

## FDA Director Peter Marks, MD, PhD, discusses COVID-19 vaccine safety & delivery

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On Jan. 29, 2021, the AMA hosted the fifth webinar in the "COVID-19: What physicians need to know" series.

### About the event

Hosted by AMA physician leaders, each installment of this 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.

The AMA welcomed back Dr. Marks to discuss the road ahead now that vaccines are available. The webinar explored safety and efficacy data, and provided the latest updates on the distribution process.

### Speakers

- Susan R. Bailey, MD, AMA President
- Peter Marks, MD, PhD, Director of the Center for Biologics Evaluation and Research at the FDA

### Transcript

**Dr. Bailey:** Good afternoon, everyone. Greetings and thanks for joining us again today for the latest in our "What Physicians Need to Know" series about COVID-19 and other important issues on health care.

I'm Dr. Susan Bailey, president of the American Medical Association. In today's webinar, we will dive a little deeper into the conversation about COVID-19 vaccine safety and efficacy as states begin to scale up their vaccine rollout plans.

Our previous webinars featured representatives from the Food and Drug Administration and the CDC to explore other aspects of COVID-19 vaccine development, allocation and distribution. If you weren't able to join us for those sessions, I encourage you to watch replays of the videos, which are available for free on our website. You can find them at [ama-assn.org/covid-19-webinars](https://ama-assn.org/covid-19-webinars) or you can simply visit our main page and search for COVID-19 webinars.

Nearly a year into our collective response to COVID-19, the pandemic is more deadly and widespread than ever. Over 25 million people in the United States have become infected, and those are just the cases that have been officially recorded. It's unlikely we will ever know the true number of those infected by this virus. Sadly, this month, we reached yet another grim milestone with over 400,000 deaths in the United States to COVID-19 less than a year after registering the first known death in this pandemic, and we're rapidly approaching half a million deaths in the U.S.

Despite the hope that comes with two safe and effective vaccines for COVID-19 that are in the early stages of distribution, the case numbers continue to exhaust our hospitals and ICUs and put physicians and other health care workers at serious risk. They are truly the heroes of this moment, but so, too, are the scientists and researchers who have been working and continue to work around the clock to develop safe and effective vaccines in record time.

As we start this new year with new leadership in the White House and a new strategy for responding to COVID-19, there is some optimism about what the next few months will bring. Now, as a specialist in allergy and clinical immunology, I can tell you that I know that physicians play an incredibly important role as vaccine ambassadors for our patients. So, to help make sure that patients have their questions answered and their concerns addressed, we need to first make sure that physicians, nurses and other health care workers have deep understanding of the accelerated vaccine process, the scientific rigor that got us here and how the available vaccines performed in clinical trials are performing in the real world. So, that's the basis of today's webinar.

To help us understand the science and data behind the vaccines now in use and those on the way, we invited our friend Dr. Peter Marks back to talk to us about the vaccine process and answer questions you may have. Dr. Marks, who we featured in our initial webinar back in October and again in December, is Director of the Food and Drug Administration Center for Biologics Evaluation and Research. He's board certified in internal medicine, hematology and medical oncology. He 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 role as director, he and his team are tasked with ensuring that the COVID-19 vaccines that ultimately reach the public are both safe and effective and that they have undergone a rigorous evidence-based and transparent process. Today, Dr. Marks will lead us on a deeper dive into the safety and efficacy of the authorized vaccines and to answer your questions about things like dosing schedules, new variants and additional vaccine candidates on the horizon.

We hope this information not only provides you with a greater understanding of the science behind these remarkable vaccines, but also gives you the information you need to assure your patients about the safety and reliability of the vaccines once they become available to them. So, now, please join me in welcoming Dr. Peter Marks.

**Dr. Marks:** Thanks very much. So, I'm going to spend about 20 minutes going through a slide presentation and then after that, we will be going ahead and having questions and answers. Full screen mode, there we go. Thanks very much. Thanks to you for everything that you do every day. Thanks for listening in today.

FDA's role for vaccines is across the entire life cycle of vaccines, from the time they're actually conceived to when they're deployed. We are involved early on in helping to select strains of vaccines when that's appropriate, and we make reference panels and reference products in our laboratories. We are involved with lot release, making sure that the quality of the manufacturing is appropriate for vaccines, and we do what most people think we do is evaluate vaccine safety and efficacy and applications that are submitted to us.

Once vaccines are out on the market, we collaborate with others, including the Centers for Disease Control and Prevention, to make sure that there's good post-market surveillance, so that we can detect any adverse events that may be occurring after deployment into large numbers of individuals.

