

## Peter Marks, MD, PhD, discusses Johnson & Johnson COVID-19 vaccine pause

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On April 13, 2021, the AMA hosted the seventh webinar in the "COVID-19: What physicians need to know" series.

Hosted by AMA physician leaders, each installment of the 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 AMA President Susan R. Bailey to discuss the most up-to-date vaccine information, including the recently paused distribution of the Johnson & Johnson vaccine.

Questions submitted by attendees are also addressed.

### 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, I'm Dr. Susan Bailey, president of the American Medical Association. I thank you for joining us today for the latest in our popular "What Physicians Need to Know" webinar series. Of course, this morning we received news that the U.S. has called for an immediate pause in administering the Johnson & Johnson single shot coronavirus vaccine over concerns about a rare blood clotting disorder that has affected at least six women. According to news reports, one woman has died as a result of the blood clotting, and another is hospitalized in critical condition.

Now, of course, it should be noted that nearly seven million people in the United States have already received the Johnson & Johnson shot, according to the CDC, and that another nine million doses of the vaccine have already been shipped to states. These events are occurring at an anxious moment in our fight against COVID-19. Distribution of the other authorized vaccines is still occurring at a remarkable pace, and yet there are growing concerns about surges of the disease in Michigan and the upper Midwest, and a possible fourth wave of this pandemic. We also continue to face barriers to widespread vaccine adoption in all communities.

Yet still we know safe and effective vaccines are the most important tool we have to defeat this virus. Joining me once again today to talk about these developments and to answer our questions about the Johnson & Johnson shot, and all of the vaccines currently in use and maybe some that are coming, is Dr. Peter Marks, director of the FDA's Center for Biologics Evaluation and Research. He's also board certified in internal medicine, hematology and medical oncology, 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. He is the perfect person to help us make sense of today's news and to talk about the safety and efficacy of all FDA authorized vaccines for COVID-19. Please join me in welcoming Dr. Peter Marks.

**Dr. Marks:** Thanks so much, Dr. Bailey. I'm going to spend about the first 15 minutes going through some slides. I will probably ad-lib a little bit because I made these slides before the events of the past 24 hours. But then I will have plenty of time I believe for questions. I am going to go ahead and share my screen here. I'll talk a little bit about accelerating vaccine development, talk about the three emergency use authorized vaccines, and we'll touch upon the events of the past 24 hours and talk about COVID-19 variants and vaccines and how we may address those.

As everyone knows, we have moved traditional vaccine development forward and ended up with COVID-19 vaccines in under a year, not by cutting any corners, but by removing dead space, white space, between phases of vaccine development and by doing something that was not generally done in order to save resources, and that is to manufacture at risk while clinical studies were undergoing. What we've been lucky enough to have to date are three emergency use authorized vaccines that have been developed into very large clinical trials, trials of a normal size that we would expect for a vaccine development program that have essentially met our standards for emergency use authorization, and which have met standards which are nearing those for a Biologics License Application.

When we think about vaccine development, we really think about things very carefully, manufacturing quality, and some may be aware that there have been issues and concerns raised about that. But this is something FDA takes very, very seriously. It's really at the heart of why the precursor to the Center

for Biologics was established, and obviously we look at the safety efficacy and very importantly, when we have to put forward vaccines in a relatively rapid manner like we did this time, we use post-marketing surveillance. We do that for all that vaccines, but it takes on a particular relevance here when we don't have as long safety follow up for the vaccines.

What we've done to accelerate the process of vaccine development has included giving a manufacturer's clear guidance on what we expect. We've been allowing them to have regular conversations with us. We've had this collapsing of clinical trials into either a phase one, two to three, or a phase one, two, three. They've been manufacturing product at risk, as I've noted before, and we've been using the emergency use authorization pathway to facilitate availability. We made clear what we were doing in two guidance documents, one put out in June of 2020, the other in October 2020, and they outline what our expectations are here, for both efficacy and for safety follow up.

One of the key part of this has been we've wanted to see vaccines that would have at least 50% efficacy over placebo, with a lower bound of the 95% confidence interval that was greater than 30%. What that actually did was it drove the size of the trials to be relatively large studies involving usually 15 to 20,000 people in each of the arms. That gives us a very nice safety data set as well as the kind of efficacy information we want to see. We also asked for a minimum median of two months follow up following the final vaccination of a series, and that's because most adverse events with vaccines appear within the first 42 days after vaccination.

