Physician leaders discuss COVID-19 booster shots and pediatric vaccines

On Nov. 18, 2021, the AMA hosted the latest webinar in the "COVID-19: What physicians need to know" series.

Hosted by AMA physician leaders, each installment of this COVID-19 webinar series aims to gain fact-based insights from the nation’s highest-ranking subject matter experts working to protect the health of the public, particularly during the COVID-19 pandemic.

Peter Marks, MD, PhD, director of the Center for Biologics Evaluation and Research at the Food and Drug Administration (FDA), joins Susan R. Bailey, MD, immediate past president of the AMA, to discuss the data and recommendations for Pfizer, Moderna and Janssen booster shots. Additionally, Dr. Marks walks through the safety and efficacy data supporting the recent authorization of the Pfizer pediatric vaccine for 5- to 11-year-old children.

Host

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

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 important issues in health care. I'm Dr. Susan Bailey, immediate past president of the American Medical Association. In today's webinar, we'll
discuss COVID-19 booster shots and pediatric vaccines, so that we're better able to counsel our patients, address their questions and concerns, and, ultimately, boost vaccine confidence. To do so, we must provide accurate and credible information, which we'll learn more about today.

This afternoon, we've invited one of the leading voices on this topic to answer your questions and share the most up-to-date information on the effectiveness of booster shots and pediatric vaccines.

Today marks our ninth live webinar on COVID in our “What Physicians Need to Know” series. Our previous sessions covered the FDA vaccine review process, vaccine development, vaccine safety and delivery and confronting vaccine misinformation. During those webinars, we featured experts from the FDA and the CDC to explore proposed solutions and the road ahead. If you weren't able to join us for those sessions, they're still accessible on our website and that information will be shared in the chat, so you'll have access to that invaluable information and those insights. Or you can simply visit our main AMA page, ama-assn.org, and search for COVID-19 webinars.

For nearly two years, our country has been battling this deadly pandemic. As of this month, we've lost 762,000 lives in the U.S. to COVID-19 and more than five million lives around the world. Data from the CDC indicates that those who are unvaccinated are at the greatest risk of contracting COVID-19 or dying from the virus. But there is encouraging news. Based on the most recent estimates, about 70% of American adults and 59% of all Americans are fully vaccinated. And about 1.3 million vaccine doses are still being administered each day. Also encouraging is that more than 96% of physicians have become vaccinated against COVID-19 to not only protect ourselves and our loved ones, but serve as an example to our patients.

The AMA fully supports the overwhelming scientific evidence that shows vaccines and boosters are among the most effective and safest interventions to prevent serious illness, hospitalization and death. As an immunologist, I can tell you that physicians play an important 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 booster development process, the scientific rigor involved, and how their effectiveness will help combat and one day defeat COVID-19. This is the basis of today's webinar.

Joining us today is our good friend, Dr. Peter Marks. Dr. Marks has been featured in three previous AMA webinars on COVID-19, at least. He's director of the Food and Drug Administration Center for Biologics Evaluation and Research. As of September, Dr. Marks assumed the lead role as 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 boosters and pediatric 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 reliability of boosters and pediatric vaccines. So now, please join me in welcoming Dr. Marks.

Dr. Marks: Thanks very much for having me again today. I’m very grateful that you’re willing to have me. So I will tell you about boosters and pediatric COVID-19 vaccines, both of which are currently top of mind, and we’ll have lots of time for questions, I think.

The next slide, please. So, give you a brief update on where things stand with vaccine development in a minute or two; talk about the Pfizer pediatric data, I’ll just review the 12- to 15-year-old data so that you can see it in comparison to the 5- to 11-year-old data; talk about boosters for the immunocompromised, for the general population; and then talk a little bit about further areas for vaccine development.

Have the next slide, please. So right now, we have the three authorized or approved vaccines in the United States, the two mRNA vaccines from Pfizer, BioNTech and Moderna, the Pfizer being the only licensed vaccine in the United States at this time for individuals over 18 years of age, sorry, 16 years of age. I’m sorry about that. And the Moderna, which has an emergency use authorization for individuals 18 years of age and up, the same is true of the Janssen adenoviral vector vaccine, the single dose Janssen vaccine.

