaccines, by the time they're actually formulated together, it's later on in the spring. And so hopefully when we merge them together in late spring, early summer, that would allow for a combination vaccine. So it's not quite as bad as having to be ready in February. So I don't want to give anyone the wrong impression.

**Dr. Bailey:** Well, I want to wrap up, there were a lot of questions, understandably, about pediatric vaccines. And especially regarding the youngest age group, six months to five years of age. Lots of concern and questions about why it's taking so long, the delay in authorization of why you're not meeting until the end of June. Tell me why it's taking so long and when do you expect we'll have decisions. There are a lot of anxious parents out there.

**Dr. Marks:** So there are a combination of things. First of all, we won't wait till the end of June if we get to our review sooner. We'll move things up as much as we can. So that I've committed. And I've committed to Congress actually on that as well. But importantly, I think one of the things that was a little challenging here is that there are a couple things. First of all, this is a more complex submission than some of the previous submissions, because we're not dealing with just one variant, we're dealing with multiple variants over time that we have to interpret the data in light of. Additionally, we're dealing with a population that we look at. We look at the safety always very carefully, but for the youngest children, we are really even under a stronger microscope, but just as another aside, unfortunately, the hype about this started last February when we thought we were going to take it to an Advisory Committee then.

It's continued, and there's been a lot of noise. And so it feels longer than it's actually been, because we have to have a complete file before we can actually start to do our formal ... we can start some of the work, but we can't do some of the formal analyses. And that hasn't happened until very recently and is still ... You'll probably hear from each of the sponsors when they fully complete their submissions. So we get it. And although we put dates out there so that people knew the latest that we might get there, we will potentially move things up if we can... because we also see what's something you noticed as well, that in the setting of increasing cases, that's leading people's anxiety to rise.

**Dr. Bailey:** Last question is going to be about the grave concern that many have about injury from the vaccines, the potential for that in this very young age group and the perception that the risk of getting a COVID vaccine when you're very young is much greater than the risk of getting COVID. Can you

quickly address that and help allay people's fears?

**Dr. Marks:** So we've gotten a lot of letters that say, well, that 99.95 of kids that get COVID do just fine with it. Unfortunately, if you're one of the several hundred parents who's had children under the age of five die from COVID-19, that's no consolation. And we don't accept that for our other infectious diseases that come across. We wouldn't accept that for influenza. We don't want to, even though we have to sometimes. We shouldn't accept it. And so we need to apply the same standards we would for other infectious diseases like influenza to COVID-19 to protect our children. I don't have any concern that these vaccines have been used in so many individuals in low enough age ranges now that I think we can be confident in their safety.

I don't think we can be confident in telling parents it's not going to change the genetic makeup of their children, which is a very common thing that seems to be spreading. That's just wildly untrue types of rumors circulating. So we need to try to help people understand that when we say these are authorized, they will be safe and effective. And the benefit risk here, even though COVID is not that common in terms of severe disease, it's frequent enough around the country right now that when it affects millions of kids, hundreds of deaths are just not ... We don't consider that acceptable in any way, shape or form.

**Dr. Bailey:** Thank you. Well, I'm going to wrap things up, and to all of you on our webinar today, thank you so much for joining us. I want to express my sincere thanks to Dr. Marks for once again lending his expertise and guiding this critically important discussion. And I'm going to raise a point of personal privilege. Dr. Marks, I'd like to congratulate you earlier this year, you were awarded the AMA award for outstanding public service, and we congratulate you on that. We have additional webinars in the work, so we'll certainly keep you apprised of future dates, topics, and events. Until then, we thank you for all of your wonderful questions. We wish you good health today and in the months ahead. Thank you.

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