We've also said that we would bring all of these new emergency use authorization requests for new vaccine entities to the Vaccines and Related Biologics Advisory Committee meeting, and that has allowed an open discussion of these vaccines. We've also posted the materials and actually our decisional memos to the extent that we have our clinical memos. They're posted in a minimally or unredacted fashion. The whole point here is that in undertaking our emergency use authorization, we kept in mind what we normally do for Biologics License Application, which is normally under the Public Health Service Act and the Federal Food, Drug and Cosmetic Act, we use a standard that there has to be substantial evidence of efficacy from adequate and well-controlled trials.

Now, for an emergency use authorization, we are not required to use that standard. Congress deliberately allowed us some leeway here, because it was known that potentially life-saving medical products might not have that level of evidence, and yet might still bring benefit. So the standard is that products may be effective, and their known potential benefits have to outweigh their known and potential risks. Ultimately, though, because we want the public to have confidence in the vaccines that we deployed, we made the standard here, and it's articulated in our October guidance that the vaccines would have to demonstrate clear and compelling efficacy from large well-designed phase three clinical trials, that there would have to be a careful evaluation of their quality, safety and efficacy, we would have the public advisory committee meeting process, and that we would undertake enhanced post-deployment surveillance.

Now, the Vaccine and Biological Products Advisory Committee has been an important element in this, and I think they've helped us have these open discussions. People may know that there's also another process that takes place after we give something emergency use authorization, which is the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention, then holds a meeting. They will actually hold a meeting tomorrow on one of the safety events that we'll talk about in a few minutes. Let's just quickly go through what we have for COVID-19 vaccines.

Just to be sure that everyone is on the same page, although we oftentimes talk about our COVID-19 vaccines in the United States, which have all of the six that are currently leading in the development process in the United States or against the spike protein, there are other targets on the surface of coronavirus, including the nuclear protein, and one can also make whole killed virus vaccines. Our advanced candidates in the United States include the mRNA vaccines, non-replicating viral vectors, and the protein subunits. We are aware of what's been given emergency use authorization here.

We had not yet issued emergency use authorization for the AstraZeneca-Oxford vaccine, but it is relevant because some of the adverse effects that have been seen in the deployment in Europe and the United Kingdom are potentially relevant for Janssen, as we'll talk about in a little bit. All of these vaccines have been studied in large trials. You can see the total number of patients in these different trials with a randomization that has led to 15 to 20,000 people per arm. They've had a good distribution across different racial and ethnic groups, and including enrolling a fair number of older people.

You'll notice the reason why the Janssen vaccine has a higher percentage of Black or African American individuals because it was conducted in part in South Africa. So they do have some actual clinical data with the South African variant. The vaccine efficacy in phase three, the most important top line message is that for all of these vaccines, they prevented hospitalization and death, about equally well. Now, there were some differences in the primary efficacy against all forms of COVID-19. But between Pfizer-BioNTech and Moderna, they're essentially the same numbers. Obviously, it falls off a bit for Janssen.

But if you look solely at the U.S. population, the number is about 72% to 74% for efficacy. The safety for these vaccines, and this is really relevant, because it's going to be important to understand what normally happens after one gives these vaccines. As you are already probably familiar with, you already know to tell your patients after they get their second dose of an mRNA vaccine, that they're going to probably want to take it easy the next day because you just don't know what's going to happen. I'm going to make a little joke at my family's expense.

I may want to have my son get a mRNA vaccine every night because the first night he actually went to sleep at a reasonable hour and woke up after sleeping a full night, refreshed, was after getting his first vaccine. Don't do that. Don't do that, of course. But let's just get serious here for a moment. The placebo numbers you see here are an aggregate placebo. So they're across different trials,

aggregating the placebo for the patients. It's not a precise correct thing to do. So the statisticians in the audience, please don't get too mad at me. But it's just to give us an idea here that headache is a relatively common thing at baseline, yet it is increased after all of these different vaccines to a modest extent.