We also over the past several years have had an increased role in trying to advance vaccine technology, learning how to make vaccines in a more efficient manner or in a more effective manner.

We do all of that, ultimately, with the hope of helping to ensure public confidence in vaccines because, ultimately, all of what we do is for naught if people aren't willing to take the vaccines that come through the development process.

So, one of the things that's probably important to be able to describe to people is the fact that the process that was used to develop these COVID-19 vaccines, was not a process that was rushed or cut corners. It was a process in which white space was taken out of the vaccine development process.

Usually, vaccine development is something that is done very sequentially in order to de-risk the process. The companies that make these products don't make a ton of money making them compared to other products. So, in the development process, they tend to de-risk the process by going in orderly

manner from phase one development to phase two development to phase three development, and each time, there's usually a matter of months to even years that go between those stages.

They don't usually start to scale up their manufacturing processes until they're pretty sure they're going to have a successful vaccine. That means that that process goes over the span of years. So, one way that you could simply accelerate vaccine development that was just taken advantage of for these vaccines is that rather than having phase one, then two, then three, some of these studies were done as phase one, two, three studies or they were phase one, two, and then phase two, three studies. That sped up the process.

Additionally, platforms that were already known to be relatively quick to use such as the mRNA platforms were taken advantage of. So, early on, that helped get things into the clinics. So, by taking away some of the white space, that helped, and then a very important part of this was that the manufacturing scale up started very early on relative to one it would normally scale up. So, the idea here is that if there was a positive result at the end, there would be a fair amount of vaccine around to deploy.

Now, we can argue whether there was enough to deploy given the need here, but, certainly, having millions of doses is better than having no doses when a vaccine comes through.

Then one other thing I should say about this, about helping to shape downtime is that, normally, we like to have six months or a year of follow up at least for a vaccine, but we're able to take advantage of the fact that we have developed very good post-market surveillance systems. So, that was something that was taken advantage of as well. I'll tell you more about that.

So, we have at FDA, we put out two guidance documents, one in June and the other in October, to help the manufacturers of vaccines and to help the public understand what we were expecting from the development of vaccines for COVID-19. The first laid out our general expectations, and the second on emergency use authorization, explained the process in more detail for those vaccines that would be submitted.

We made it pretty clear, particularly in the emergency use authorization guidance, that any vaccine would have to demonstrate clear and compelling efficacy in a large well-designed phase three clinical trial if it was going to get the authorization that would have to have careful evaluation of the quality, safety, and as I've noted, the efficacy that we would take these vaccines to public advisory committee meetings, and that they would all need to have enhanced post-deployment surveillance.

All of this is to make sure that people understood that the standard for an emergency use authorization, which was really developed for times like these, when one has a biologic threat that was not present before, you need to use products that might not have been through the full approval process. It was developed, really, originally with the thinking of therapeutic products in mind, where

you were giving them to sick people, but for vaccines that are given very often to healthy people, we really felt that it was necessary to articulate the fact that the standard we were using used the emergency use authorization as a floor.

The standard for emergency use authorization is a product maybe effective and its known and potential benefits have to outweigh its known and potential risks. So, what we did by articulating this in our guidance was to say that, "Look, that's the floor," but we're operating at a much higher level, much closer to the ceiling of what would constitute a full approval by saying that we would have to have clear and compelling efficacy. As you'll see, the clinical trials programs for these vaccines were every bit as large as most of the clinical trial programs for our approved vaccines.

The safety monitoring that we're talking about after deployment is actually an overlapping set of safety systems by both the Centers for Disease Control and by FDA working together, and we're working actually in conjunction with other federal and non-federal partners. So, we have passive monitoring systems, which include the Vaccine Adverse Event Reporting System. That's the typical MedWatch forms that people fill out. That can be filled out by providers or patients or even family members. We go through those reports.

The CDC has a text-based monitoring system, the V-safe system, that is an opt-in system whereby when you go to get vaccinated, you can opt in for several days after you're vaccinated, and then on a weekly basis, and then on a several monthly basis a text message is sent to report certain adverse events. If certain adverse events are reported, CDC actually reaches out and telephones people live back to get more information.

So, those are the passive monitoring systems, but there's also active monitoring because we want to be able to find certain things that might be very rare that we wouldn't be able to sort through otherwise. So, CDC has the Vaccine Safety Datalink and the Clinical Immunization Safety Assessment systems. Those cover millions of people, but can do so in near real-time. At FDA, we have the Sentinel/BEST system, which now covers hundreds of millions of lives. It allows us to use claims data, which in some cases is linked to electronic health record data, so that we can monitor outcomes of interest. In the case of the COVID-19 vaccines, we're monitoring about 15 safety outcomes of interest.