Now, there are a couple of other vaccines that are kicking around in development. The AstraZeneca-Oxford vaccine, which has been used very extensively globally, is something that has been studied in the United States and we anticipate that we may see that coming towards FDA at some point. And then there are two protein subunit vaccines that are relatively advanced in development, one from Novavax and the other from Sanofi-Translate Bio, and those are coming along through phase three trials, either completed or in progress towards FDA. So, we may see a protein subunit vaccine in the not-too-distant-future in the new year.

And then the next slide. So ... the Pfizer approval on August 23 occurred because we actually had the biologics license application, we had six month follow-up data on more than 12,000 people, and we were able to review the normal data that we would review for any biologics license application on a relatively large clinical trial. This approval, though done in record time of under 100 days since its submission, was one in which no corners were cut and actually there were probably more eyes on this review than on most.

If I have the next slide, let’s move into the adolescents. So just to recall, the Pfizer dose for adolescents is the same as the adult dose, the schedule is the same as the adult dose. So 12- to 15-year olds get a 30 microgram dose. The clinical trial that they did in 2,260 people, ages 12 to 15, and they compared those individuals to people from the clinical trial that was done in the 16- to 25-year-olds. That was the original clinical trial and looked at a cross section here. You can see that the cross
section of enrollment, it's perhaps not absolutely as good as it was in the 16 to 25 or the older trial, but not bad.

If I have the next slide. If you see the younger children, 5- to 11-year-olds, instead of being a one to one randomization, the trial was a two to one randomization. And they, based on a dose finding study, received a 10 microgram dose, that is 1/3 the adult dose was given in this age range. Again, cross section of individuals about 20% of the 5- to 11-year-olds had some comorbidity.

The next slide. The adolescent immune responses, as you've heard before, were excellent. Geometric mean titer ratios of 1.76, indicating really quite excellent effectiveness in terms of immunogenicity in this population. The next slide. Now that's with a 30 microgram dose. The 10 microgram dose in children really matched up very nicely to the 16- to 25-year-olds in terms of the geometric mean titer ratio of 1.04. And I just remember this for a moment when we come to the safety profile that I'll show in a minute.

Have the next slide, please. So the adolescent efficacy was excellent, no cases in the 1,000 or so vaccinated individuals, 16 in the saline placebo individuals. Just to remember, this study was done before Delta. If I have the next slide. The pediatric efficacy though in the 5- to 11-year-olds was done during Delta. And there was the dose difference, and so, there were three eye cases in the 1,300 or so 5- to 11-year-olds versus 16 in the 663 5- to 11-year-olds who were treated with the saline placebo. Vaccine effectiveness here when you do the math is 90.7%, not bad in the era of Delta.

And if I have the next slide, please. The adolescents had a safety profile in terms of injection site pain, fatigue, et cetera, that was very similar to the adults. The next slide. The younger children who were treated with the 10 microgram dose had a somewhat better profile in terms of the fatigue and flu-like symptoms, still a fair amount of injection side pain, but if you can go back one slide, you'll see that the placebo in the 12- to 15-year-olds, and you come back forward one slide, the placebo group in the 5- to 11-year-olds had a very similar number of events. And so we don't think they were under-capturing events here. So we think this could represent somewhat of a more favorable safety profile, but we'll just see with time as we do more safety surveillance.

The next slide. So in terms of observed safety signals, we continue to watch very closely. In the pediatric age range, I just wanted to put this slide here so I'd remember to say that for myocarditis and pericarditis, we continue to monitor very closely. There is this concern that there does seem to be a peak in males in the ages of 16 to 17 that risk of myocarditis seems to extend up into the approximately 30- to 40-year age range although it tails off at the older ages. In the 16- to 17-year-olds, risk in males probably somewhere on the order of one in 10,000. The good news is those events have generally been mild, 98% of them have been associated with a mean hospital stay of one day. And the most common medicines given during that hospital stay, from CDC's review of that, have been non-steroidal inflammatories or acetaminophen. So not something we want to have happen, but thankfully not the type of immune mediated myocarditis that one can see with certain other vaccines.
like the smallpox vaccine.