Then there are the flu-like symptoms that occur. I'm showing you the second dose symptoms with Pfizer-BioNTech and Moderna compared to the Janssen vaccine. It's important here to note that you are seeing headache and flu-like symptoms after the Janssen vaccine that's over placebo. It's very important to note though that these usually occur with onset 12 to 24 hours after vaccination, and they should be resolving within days afterwards. Now, the safety signal that we'll talk about that was seen from days between days six and 13. The original safety signal ... that we picked up with these vaccines was actually with the mRNA-based vaccines was this issue of anaphylaxis, which has really calmed down.

And I think serves as a paradigm of what can happen when we take appropriate mitigation measures because we were originally having these allergic reactions, and they were quite scary. Now we know how to deal with this. We know how to ask people about whether they've had previous allergic reactions to medications, and particularly to vaccines, we know to have anaphylaxis kits on site, and we know not to wait until someone has full blown anaphylaxis to start to use those management kits. I think now we're at a rate where the number of reports are down at about one and 250,000. So one of these events in about 250,000, and they have generally been very treatable here.

Something that I think is a success of what you can do when you manage properly. I think this is ... I say this as a paradigm because obviously we continue to monitor through passive systems, the VAERS system and active systems, which include both active systems by the CDC such as the Clinical Immunization Safety Assessment, and our own Sentinel/BEST system. The safety signal that was announced today was actually detected through the Vaccine Adverse Event Reporting System, and it became apparent, really only fully apparent, over the past week.

Just to back up for those who may not have been following this, over the past number of weeks, it's been increasingly clear that the AstraZeneca vaccine has been associated with a syndrome of thrombocytopenia associated with rare venous thromboembolism, either cerebral venous sinus thrombosis and/or splanchnic vein thrombosis. That constellation of those two things together are pretty, pretty rare. For all the world, they look like heparin-associated thrombocytopenia, and indeed, it looks like the autoimmune response here is potentially two platelet factor four, and giving heparin actually makes things worse.

We have that under good authority from what happened in Europe, and it's been published now. If one goes to the "New England Journal," either last couple days or looking today's online, you'll see a number of publications, as well as what the recommendations are here for management, which include use of non-heparin alternative anticoagulants, and potentially the administration of immune

globulin. The reason why a pause was recommended today was not just because we just wanted to pause this because we felt that the number of cases was growing out of control, but because we wanted to be able to have time to educate providers to know what to do.

Because of the six cases, there was one death, and one of the individuals who received heparin clearly had complications related to the receipt of heparin. I can't say there could have been more than that. But for right now, I can speak to that, and we want to make sure that providers know what to do. It's also important that providers know what to do in terms of seeing people. So if you see somebody who's just received a vaccine, who has mild to moderate headache, and myalgias, typical flu-like symptoms, that's much less concerning than if you see somebody 10 days later who has a very severe headache or who has symptoms of blood clots or symptoms of petechiae.

There, I would probably say to you that it's really important now if you see somebody with new onset thrombocytopenia, and the thrombocytopenia here is generally pretty profound with platelet counts in the 10 to 25,000 range. Or if you see somebody with a new onset blood clot, particularly in an unusual location, such as cerebral venous sinus thrombosis, splanchnic vein, but probably even pulmonary embolism, one is going to probably want to check for the constellation that one does not have accompanying, either blood clot accompanying thrombocytopenia. In the setting of asking the patient if they have had a recent vaccination, and if the timing is right, you may want to obtain additional studies accordingly.

Our goal here is to try to help educate people. It's also by putting this pause on to try to help ascertain whether there are additional cases that we're not aware of. We know from our European colleagues that when they paused things and put out the word, many of these cases came out of the woodwork, and we would encourage anyone who thinks they've seen this to submit a MedWatch report to the VAERS system because it's very helpful to understand the extent of this. Once we understand this, we believe we'll be able to make appropriate mitigating recommendations, and those will be discussed.

As I noted, the Advisory Committee on Immunization Practices will meet between I think it's 1:30 and 4:30, or 1:00 and 4:00 tomorrow and that can be watched online, after they make their recommendations, and they may decide they need a second meeting. But if they make recommendations, we at FDA will consider their recommendations in the totality of all the evidence that we have about adenoviral vectored vaccines. There is a lot of controversy here because obviously the vaccines are tremendously safe. We are talking, as Dr. Bailey noted, about six events in 6.85 million doses that have been administered.