That is very helpful because things that we might be concerned about that we wouldn't have the normal amount of time of a year, perhaps, we can continue to look for over the course if some signal were to emerge.

Now, just to move in to the vaccine candidates, we've authorized two mRNA vaccine candidates, which I'll tell you a bit more about, the Pfizer-BioNTech mRNA vaccine and the Moderna mRNA vaccine. Those emergency use authorizations were granted in December. There are two non-replicating viral vector vaccines, which you probably have heard about, one by Astra Zeneca-Oxford. That's the chimpanzee adenoviral vector vaccine that has been deployed in certain places, and

recently has a positive opinion from the European health authorities, and that is currently in a phase three trial in the United States.

The Janssen vaccine, which is a human adenovirus 26 vector vaccine. People may have heard or this may be news for them today. They've released a press release about having a positive study from phase three for that vaccine, which is a one-dose vaccine. All of the other vaccines I've told you about so far are two-dose vaccines. The Janssen vaccine is a one-dose vaccine. FDA has not yet reviewed those data. So, I can't comment a lot more, and I'll do my best to answer questions because we haven't actually reviewed the data. Although, we're aware of the same press releases that you probably are.

Then there's protein subunit vaccines, one from Novavax and one from Sanofi. The Novavax is actually in phase three trials. The Sanofi is in phase two. The Novavax actually issued a press release earlier this week about their phase two, three program in the United Kingdom and in South Africa, again, reporting some positive results, which, again, we have not reviewed yet at FDA, but I think the nice thing to be able to say here is that there is a portfolio of vaccines here that does seem to bring good efficacy here. Certainly, the mRNA vaccines I'm about to tell you about appear to be very effective vaccines with reasonable safety profiles and the other vaccines here are in various stages of evaluation.

So, I'm just going to tell you a little bit more about the Pfizer-BioNTech and Moderna vaccines. Some people, their eyes glaze over when we talk about what's in a vaccine, but the reason why I put up this is so that you can understand that these two vaccines are very similar. They both contain modified mRNAs. They contain lipids. The lipids are slightly different. They both have in common the fact, though, that part of them are derived versions of polyethylene glycol 2000. I'll come back to that a little later. I can see Dr. Bailey, probably her ears will perk up there because that may have to do with some of the allergic issues that might come up.

Then we have the buffers that go into these. The difference from a practical standpoint for these vaccines is actually storage becomes something of an issue. The Pfizer-BioNTech vaccine has six doses in relatively small volume. They're 0.3 mL doses, generally should be given with a lower dead volume syringe. The vaccine has to be stored in an ultra-cold freezer, -60 to -80 Centigrade.

The Moderna vaccine has 10 doses, half mil doses in their vial. It's not reconstituted like the Pfizer vaccine is. It's just drawn from the vial, and those can be stored in conventional freezers. So, similar in many ways, different storage conditions, different doses in terms of the volumes.

In terms of the trials, I told you that these were respectably sized trials and our average trial for a newly authorized vaccine, the average size is in the 20,000 to 30,000 range in terms of the number of individuals who would actually receive the vaccine. When you look at this, these were randomized trials one-to-one, and the Pfizer-BioNTech trials, about 43,500 some odd individuals, Moderna, 30,400

some odd individual. You can see that the people enrolled in these trials, we encouraged enrollment of a cross-section of individuals from the United States.

Indeed, the manufacturers both really listened to this. So, we had about 10%; we see there's about 10% people who characterize themselves as Black or African-American, 20%-25% or so Latinx and about 20%-25% people over the age of 65. Those are nicely sized datasets. You can see that in both of these trials you had enough people in the vaccine arm who are over age 65 that we have a dataset of over 3,000 individuals, which is what we like to see in a group to really feel like we're getting a good idea of the safety profile.

You probably all have heard about the efficacy. You have to be under a rock if you hadn't heard about that at this point in the United States. These vaccines both have 94%-95% efficacy. They both do a very good job of preventing severe COVID-19.

I think the one thing I'll point out here is that both of them, the efficacy, though it may tail off a little bit in older individuals, it doesn't tail off much. That's really something that is at least to me when I think about these mRNA vaccines is one of the things I'm still very interested in better understanding because many of our vaccines, as one gets over age 55, the efficacy goes down pretty significantly, and that's not the case here. Very nice to have a little bit of luck here that these vaccines were really very efficacious across the board pretty much. So, a nice thing to see.