We will continue to watch closely here. We’re a little optimistic in the 5- to 11-year-old age range that we may not see myocarditis the same way we’re seeing it in the 16- and 17-year-olds and up, and that’s because the current thinking here is that this is possibly a cytokine mediated event, an inflammatory mediated event, an inflammatory mediated event, that is probably happening in males because there’s some interaction there with androgenic steroids. It’s a working hypothesis. We’ll see if additional work makes that a reality or not in terms of a scientific theory. Go ahead for the next slide, please. Just to mention, obviously, we have the authorization now for vaccines in the immunocompromised, this third doses, and these are for 12 and up for the Pfizer, and 18 and up for the Moderna vaccine. In general, though, just to make sure, I just want to point this out that with the mRNA vaccines, those with diabetes seem to respond quite well and there doesn’t seem to be any difference between the response in people with diabetes compared to the rest of the population.

On the other hand, those with hematologic malignancies or solid organ transplants often don’t respond so well, in particularly solid organ transplant recipients and those receiving similar immunosuppressants to that which solid organ transplants receive. They can have reduced responses. So there, even when you boost, you should be aware that the rates of protection do not get up to the range usually that we see with those who don’t have immunocompromise. Can I have the next slide, please? I already mentioned this, that we have the third dose authorized after at least 28 days. To the next slide, please. So, boosters to the general population are all the rage, and some of you are probably listening to me sitting in states which are already boosting the entire or general population. Stay tuned here because there is a lot of action happening.

I wish I could tell you more about that, but a lot moving in this area. And I think the concern here is that with the waning of protection, particularly in the setting of Delta variant, there is concern that particularly the oldest of the population, and then even tailing back perhaps even to some of the younger members of the population who were vaccinated 10 months ago, may not have sufficient immunity to protect them against Delta variant. And then there's evidence coming out of various states that, that probably is the case and that's very recent over the past few weeks. So, the additional vaccine dose may provide more durable immunity. And besides preventing hospitalization and death, we need to make sure that we try to also prevent some of the serious complications of COVID-19 such as long COVID, which can still occur in vaccinated individuals.

There was originally some hope that if you were vaccinated, you could not get long COVID, but unfortunately we now know that vaccination helps. It probably reduces by 50% your chance of getting long COVID if you get COVID-19, but it's not perfect. We also want to try to avoid disrupting critical services, particularly if we start to have another significant wave. It'd be good if boosters would help prevent having a lot of illness due to COVID-19. And finally, this is not something that we label things for in the FDA, but it's something we have to consider as public health professionals, that if many
people start having vaccine breakthroughs, essentially vaccine failures, they tend to lose confidence in the vaccine, and in this case, it may not turn out that the issue here is that this is a true booster in the sense of the vaccine given according to its appropriate schedule is waning in protection.

It may just be that we don't have the schedule right first out of the gate. And it's understandable because we didn't have time to study these like we would normal vaccines. And that's why we know, for instance, for the recombinant zoster vaccine or recombinant hepatitis vaccines, they're given at zero and six months or zero in six months for some of these vaccines. It may just be that this is something that we'll learn, and ultimately the primary series for COVID-19 or its successor will be a regimen that's separated in part by more months.

Can I have the next slide, please? The boosters though, I will tell you, the little bit of data I can tell you about boosters is public from Pfizer, that they did do a clinical booster study in 10,000 subjects from the original trial who were randomized one-to-one to receive a booster dose or a placebo a median of 11 months after they were first vaccinated, age spectrum, median age about 53 but across the age spectrum. Can I have the next slide?

Bottom line is, boosting did restore relative vaccine efficacy to about 95% to 96% and that was measured at a meeting of two and a half months. And we're hoping, as these individuals are followed for a longer period of time, that maybe we'll see more durable immunity here than after the first two doses. Next slide? We also, as you're aware, have the mix and match. I just mention that because ... I think we're pretty comfortable seeing these vaccines mixed if necessary and matched if necessary. Although, in general, I think the going feeling is, if you've got something, stick with it. Next slide. We won't know for a long time what the most optimal combination is. And the current state of play is that we're recommending boosters for everyone over age 65, anyone who got Janssen vaccine, and if you're 18 to 64 and you're not in a state that's already declared otherwise. You'd be getting a booster if you had a comorbid condition or you were at high risk because of occupation or where you're living.