But when you look at the narrower population of 18- to 48-year-old women who have had these events in the United States, and you look at how many of those have received vaccine overall, one has a higher relative risk for that particular population. We have to actually see if there are mitigation strategies that we'll need to put in place. Obviously, our ultimate goal here is to get as many people vaccinated with a safe and effective vaccine as we can, and to have people have confidence. But we



feel like we have to take action here to make sure we do that in a safe manner. I'm just going to finish up for a couple minutes and then take questions.

Obviously people are worried about the COVID-19 variants. There are a variety of variants. My top line message to you about these variants is that all of them today, in least in the laboratory, seem to be susceptible to the immune response by the currently deployed vaccines. Granted, some of them have a somewhat greater resistance to that neutralization. But one of the rationales for giving both doses of the mRNA vaccines is that when you get one dose, your antibody titers are actually not very high. It's the second dose that gets the very high titers that are capable of neutralizing things like the South African variant.

We are planning on dealing with the issue of whether these vaccines will need to be adapted. We don't know that this is going to have to happen, but we have to be obviously cognizant that it could need to happen. What we've put forth, there's guidance that makes it clear, and to go through a couple slides in a few words. We're not going to require full-blown clinical studies in using a efficacy endpoint. These are going to be immunogenicity studies in several hundred people so that we can understand that the safe to give these variant vaccines and that they give a good immune response against the new variant.

We need to understand how well they retain efficacy about the older variants that are circulating. We also need to make sure that these are safe when they're given to somebody who's never been vaccinated previously, as well as when they're used as a booster to people who've already received vaccination. There is need to make sure that a third COVID-19 vaccine doesn't cause more side effects yet again. Although given the amount of time, that will likely have passed, we're hoping that there's no issue there. There's been a lot of noise about things, and I just leave you with the fact that delaying administration of a second dose is not a good idea.

Single doses of two-dose vaccines probably not a good idea, because once somebody is vaccinated, they change their behavior, and they should be. We'd like to see them protected so they don't take risks when they shouldn't. Half doses of certain vaccines is probably not a good idea. Mix and match of vaccines probably not a good idea. Don't do those things. If you don't have time to do it right, what makes you think you'll have time to do it over? That is a little bit of the precautionary principle that we're using here. There was tremendous consideration, very thoughtful dialogue that went behind this pause.

Everyone knew that there was the potential that we would cause some concern here, and that it could cause a hit, so to speak, to vaccine confidence. On the other hand, the larger concern was if we made some announcement about this did not have a pause, and in a few days collected another dozen or so or 18 cases, including other adverse events, we would really potentially be in a situation where we had not taken the right steps to inform providers and make sure everyone pays attention to this issue. With that, I will stop and look forward to taking questions. Thanks very much.

**Dr Bailey:** Thank you, Dr. Marks. Sounds like my father. If you don't have time to do it right, when are you going to have time to do it over again? We got over 150 pre-submitted questions for this webinar. Obviously we're not going to get to all of them, and those were all questions that were submitted before today. I'm going to ask some questions regarding the Janssen vaccine because obviously that's top of mind. With past webinars, we received a number of questions related to vaccine distribution and that's not the FDA's purview. We will not be discussing vaccine distribution today.

We know there are lots of issues with that. But this is not the place to deal with those questions. The purpose of the pause for the Janssen vaccine, we know that the Advisory Committee on Immunization Practices is going to meet tomorrow afternoon. Presumably, they'll look at this data. What do you think a best-case scenario might be for the pause to be lifted? Basically, the purpose for the pause is really just to review the data. What types of things are they going to be looking at?

**Dr. Marks:** Two things will happen here. The Advisory Committee for Immunization Practices will look at the data, they may make recommendations about what can be done to make sure that people know what to report, and they say that we should warn people or tell people that if they develop certain symptoms after day seven, they should seek medical attention, or they could suggest any number of other things including whether certain populations should avoid this vaccine. They could make that recommendation as well. I don't know whether they'll go there. We'll have to see.