I should say that they also are associated with some side effects. The good news is most of the side effects have been mild to moderate. The mild to moderate side effects tend to be worse after the second injection, and you can do yourself a favor as a provider by telling people that because it's sometimes helpful for them to know that after the second dose, they may have a higher chance of seeing some of the side effects.

Injection site pain, pretty common. The other common things are very much flu-like types of symptom: fatigue, myalgias, arthralgias, chills, fever. Again, it tends to happen more after the second dose than the first dose. Interestingly here, it tends to happen less, somewhat less in older individuals for both of the vaccines than in younger individuals. So, younger individuals tend to experience more in these symptoms.

I've done pretty well so far by advising people who have asked me, "The day after you get your second dose, you might not want to have a full schedule plan or make that day the day you're going to run the half marathon," socially distant, of course. People have generally thanked me for that. Then if they have nothing happen, they're very grateful for that. So, no one generally had said they're upset at me for canceling part of their virtual day.

One of the things that did emerge after these vaccines were deployed were very shortly within days after being deployed, the United Kingdom reported some severe allergic reactions. This was a great

initial test of our surveillance systems, our international collaboration and our ability to sort things out because very rapidly, international regulators got together. We put together the data from various countries as the vaccine continued to roll out.

We now have a pretty good handle that both of the Pfizer-BioNTech and the Moderna vaccines are associated with it. An incidence of severe allergic reaction is probably in the order of 100 in 100,000 to one in 200,000 individuals who receive them. That's why we have the warning that they should not be administered to people who have a known history of a severe allergic reaction to the vaccine or any component. If somebody's had a severe reaction to one of these vaccines, they should not get it again unless they're under the care and it's done with caution of an allergist immunologist. We are not recommending that. Really, for anyone who's getting these vaccines, it needs to be where there's appropriate medical treatment available to manage severe allergic reactions.

This is also a good check on things. We didn't see when these allergic reactions first happened. We were really concerned how did we miss these. Now, in retrospect, now that we know that they're happening in one in 100,000 to one in 200,000, it's not surprising that even when you combine both of these clinical trial populations, you're still dealing with a small number relative to the incidence of this. So, you probably just didn't have enough people in the clinical trials to see this.

Anyway, this is a good example. We now have very good surveillance ongoing for this. The CDC and FDA actually look at the number of allergic reactions on a daily basis, and we sort through these, and we'll continue to do similar.

One of the final things I just want to spend two or three minutes on is it has not escaped us that vaccine confidence is very much something that over the past years has drifted downward. There were various circumstances, which I will not go in to now, but you're free to imagine that it might have happened over the past two years that probably reduced vaccine confidence more.

Some of that has to do with our social media, et cetera, but we decided that because it's so important that we help reestablish vaccine confidence, and not just for COVID-19 vaccines, for influenza vaccine, and for measles vaccine, tetanus, I can go on and on, these are vaccines all of our vaccines are things that have probably next to figuring out that you needed to keep your water supply and septic systems separate, they are probably the greatest advances of 20th century medicine. It's a shame to have people not understand that and take advantage of that.

So, we actually asked one of the partners of FDA. There's a foundation that was created to help support the FDA's mission, Reagan-Udall Foundation. We asked them to help us by conducting listening sessions about COVID-19 vaccine concerns. These were really unstructured sessions. The idea was, ... they were structured, but they weren't directed with questions of X, Y or Z. They were really listening sessions rather than directing questions and answers like we sometimes do.



We really learned a tremendous amount from these, including what messages appear to be most effective, and who are the most important messengers. It was interesting because many of us thought that there would be local leaders, clergy people, but it turns out that the top messengers were doctors, nurses, pharmacists and health experts. So, you make a difference when you speak to patients about vaccines.

It turned out that the top five messages that we learned included the important fact that, really, sharing information about COVID-19 vaccines from the FDA is something that FDA is doing, so that people can see the evidence for themselves. The other message was that only safe and effective COVID-19 vaccines that have been rigorously tested on tens of thousands of volunteers will be approved or authorized; that scientists and career public health officials, not politicians or their appointees will decide when a COVID-19 vaccine is safe, effective and ready for public use.

Importantly, ones that really went over very well were by getting a COVID-19 vaccine, you're protecting yourself, your children, parents, grandparents and other loved ones. You can see why that might resonate with people. Then COVID-19 vaccine development is moving faster than normal because the medical and scientific community have made it their highest priority not because any steps have been skipped. So, all of those things have been very helpful.