Next slide. The final thing I'll just end with is, where are we potentially going? Well, there are more vaccines in development, but the most common thing that people are asking about now is, what about vaccines for younger children? And there are some special considerations. One has to further dose deescalate as one goes down below age five. We want to make sure the safety right here and we want to make sure the benefit risk considerations are right. Unfortunately, there have been deaths of children in this age range and so we do need to get through this development process. And the various companies are working through trials, and we expect them to come to FDA by early 2022 and we'll obviously work very rapidly, as rapidly as we can, to evaluate those data. But, obviously, we'll do it with the same care that we have the other authorizations. So, I think I've gotten to all I wanted to tell you today and we can go from there.

Dr. Bailey: Well, thank you. Very interesting data and I have lots of questions, so I know we'll be able to fill this time. We got a lot of questions from physicians who are very concerned about the wisdom of
vaccinating the pediatric population. Since children, although we know they do get COVID-19, they get long COVID and they die from COVID, there’s some concern that the risk-benefit analysis for vaccination of the pediatric population really hasn't been established yet. Can you talk about this a little more?

**Dr. Marks:** I think we were pretty careful to spend a lot of time on this because people are concerned obviously about risk-benefit. We were already getting back data in the 12- to 15-year-old age range so I think, in the adolescent population, I think we’re pretty convinced that the risk-benefit is in favor of vaccinating adolescents. And I think we’re pretty convinced, or we wouldn’t have authorized it, that in the 5- to 11-year-old population that it makes sense to vaccinate these children too and that's because you reduce the number of cases of COVID-19. You reduce the number of infections, reduce the number of cases diagnosed, you reduce the number of hospitalizations very significantly. And if what I've hypothesized turns out to be true, and we'll know pretty soon and the reason why we'll know pretty soon is because if you look at the numbers of 5- to 11-year-olds who have been vaccinated now, we'll know in about a month after they get their second doses if we are correct.

Our assumption is that we should see a lower risk of myocarditis there. Even modeling that same risk of myocarditis that we're seeing in the older adolescents, the benefit risks still came out in favor of vaccination because hospitalization from COVID-19 and the hospitalizations from myocarditis are not the same. The median hospitalization for a child or an adolescent or a young adult with myocarditis is one day and, as I said, acetaminophen or a nonsteroidal anti-inflammatory. So yes, they probably get an EKG. Yes, they get some troponin levels drawn. The median hospitalization, non-ICU hospitalization, is four days for COVID-19 for a child, and four days in the hospital for a child is actually a somewhat traumatic experience. And unfortunately, there is a subset and thankfully it's not large, but there is a subset that get MISC and end up in ICUs, and those are longer stays.

So, when you do this risk-benefit, I think, as we see it, it's still clearly in favor of having children vaccinated. My guess is it will be helpful once we have data on one million, two million children in the 5- to 11-year age range to show that what I've just told you about our thoughts about myocarditis pan out, but even if I'm wrong and the numbers are more like the adolescents, we're still comfortable that we've made the correct risk-benefit decision.