... That will all then go to FDA, and we will then look at that in the totality of the evidence that we have because we have a slight advantage over the ACIP in certain respects because we have IND files of vaccines that are adenoviral vaccines that I can't discuss. But we can be informed about when we look at to make sure that when we make some recommendation, it's the totality of the evidence that will inform us so that we can get back to vaccinating. I think we're all very committed to trying to do this as quickly as possible.

We know that each day that goes by, that's something that's suboptimal. We know that there are plenty of critics out there who said, "Why? It's just a couple of cases. Why don't you just move along?" But I will tell you in the history ... I mean, I'm a student of history to the extent that I know the Cutter incident very well. For those of you who aren't familiar, the Cutter incident is a terrible incident in the history of vaccines when some polio vaccine that was not fully inactivated was deployed and created some terrible complications. I'm aware of what happened with swine flu in 1976, and there have been some others.

We don't, in the United States, have a lot of tolerance for friendly fire. Okay? We know we are fighting a war against COVID-19, and we know that COVID-19 is a devastating foe. But we also know that when our medical countermeasures injure people, we don't have a lot of tolerance for that, and that tends to undermine vaccine confidence. We simply have to do whatever we can to minimize or eliminate issues that might be considered friendly fire. I'm sorry to use that analogy, but I think that is an apt one in this case.



**Dr. Bailey:** Speaking of adenovirus vaccines, the AstraZeneca vaccine, which of course is not available in the United States, but is in use in Europe, and the Janssen vaccine use adenovirus vectors, one chimpanzee, one human, are there other adenovirus vector vaccines that have been in widespread usage in the past, and have there been similar problems associated with them?

**Dr. Marks:** There are adenoviral vector vaccines that have been deployed in smaller numbers of people in different circumstances. There are also ones that have been used under investigation in new drug applications. The most recent deployment of a like adenoviral vector vaccine actually has been the use of the Ebola vaccine from Janssen, which uses the same vector as the COVID-19 vaccine. Now, that was deployed primarily in Africa, and it's in a few 100,000 individuals and it's hard to know for sure whether you're not seeing a safety signal there because of the complexity of surveillance in that area.

We will look obviously very carefully, and that's part of what this pause is allowing us to do to work in all the nooks and crannies to make sure that there's information that can potentially inform us, and then take that into consideration as we move forward.

**Dr. Bailey:** If a patient ... We're already getting calls from patients about this, because they follow the news, and bad news travels a lot faster than good news does, if this isn't bad news. We don't really know yet. What I'm hearing is that only probably ... well, there were some men in the AstraZeneca cases in Europe, but there were not any men involved in ours. These are women of childbearing age, do we know how many of them were on oral contraceptives because we know that that can cause clotting as well, or other things like Factor V Leiden or other clotting disorders like that they may not know yet?

**Dr. Marks:** I can tell you one of those, which is that there's no clear association with the oral contraceptive because we know that about the women, and it's not like they were all on oral contraceptives. In fact, the minority were on oral contraceptives. That does not seem to be dissociation. We don't know about the full hypercoagulable panel on all of these individuals. If you want to read the "New England Journal," you can see what was done on some of the people with the ... vaccine, and you can see that that some might have had hypercoagulable risk factors.

But it's very hard to tell because some things like Factor V Leiden and prothrombin gene mutation are pretty common in the population, then it's hard to know what that actually means here. Equally important, maybe understanding whether there is some HLA association that leads to this immune response, because that would actually be or understanding that might be helpful as well. Finally, we will obviously have to continue to look at various risk factors here in conjunction with CDC in order to try to understand as best we can on these vaccines.

**Dr. Bailey:** In terms of what questions do we ask our patients when they call in and they're concerned if they've had the Janssen vaccine, we ask about headache, and it's not the typical mild headache

right after a vaccine that's associated with maybe some chills and myalgias and maybe some fever. It's a much more severe headache. Abdominal pain, leg pain, shortness of breath, maybe stroke symptoms, petechiae. If the patient has those symptoms, I assume we send them to the emergency room.