We also, out of this, had some recommendations about giving the message. They included that it really turned out that a lot of focus needs to be how you get the message out there. It was very clear that show, don't tell. What was meant by that is people wanted to know, "Did you get the vaccine, Dr. Marks?" I'd have to be honest. I haven't yet because I'm not a front-line health care worker, but I will soon, I hope.

Tailor messages to the audience. Explain the vaccine development process. This is why I'm very grateful for you watching this and learning a little bit more about what was done here. Really, come to people and try to understand their concerns. Meet people where they are. Acknowledge people's concerns and fears. It's okay to be a little unnerved by this. It's okay. Consistently repeat the core themes. Focus on the "persuadables." That was an important piece because there are some people who we're not going to convince to take these vaccines, but there are people who having their questions answered will be willing to take the vaccines, and it's just getting over the anxiety that comes with something unfamiliar. Then be ready to respond to vocal critics. We're here at FDA to help you with that as we can, and CDC is there as well.

So, really, I'll just conclude by saying it's really important to understand that here we've had vaccine development timeline shortened without compromising safety and efficacy. We're trying to do this in as transparent a manner as we can because we think that if people see what's going on here, see that we are trying to share in an open, truthful way, that will make a difference. We'll continue to do this as we try to address some of the additional challenges that are emerging, including these variants that are now coming up. So, I'll stop there.

**Dr. Bailey:** Thank you, Dr. Marks. That was so interesting. As usual, I really do appreciate your presentation. We, again, received over a hundred questions. Very good questions for this webinar. Don't worry. I've condensed them down. Some of the questions were related to the distribution of vaccines, which is really outside of FDA's purview. So, we won't be able to cover those questions here, and I know that those are very pressing and important questions now about vaccine availability.

We got a whole bunch of questions about the new variants that have been discovered, the B117, B1135, and others. What do we know? We've heard that there is some efficacy against these new variants. Can you tell us what the state of knowledge is today about efficacy against the new variants?

**Dr. Marks:** Right. So, we know that at least there's work been done in vitro, in other words, laboratory work done that seems to indicate that the mRNA vaccines should maintain efficacy against the most of these variants, and particularly the one that people are quite concerned about, the B1351 variant, which is also the 501V2 variant. They go by two different names. Same variant, two different names, but we don't have the clinical data there yet.

This determination was based on the titers that would take to neutralize and what's achieved with the mRNA vaccines. I know that the manufacturers of both vaccines are working very actively on getting additional data here because this is obviously really top of mind for us at this point, and understanding these variants and others are very important.

**Dr. Bailey:** Especially the mRNA vaccines, those were able to be ramped up so quickly once we had the RNA sequences that I would hope that new vaccines that would be more effective against new variants would also be able to be ramped up pretty quickly. Is that true?

**Dr. Marks:** Great question. So, I think the issue I think you're asking if I understand is if we were to need, if somehow the variants were to get far enough off that we felt that the current vaccine was not effective, could we shift over to a same vaccine platform but a different sequence to address or a different viral vector to address that? Is that correct, Dr. Bailey? That's what you're asking?

**Dr. Bailey:** Yes.

**Dr. Marks:** So, we have been trying to think about this for a while because I think what we learned very early on as we started to see variants emerge was there was the potential that this could happen, right? Because of that, we're not going to get caught off guard. So, we started to put together our thoughts about what this might look like and we basically now, I think, are in the process of working with our industrial and federal partners to essentially put together a playbook for how this will look if we need to switch over to a different sequence.

With the mRNA, it's very convenient because, basically, all you do is change a computer program and the synthetic for the synthesizing portion of this, and you can change the vaccine, but the question is,

what do we need from the FDA perspective to feel comfortable having that deployed. What I can say is we're working on finalizing what that will look like, but I can tell you what it will not require.

It will not require another clinical trial for efficacy. It will probably require some small clinical trials to just make sure that the vaccines are immunogenic, that they produce an immune response against these new variants, and that we can understand whether the protection against that new variant, does it only cover the new variant or does it also cover the old variant? Because that will help us understand whether we can have something that's a strain change that is, do we change to one new vaccine or are we going to have to have multivalent vaccines where we have the new strain or the new variant and the original or wild type virus also covered ...

**Dr. Bailey:** ... which is what you do with the flu vaccines. So, you won't have to go through a completely new clinical trial. Will the authorization process be the same? It sounds like it will be very condensed.