**Dr. Bailey:** Okay. So if the theory that it might be a cytokine effect that's being magnified by androgenic steroids, then it's a better idea to vaccinate boys young than it is to wait until they're after puberty. Will pediatric populations eventually need boosters? I know you don't have a crystal ball, but there were a lot of concerns about that. And parents are very concerned. I tell you, I've gotten more calls since the pediatric vaccine was approved than I did about the adult vaccines. So, what do we tell parents about their concerns about long-term safety, the data on pediatric vaccines, because most pediatric vaccines have a number of years of study once they're licensed?
**Dr. Marks:** This is normal. I think parents, it is normal to be concerned for your child. And this is a very unusual situation, the likes of which probably were not seen since years and years ago when we first had the introduction of some of the other vaccines that transform our lives now. People don't understand what it was like to have measles and to see children die from measles pneumonitis, or measles encephalitis. Why? Because we don't see it, if we're lucky, because we're so well vaccinated here, and a number of other illnesses. So, I know it's hard for people, but essentially there have been a lot of eyes on these vaccines. They have a lot of experience. We have a lot of experience with them. We're watching them very closely. I think ... you as a parent, obviously, have to feel comfortable with this, but I would encourage people to get the information that they need. Ask their provider. And the most helpful thing is just tell the provider what your concerns are, because in some cases, parents, their biggest concern, and I've been doing a lot of outreach lately, and in some cases parents' biggest concerns is they've seen on the internet that these vaccines cause infertility in the children, and that really scares them. And that sometimes they're just afraid to ask that even because they know it came from a source that might be a little sketch but it's still enough. It's like this weird place, they trust it enough to put doubt but they don't have a ... they need to feel comfortable being able to ask those questions, so I would have an inviting environment. No question is to me an outrageous question when it comes to helping move someone closer here, so I'd encourage parents to ask about this. There are going to be some parents who are early adopters and some who are late adopters, our goal is to try to move the curve as fast as we can over.

**Dr. Bailey:** So all children are being recommended to get the COVID-19 vaccine, not just those that have a fragile health status, but are there any contraindications in the pediatric population? Obviously an allergic reaction to one of the ingredients is one, but are there any children who shouldn't get vaccinated?

**Dr. Marks:** Really, really good question. Obviously, if a child has a known allergy to any of the vaccine components, if you have a child who's been getting medications and they've ever had an allergy to polyethylene glycol or polysorbate, I think you'd want to speak with an allergist and not just go to some clinic because that would be obviously something that would be an issue. I think obviously there are children who probably don't need to be vaccinated only because it's not going to work, which is if a child is undergoing cancer chemotherapy for a hematological malignancy, there's no point because they're not going to generate an immune response and it's better to know that you probably have to use some other method of dealing with COVID-19, either post-exposure, or prophylaxis, or hopefully in the future, pre-exposure prophylaxis. But there's not a lot of exceptions to this. I'm doing the old head scratch, trying to think of one.

**Dr. Bailey:** Well, what about children, or adults for that matter, that are on long-term steroids for various conditions or even short bursts of steroids where we'll tell them, "Well, why don't you wait until after that's done to at least get your flu shot?" How does that impact the COVID vaccine?
**Dr. Marks:** The short-term bursts of steroids don't seem to matter a lot. And the reason why I think we probably have a good answer for that is because people have already studied by giving cyclophosphamide and other ... I'm a hematologist oncologist by training, oncologists have looked at what happens there and if you give the ... as long as you're not doing it on the same day, separating out by a week or two, the vaccine is probably good. So probably might be ideal not to give it the same day you gave a big ... of Solu-Medrol. But I guess you can't avoid it, you can't avoid it, but it might be best to try to avoid not doing them right on top of each other. But probably you'd still get a reasonable immune response.

The people who are not responding, and because even moderately, people on moderate immunosuppressants still respond, it's the people with solid tumors who are on multiple immunosuppressants, cyclosporine and something else, mycophenolate, or tacrolimus and mycophenolate, those are what we're seeing very poor responses.

**Dr. Bailey:** So along those lines, boosters in the immunodeficient population, I know that you touched on that in the slides. First of all, for those of us in practice and we're monitoring antibody responses for our immunocompromised individuals, is there a cutoff level where we can say, "Yes, you're immune," "No, you're not immune"? Do we just keep immunizing immunocompromised individuals until we get them up to a certain level? And how long do we wait between shots?

**Dr. Marks:** This is a real challenge because the studies ... if you have access to a research-grade neutralization assay then perhaps you can follow people with immunocompromised based on the levels. But you don't want to just use a run-of-the-mill assay to try to determine if somebody is immune or not because they're just not sensitive.

There is one authorized test for getting titers, but that's not been calibrated for the vaccine so you can't even use that. So if you want to know, really, you need to be at a place that actually has a research test that you can use. And then if people are above a certain titer in a pseudo virus or a viral neutralization assay, you could probably say, "Okay, this is good enough." Right now, what we're saying is, in general, it looks like after a third dose, somewhere between 40 and 60% of people moved from being poor responders over to being better responders. But it's certainly not 100%.