**Dr. Marks:** Now I'm putting my hematologist hat on. I think I would do that. I would say, do you have a little speckled spots? Okay, do you have little speckled spots on your hands and your shins? Time to go to the emergency room. If you're feeling short of breath, time to go to the emergency room. I'm not a neurologist, but the neurologists that I've been around ... Is this like headaches you've had before, or is the quality of the headache something that you've never experienced before? If they've never experienced a similar quality headache before, it may be worthwhile if the timing is right, particularly between, a week after and that three week window.

That's when we these events have generally occurred, not just in these six cases, but I would put it to you that these cases look very, very similar to the cases with AstraZeneca. Although I can't definitively say they are absolutely the same, I think that we can take information from the AstraZeneca vaccine cases with that adenoviral vector and use some of that to help us here. I just also want to just make a plea. Let's not get blinded by the fact that in Europe it was about two women to one man, and this could just be a statistical aberration.

Dating back to the issue that if we look back now, in retrospect, at the clinical trial, and this is actually posted on our website, if you go back to the briefing books, there was one instance of cerebral vein thrombosis with thrombocytopenia in the clinical trial. That's one in 20,000, approximately, with Janssen, and that was in a man. I think we have to know that it just ... my plea is don't dismiss a male who says, "I got Janssen a week ago, and I have a headache that's nothing like I've ever had before, and I'm not quite feeling myself." That person probably should be evaluated.

**Dr. Bailey:** When the patient's in the hospital for our, excuse me, primarily physician audience out there, I assume that they would do the typical imaging studies if they expected some type of thrombotic event. But in terms of labs, I know with the AstraZeneca cases in Europe that D-dimer was elevated, and they're recommending that a peripheral smear is obtained to make sure that all the other cells look normal, obviously, platelet counts, and very important to not give heparin, use other anticoagulants and consider IVIG. Some patients are asking, "Well, is there anything that I can do to prevent this from happening?" I'm assuming we want to say, "No, just don't take aspirin, don't do anything on your own without consulting your doctor first."

**Dr. Marks:** I think that's the right answer. I mean, the issue here is I ... the good news, and just to reiterate, this is a very, very rare event. We are doing this out of an abundance of precaution because our commitment to the American people was that we would make sure that we would take care of the safety of these vaccines very carefully as if we ... for our families. This is part of our family, our larger family. We understand the need to get the country vaccinated against COVID-19. But just remember

now, we have a very nice supply.

It's not like we're stopping vaccination because the supply of both of the mRNA vaccines are flowing. I would love it if we can get the supply of these vaccines flowing again. Behind these, we have protein-based vaccines in development. That is encouraging too. We want to get more vaccine out there, but we have to do it with the confidence that people know that if they receive a vaccine, that their health is first and foremost in our minds.

**Dr. Bailey:** Well, I think it's so important for everybody to remember that there have been over 100 million doses of the mRNA vaccines given. Are we seeing any kind of new safety signals with those vaccines?

**Peter Marks:** Wow. Thank you for that question. It's almost like someone planted that. That's a great question. I didn't plan it. Either 180 million doses of the Pfizer and Moderna vaccines, there have been three episodes of cerebral vein sinus thrombosis reported, none of them with thrombocytopenia. We take those to be the base incidence of cerebral veins sinus thrombosis. For those who aren't aware, this is a relatively rare clot. We see these ... the rate is estimated to be, depending on who you look at, two to five in a million, or there's a Dutch study that suggested could be as high as 14 per million. But you can see it's relatively rare compared to the clots that we're more used to, like DVTs and PEs.

**Dr. Bailey:** We're not seeing safety signal ... anything new falling out with the mRNA vaccines. That's very encouraging. I think we have to remember that every case of hospitalized COVID infection has ... those patients have a one in five chance of having some type of significant thrombotic event. It's much more important to prevent new cases of COVID, in my opinion. I'll shift gears just a little bit. I'm sure you'll be happy to hear that. In the duration of immunity, there was report recently that for the mRNA vaccines, the six month evaluation showed excellent maintenance of immunity. Unfortunately, some people misinterpreted that to mean that it was only six months, which is not the case at all. But do we have any kind of idea about how long this immunity last? But the current thinking is on the need for boosters.