**Dr. Marks:** We would assume to have a pretty streamlined process. It's possible we'll go to our advisory committee to make sure that they're comfortable with the data the first time. My guess is the first, if we have to do this, the first times we'll do it we're going to probably try to understand how to do it, and it may be that with time, we will need even less data, but the first couple of times we do it, we'll probably require some clinical study, but as I say, not with an efficacy endpoint, but more likely with an immune response endpoint. It probably will not be very, very large studies. They'll probably be studies involving a few hundreds of people, not thousands of people, again, to make sure that when we deploy something, it's doing what it says it is and also so that we can understand some of these features of the immune response.

So, we would intend to try to be pretty nimble with this, as nimble as one can be when you're dealing with a large infrastructure like vaccine manufacturing, so that we get these variants covered as quickly as possible because it is clear that they can spread pretty quickly.

**Dr. Bailey:** Yes. Now, you mentioned this morning's press release about the Johnson & Johnson safety and efficacy data on their single-dose vaccine claiming around 70-72% efficacy. Of course, the media is already saying, "Oh, my gosh! This is a failure compared to 95% efficacy for Pfizer and Moderna." I know you can't say a whole lot specifically about that and the Novavax vaccine, but we're going to get questions from our patients about it. So, how do we discuss this with our patients in terms of comparing 70% versus 90% efficacy? How do we reassure our patients? How do we recommend which vaccine they should get as the new vaccines come online?

**Dr. Marks:** So, first of all, I would say that as we hear these vaccine figures, let's all take a deep breath first because these are company reports, not verified data by FDA, and there sometimes are changes that occur after we go through and look at case adjudications and other things. That said, I do think that if there is a difference here, this will come out through our advisory committee meeting

process. Any of these vaccines will come if they're submitted for emergency use authorization, and I expect they will be.

They will go to a public advisory committee. There will be a discussion of the various data, the various subsets of individuals who seem to benefit more and benefit less. I think it's too early to be able to really tell your patients, "Well, this is a failure or a success," because we need as many tools as we can here. So, it may turn out that these vaccines provide us with a very good vaccine in a certain population of patients.

Right now, if you had a population of patients that could get very nicely 75 or 80% efficacy with any vaccine, I'm not talking about any specific one that was mentioned today, but with a single-dose vaccine, you might say, "Well, if we can get people with very minimal side effects and get people vaccinated quickly, that might be a good tool to have if it can help bring us towards herd immunity more quickly.

So, I think, and I'll offer this up. When you're in a situation like we are now with so much uncertainty and with so much need to get this pandemic under control, I think we can't ignore any tool in the tool chest. So, we'll have to think about these, look at them. I think we will have to do our best to try to make sure that we find the populations that benefit the most from each of these vaccines and deploy them in a very thoughtful manner.

I do think we have to be very cautious for vaccine confidence not to let anyone think that they are getting an inferior vaccine for some reason just because they're who they are. We need to make sure that people feel that they're making a choice, perhaps, that if you have very good data in a given population, they may choose that, "Well, I can get this earlier and get it right now. It doesn't seem to be associated with this many side effects, and I'm willing to take five, 10," or whatever your individual risk profile is, "percent less chance that it protects me."

So, I think that's the kind of conversations that we'll have to be having. It's just a little early. As I say, unfortunately, my crystal ball today is at the repair shop, so I can't tell you exactly how those discussions are going to end up after our advisory committee meeting.

**Dr. Bailey:** Do you have another advisory committee meeting scheduled yet for the next batch of vaccines?

**Dr. Marks:** Stay tuned. It's probably in the not too distant future. We'll see that happening.

**Dr. Bailey:** Okay. Now, so at what point will the FDA stop using the EUA process for new vaccines? When is it no longer an emergency? At what point will the FDA demand that a currently available vaccine actually be the comparator group for new vaccines that are coming on as opposed to placebo?

**Dr. Marks:** Great set of questions. Let me unpack them a little bit. For right now, until we have approved vaccines that ones where we received a biologics license application and that includes, when a biologics license application is submitted, it includes having all the manufacturing information, which includes having multiple lots of the vaccine manufactured and characterized and all the data wrapped up. Until we have that, we will probably continue to do these emergency use authorizations, bringing them to advisory committees to the extent that these trials can be conducted without an active comparator.

At this point, I think we would continue to see that. It seems like, at least this first wave, is managing to make its way through without having an active comparator, but it's something where we have really encouraged the manufacturers that after they have their emergency use authorization, they should soon after start to think about their biologics license application. That is something that they are going to be submitting probably, for each of the ones that have come through so far, probably within the next few months we expect. So, we'll expect to be seeing those, and then we'll get those vaccines, then they will be approved.