**Dr. Bailey:** So no recommendation for fourth doses as of yet—

**Dr. Marks:** Not yet. Not yet.

**Dr. Bailey:** As far as the mix and match situation, are immunocompromised individuals, benefits of the mixing and matching, can it be assumed that, well, they might have a better response to the J&J vaccine if they got the mRNA vaccine first or vice versa?
Dr. Marks: So great, great question. Hopefully, clinical research will show that. I mean, there's some data coming out of Europe where it's not one of our vaccines that we have, it's AstraZeneca matched with one of the mRNA vaccines that seem to show that mixing and matching an adenoviral vector and an mRNA vaccine gave very nice responses. But there are a lot of variables here because in some cases there was longer distance between the time between the first and second doses. So, I think when we see well-controlled trials here, we'll all feel better about saying this.

Right now, though, the good news is homologous boosting seems to do really quite well and trying to eek out that little bit of extra ... I know people saw the booster data and they saw some of the, "Oh, I want to get this combination," but the answer is, for right now, I don't think we can say that any one is better than another. Just getting the correct booster regimen is the right thing to do.

Dr. Bailey: Do we have any information about the risk of myocarditis after the booster shot?

Dr. Marks: Great question. We do have some, and that's because Israel, which has a population of about seven and a half million, seven million, seven and a half million, they've vaccinated enough of their population and they've now boosted enough of their population and followed those individuals for more than a month. And so, the data suggests that in 18, it's actually 16- to 40-year-old men, the rate of myocarditis after a third dose much more resembles the rate after a first dose than it does the second dose. That's leading in part to supporting this theory that maybe what's going on when you give the two doses up front is that there's some stacking of a cytokine phenomena or an inflammatory phenomena that's going on there. But we'll have more data soon.

But it does look like the good news is at least the third doses do not seem to have quite the same ... it's probably at least, if you ... the Israeli data are actually online, you can look at them, the data looks like it's a little bit higher than first doses in 18- to 40-year-olds. It's actually lower with boosters than first doses and second doses in older individuals, so we'll just have to see where all this goes.

Dr. Bailey: So it sounds like you're saying that even if, let's say, a young man has had myocarditis from one of the doses you would still recommend that he get a booster?

Dr. Marks: Yes, I would have that individual talk with their physician, okay?

Dr. Bailey: Okay.

Dr. Marks: Because I think we want to understand what kind of myocarditis did they ... I mean, the problem with the word myocarditis is it's like many, many medical terms, there's a lot in myocarditis. Myocarditis could be a troponin of two and a nonspecific T wave change that goes away in a day. Alternatively, myocarditis could be somebody in an ICU on dobutamine drip.
So, if the person had myocarditis in that latter scenario, I might think twice. On the other hand, if it was the person in the former, I might. And there are actually some case reports coming out of Israel where they have vaccinated people who've had myocarditis with a third dose and they don't seem to have recurrent myocarditis, but it's not enough data. I would consider it anecdotal experience rather than real data yet.

Dr. Bailey: Well, what about giving them the J&J vaccine, assuming that they got mRNA previously?

Dr. Marks: Be my guest. A great solution to that problem. Exactly.

Dr. Bailey: Well, what about boosters in patients that have had their first two vaccines but have had breakthrough infections? What about boosters in that population? Do they need one and what's the timing?

Dr. Marks: Really great question. I think if someone had a breakthrough infection I would probably use the same guidance that we say after if somebody had COVID after their first dose, which probably would wait about 30 days afterwards. Because probably it's during that immediate period there's probably high enough antibody titers from the infection and there's also possibly some inflammation going on, probably just best to wait about 30 days. That's what CDC recommended, and I think it still makes sense.

Dr. Bailey: We've had a number of questions about natural immunity versus vaccine immunity. What do we know now, especially with the Delta variant, about the differences between natural immunity from acquired infection versus vaccine-induced immunity?

Dr. Marks: Really nice question because this is one of the most ... there are some people who are just all over this ... and they're essentially adamant that natural infection is good or better than vaccination. And I think the issue here is this isn't quite like the measles. We're dealing with a different kind of infection.