That will again, there again, my crystal ball, I don't have it. That might change the development of future vaccines, but I can't say exactly how. Emergency use authorization is a great tool that we've had in a public health emergency because it did help us really make very broadly available the vaccines without the need for written informed consent, which is what we have to do if it was some big expanded access program or the need for the vaccines to get all the way through the approval process, which, really, it's quite a lot of requirements because we generally want our vaccines to make it through a rigorous process.

So, it's a nice way of having the relatively rigorous process, but not have to go through all of the administrative paperwork, and some of the requirements that might have slowed things down.

**Dr. Bailey:** Thank you. Lots of question about vaccines and pregnant women or women that are breastfeeding. We know the WHO announced this week they weren't recommending the Moderna vaccine for pregnant women. CDC recommendation seemed to be different. Can you discuss the use of these vaccines in pregnant women, breastfeeding women and/or women that are just of childbearing age that are thinking about becoming pregnant in the near future?

**Dr. Marks:** Let me start with the easiest one. If you're a woman of childbearing age and thinking about becoming pregnant, I would say it's absolutely reasonable to get the vaccine. That's what they did in the clinical trials. They deliberately enrolled women who were not pregnant, who are of childbearing age, who might get pregnant. So, I think it's a very simple one. There's no evidence, granted small numbers, but nothing striking in an adverse way from those trials.

For pregnant women, the press gets very excited about the differences between the WHO and what we have from CDC. Remember that WHO, they have a different constituency than we do in the United

States. I think we in the United States have health care providers like you who are listening, who are capable of having benefit risk discussions with individuals that are relatively deep and meaningful.

I think if I had a pregnant woman in the office, I think I would have a conversation about the risks of COVID-19 when you were pregnant versus the unknown as of yet risk of an mRNA vaccine, which so far has not been associated with any adverse effects on pregnancy that we know of.

Now, there are hundreds of women now that are entered into a registry and will be following them. CDC will be following them. So, I think it's a provider-patient conversation there and risk to benefit. Some people have a more difficult time living with uncertainty not knowing that's absolutely fine, but for those who feel the risk that COVID-19 presents to a pregnancy, they may decide that it's very reasonable to take the vaccine.

Lactation has been another one that's been a little challenging to deal with. These vaccines, just so we understand the science here, these are injected into muscle. The mRNA leads to the expression of protein on cells probably for somewhere in the order of a day, day and a half at most. The antigens are presented to the immune system, where they go to work. It's not like these mRNAs are largely circulating.

So, there has been some suggestion that this is, again, if a woman is lactating, a benefit risk. Some people have suggested that through a day or two after the vaccine to have prepared by pumping breast milk and then after two or three days, after the vaccines, it's reasonable to go back and start nursing again.

I don't have a specific recommendation from FDA on this, but, again, I think the most important thing is that conversation between patient and provider because, again, when we don't have evidence, some people, that bond of breastfeeding is so important to them that it's very disturbing to have that interrupted, and they're willing to take the risk. Others might say, "Well, okay." So, I think it is a luxury that we have here.

So, again, I don't think ... WHO has to deal with situations that have to be a little bit more automatic in nature. Whereas I think we have the luxury of having wonderful health care providers that can have these conversations.

**Dr. Bailey:** Great. Lots of questions about dosing schedules. Should the dosing schedule be increased because we don't have enough vaccines? Is there any data to support that this is okay? If you missed your second dose, how much protection do you have from the first dose? So, lots of questions. Just go ahead.

**Dr. Marks:** Great questions. I'll start here. So, ideally, people will get these vaccines according to the dosage and schedule that they should. When you have something that gives you a 95% success rate,

you want to try to get that and you don't want to try to mess with success. You also want to try to do things right on the first try. So, ideally, you get it right, but in life, things happen.

FDA, I think, and CDC are in complete agreement that if the second dose has to be delayed and it's delayed, we feel like up to six weeks is okay if it has to be. Ideally, it's not., okay? We would not recommend ever intentionally delaying that second dose., okay? In the event that it is, it's not unreasonable to give that second dose if the person comes back at six weeks instead of at four weeks, but we would not recommend, as I've heard that some people that because of the scarcity have we heard of scheduling at six weeks out, we would certainly not recommend intentionally doing that because although we have some data on people in that range, that's not how the clinical studies were done.

Additionally, it may not be providing that individual with the additional protection that they might have from getting vaccinated on schedule. So, it is a challenge because of the vaccine supply issues, but, hopefully, those are going to be getting better. We do not think that it's a good idea at all to do mix and match vaccines. So, we would try absolutely our best not to have to mix and match the vaccines. Really, the only time that you might end up that way is if somebody had absolutely no idea, you couldn't get records of what they got the first time, then you're going to end up giving them whatever vaccines happens to be there the second time, but, really, we shouldn't be mixing and matching these because, again, it's a little bit ... I know I'm starting to sound grandmotherly. Why mess with success? You've got something that's really working well there.

I think most of us were really incredibly happy to see, I mean, beyond some of our highest expectation that we've seen these really high efficacy of the mRNA vaccines. We should try to keep them up there by giving them appropriately. This concept of maybe I'll give a half dose or maybe I'll give just one dose, that's probably not a good idea. This one-dose idea for these mRNA vaccines is really one that personally disturbs me because people have looked at some of the data and said, "Oh, well, one dose seems to give some protection."

We don't know the duration of that protection because in the clinical trials, nearly everyone in the Pfizer trial and over 90% of the people in the Moderna trial got two doses of the vaccine at the end of the day. So, we know in the middle how people did with one vaccine, but when you see in the long run, we don't know how long the duration of protection will be if people just get one vaccine. So, in summary, dose according to the schedule.

Dr. Bailey: Stick to the schedule. All right. Well, in the few minutes that we have left, I want to dig in a little bit into allergic reactions, of course, being that's what I do every day, and just side effects in general. The polyethylene glycol aspect, I personally have had a patient that had anaphylaxis to a bowel prep for a colonoscopy. Based on history, I just diagnosed him with a PEG allergy. I wish I could remember his name because it was before we had our EMR, and he's probably not a good candidate for these initial vaccines.

Another ingredient, the polysorbate 80, I think, has also been implicated. Now, my understanding is, is that PEG is not a common ingredient in vaccines, typically, but polysorbate 80 is fairly common in vaccines, as well as other injectable drugs. So, tell us a little bit whatever you can about this.

**Dr. Marks:** That is a great question. We still don't know what the actual allergen is, and we actually have studies going on both the government and in academics to try to understand whether it is polyethylene glycol, also known as PEG or whether it's polysorbate. They're both in that same category of molecules that we tend to see these allergic reactions. The intriguing reason for polyethylene glycol is it's common in both of these vaccines.

You're right. It's not in a ton of parenteral, but it is in some parenteral drugs. You're right. Polysorbate is in some vaccines. It turns out, though, that polyethylene glycol exposure, we get it now through laxatives. Besides bowel preps, there's some now more common over-the-counter laxatives, which people get exposed. It turns out, and we're not really sure about the significance of this and this was pointed out to me, many cosmetics, particularly facial cosmetics, the thickeners, the things that tend to get rid of wrinkles, the thing that makes them thick is, one of the things that helps them is polyethylene glycol derivatives.

So, that may also be a source of exposure. It's very intriguing to us because although allergic reactions tend to be more common in women, in this particular case, when we go through the database, for this case, they are overwhelmingly occurring in women. So, it's intriguing. We don't know, but it's just one of those intriguing things. So, lots of work getting done. They're actually looking for IgE to the polyethylene glycol in various studies.

**Dr. Bailey:** Look forward to hearing about that. A physician reported that he experienced Bell's palsy after his first dose. We know there were reports of that, especially with the Pfizer-BioNTech vaccine. Should he get the second dose? What are the thoughts on that?

**Dr. Marks:** That's a discussion to be had with his provider. My guess is it would also depend on whether the Bell's palsy is completely resolved, but I think it would probably be a discussion with the provider. We don't have any evidence yet that there is an increased incidence of Bell's palsy with these vaccines over what we see in general. So, it's very hard to make a firm recommendation. So, I think that has to be an individual patient-provider discussion of benefit risk because, as I say, this is one of these things that were querying our databases for. We're actually globally pulling the data to try to get as much information as we can. So far, nothing seems like it's so distinctly different from the baseline rates for Bell's palsy to make us think that that's related to the administration of the vaccine.

**Dr. Bailey:** Well, thank you. Other questions that I would love to ask, but, unfortunately, we have run out of time. Dr. Marks, I want to thank you again. I want to thank our audience again for joining us today. Dr. Marks, your expertise continues to be amazing. What amazes me is our first webinar was only three months ago, the day after the EUA process for vaccines had been released. Now, here we



are with two having been given to millions of people and looking at their third and fourth vaccines. So, it's just mind boggling, the amount of work that the FDA has done. Thank you. We're so grateful.

For our audience, we have additional webinars in the works. So, we'll, of course, keep you apprised to future dates, topics and events. Until then, thank you for all your wonderful questions. I'm sorry I couldn't get to all of them. We wish you good health today and in the months ahead. Thank you for joining us.

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