Coronavirus and measles ... I mean, unfortunately viruses aren't all alike. Measles is a virus that doesn't change a whole lot and coronavirus, on the other hand, is one that does change a lot. And coronaviruses, if you look at the family, they seem to not be the greatest at making us have durable immune responses. Why? Because we get the common cold over it again, sometimes from slightly different members of the coronavirus family.

So what I'm getting at is that what we know is that at least right now, if you had COVID-19, particularly if you had it months and months ago, it's probably a good idea to get vaccinated because Delta variant is not what you saw months and months ago. And we do know that at least in data now, at least I'm aware of, I think two solid publications, and there're probably more, where the effect of vaccination seemed to be about roughly twice as good as natural infection in terms of conveying protection. So,
seems like a good idea, and I mean probably a good idea always, but it's probably a really good idea if you say, "Well, I got infected back in March but I think I'm immune," because this is not like getting measles back in March. If you had measles back in March, you're probably going to be immune now, but that's not the true thing for COVID-19.

Dr. Bailey: Okay. More about boosters. The Moderna booster is half the dose of the regular dose, but the Pfizer booster is the same dose. And also had questions about why was the pediatric dose one third of the adult dose? Can you give us a little information about how all those decision were made?

Dr. Marks: We can start with Moderna. Moderna decided to use ... they looked at the immunogenicity of 50 and 100 micrograms. Honestly, the difference between 50 and 100 micrograms with Moderna, even in their initial trial, was not massive. And when they went back to boost, they felt that the potential benefits of a lower dose in terms of side effects, and their stated reason as well was that they could make the number of booster doses go further, was to use this.

Their booster essentially increases the geometric mean titer ratio by about 1.8 fold, which is reasonable. Pfizer's full dose booster increases by about 3.3 fold. But since Pfizer, you start off at a lower level, at the end of the day, people getting 50 of Moderna and 100 of Pfizer are probably getting boosted to about the same, roughly. We didn't do the head to heads, but they're getting boosted roughly to a same level in terms of protection. So, they decided to do that based on their studies. They showed reasonable immunogenicity in their booster study that met our criteria, so that 50 micrograms was authorized.

Now for the kids, why go down in dose? Well, there are various vaccines that have pediatric doses and adult doses, and that's because of the difference in size between an adult and a child. And also, because of the difference in the immune systems between the two, as we get older, we may not respond as well. And frankly, we know that even from some of the early work that was done for the mRNA vaccines that doses that have been used do create a slightly lower titer in older folks than they do in younger folks. It happens to be good enough against COVID-19.

And so, the youngest people are likely to have even a better response. And you could see that, that 10 microgram dose, they did the work. They did a careful trial. They did a dose ranging study and they showed, and they used a dose where they got to an approximate immune response that was similar to an adult immune response. And so, that's what they saw and that's what they decided to use. And to the extent that there is less ... and we'll only know this with time, so take this as preliminary, with a grain of salt.

If you have kids it's just nicer if you can reduce the incidence of fever and malaise in your kids by a third or a half, by using that slightly lower dose, and you're not taking a significant hit in terms of effectiveness, it's probably a good thing because more parents will be happy giving their children the vaccine.
After all, the reason why we moved from a whole cell kill pertussis vaccine to the acellular pertussis was because of the reactogenicity. Parents didn't like kids with fevers. In retrospect, the older whole cell kill vaccine was probably a better vaccine in terms of giving you durable immunity. So, we do care about these things when we develop vaccines. So, probably something to be said for getting the dose in the sweet spot where you've got enough protection, but you keep the side effects minimized.

**Dr. Bailey:** Very good. That's not the main reason that we're giving the lower dose is for fewer side effects, it's just a pleasant ...

**Dr. Marks:** No, it's a pleasant ... no, that's why I'm telling you, this is just something we'll find out over time. The major reason why we're doing it is it's the right thing to do because that geometric mean titer ratio of one is spot on, it's where you want to be. It means that you're getting an immune response in a child that's similar to what you'd see in adult.

**Dr. Bailey:** Great. Well, I'm going to shift gears here a little bit in the time that we've got left. Many physicians are being asked to write vaccine exemptions. None of my patients have asked me, probably because they know me too well, but is there anybody who you think might, other than someone who was allergic to one of the ingredients, and if that's the case, I recommend you send them to a good allergist. Are there any genuine contraindications? Is there any reason we should ever write a vaccine exemption?

**Dr. Marks:** Well, I find it pretty hard to see, because I treat bleeding disorder patients and even people, you can get an intramuscular injection with hemophilia. So, there's not ... I'm trying to think of things that would be a problem with the injection itself. It's really hard for me. What we do see is people who are vaccine hesitant for various reasons.

I think if somebody asks you for that vaccine exemption, it's probably a good time to ask them, what are their concerns about being vaccinated? What is it that's really getting at them? Some people may not tell you. It's a challenge for us, particularly because at this point in time, as we see another wave of COVID-19 coming along, it's pretty clear that those locations around the globe that have gotten really high vaccination rates are going to come out of this sooner rather than later. And you can see what happened in Israel, for instance. When they got their vaccination rates and their boosters up, they're basically able to reopen their societies.

**Dr. Bailey:** What are the expectations? I know that there've got to be more variants out there. I know that there have been some like Lambda and Mu that have been described, but they all seemed to respond to the vaccine. Do we know anything about other variants and how well the vaccine protects against them?

**Dr. Marks:** Great question. There's work going on right now to look at the AY.4.2 variant Delta, and we'll see how well that does. As these variants come up, various neutralization assays are done with
plasma from vaccinated individuals to see how well these may protect. There are a few scary variants that have come up. The great news about those is that for whatever reason, those scary variants, some of them are not very well transmissible. The thing about Delta that's made it a nasty thing is it's pretty virulent, but it's also, it's just so much more transmissible. So, it's managed to essentially out-compete everything else.

And in fact, if you look across the globe, when Delta came in, it's amazing how fast Delta spread across populations. I mean, it was really, I mean, it just ... as a biologist, it's just breathtaking how fast in various countries within two months they went from no Delta to nearly all Delta. So, quite impressive.

**Dr. Bailey:** Right now, I remember us talking about this last year that if new variants do come along, we don't have to start from scratch, and with all the clinical trials, we can make those adjustments much more quickly.

**Dr. Marks:** Yeah. I actually think we're in a really good place with the technologies we have, because if a new variant came along, it would probably be a matter of very few months before we would be mass-producing a vaccine against that variant. So, that would mean, yes, we would have to boost people again or immunize people against that variant. I think we are, now, in a much better place to be ready to do that because we have these vaccine platforms set up and because the spike protein, if it changes, it can be easily then shifted back into the vaccine manufacturing process, not just for the mRNA, but for other vaccines as well. We won't have to go back to square one and do large scale clinical trials.

**Dr. Bailey:** That's a relief. Here's one that I didn't ask before. Back to boosters. Do we have booster data in pregnant women? What are our recommendations there?

**Dr. Marks:** We don't have booster data in pregnant women yet, but my guess is that, given how we think about COVID-19 and pregnancy, I would probably say if you are due for a booster, I would go get it. Because the general thing in pregnancy has been COVID-19 is definitely worse than these boosters or the vaccine itself. Obstetricians and gynecologists, originally, that were hesitant in the first trimester, now it's basically, pregnancy and lactation, it's reasonable to take these vaccines. And we have the data now from thousands of pregnant women that are not showing any adverse issues. We also have the data from women who have gotten COVID-19 and have lost pregnancies and had significant morbidity. So, I think the benefit risk here is clearly in favor of vaccination.

**Dr. Bailey:** I think that pregnancy of that women who are pregnant are relatively immunocompromised, and that's how they're able to have a successful pregnancy and that we need to really, really take care of women that are pregnant.
So, I think I have pretty well run through all of my questions. To all of you on our webinar today, thank you again for joining us. And thank you, Dr. Marks, for once again lending your expertise to this discussion. I really feel much better prepared to discuss boosters with my patients and to answer all those pediatric vaccine questions and calls that I need to make before the weekend.

We do have additional webinars in the works, so please stay tuned to learn about future dates, topics and events. But until then, we thank you for all of your wonderful questions. We wish you good health today and in the months ahead. Take care.

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