**Dr. Marks:** It's a great question, Dr. Bailey. I think what we know is that we're believing that it's probably going to last at least nine months, but we're going to be checking this. Obviously, we need to be careful that in more immunocompromised individuals, particularly the older individuals, the oldest people who are vaccinated, we don't see that drop off more quickly, and we'll be looking at that. It is possible. We don't know for sure that somewhere at nine months a year, we may need to have boosters. But we'll get a better sense of that. Probably with each month, we'll get more certainty about when that might be necessary.

**Dr. Bailey:** It seems to me that a booster might be necessary as much for the emergence of new variance as it is for waning immunity from the original vaccine, but I guess we'll just have to ... that's another we'll have to wait and see the kind of question.

**Dr. Marks:** It may turn out, though, that we're a little lucky with coronavirus. I apologize if I did this on a previous webinar, but I'm about to use an audio visual aid. If you're the spike protein, you are essentially a big ... you got to stock and you got a head. The antibodies where a lot of the changing is going on is where my fingers are wiggling. Unlike influenza, where you don't have a lot of real estate where my arms are, you have more real estate. What we're probably seeing here with these vaccines, the reason why we're probably still getting reasonable neutralization of virus against with the current vaccines is because there's enough real estate that hasn't shifted that it can be neutralized.

Now, obviously at some point, the things may shift enough in that stock that there won't be enough real estate for antibodies to neutralize. But we're lucky here that it may be that by just ... it might even be that by boosting—I'm not saying this is the case—but it may even be that without even shifting the variant that against which the booster is against, it may just be by boosting with the same vaccine, you'll get high enough titers that they would take care of these variants. That's something that's being looked at right now. There is something to be said for trying to keep it simple. Because the more different types of vaccines that one has to manufacturer, you basically take away from some of the capacity you manufacturer as much vaccine.

**Dr. Bailey:** Okay, let's talk about post-vaccination infections. There have been enough vaccines given now and there is enough COVID disease still rampaging through our communities that we're starting to hear more reports of these. Do we have any idea what the rate of post vaccination infection is? It seems that these infections are very mild, if not asymptomatic. Can you talk about that a little bit?

**Dr Marks:** Yeah. The best day that I've seen have come out from ... have been some of the data from Pfizer and others have published it from other series of real world evidence where it's probably somewhere on the order of 8% to 10% of these breakthrough cases over the course of six months. You're absolutely correct. They tend to be mild cases. These are not ones that put people in the hospital, but they're breakthrough cases. At this point, there's a lot of sequencing going on to make sure that we try to understand. I can't report to you the outcome of that sequencing, but people are trying to understand why we're seeing these breakthroughs, whether it's waning titers of immunity or whether it's something about a different variant in that individual.

It could be either, or both. But I think that to me is a little bit reassuring here that even the breakthroughs tend to be mild. I don't wish COVID though on anyone because seeing some of the long-haul effects that we're starting to see, it would be nice to keep this away. It'll be interesting to see if those who get these breakthrough infections when they are followed over time, whether they have lower incidence of any kind of long-haul symptoms.

**Dr. Bailey:** That will be very important information. We're now starting also to get some good information about reduced transmission of COVID after immunization. Can you tell us about that?

**Dr Marks:** Through real-world evidence, and other studies that have been done, again complimentary studies, it's not perfect. It's not zero, of course, but it looks like there's a 70% to 80% reduction in the ability to transmit asymptotically, which is a really nice piece of news because we would like to make sure that particularly as younger people who can have asymptomatic COVID-19, that once they get vaccinated, we are not transmitting as much. We'll probably have better and better data with that as we move along because there are a variety of studies that will look at that in the real world. But it is increasingly reassuring, and some are actually ... the most definitive studies of looking at exactly when that kicks in are also ongoing.

**Dr. Bailey:** We're looking at expanding the populations in which we give the vaccine. I know Pfizer has submitted its data for its EUA in 12- to 15-year-olds. Well, first of all, is this patient population getting a full dose or half dose? Is it the same dose as adults?

**Dr Marks:** Great question. The 12- to 15-year-olds, they actually were studied. Actually, about 100 of them were studied in the original Pfizer data that was submitted. They used the full dose. In that age range, the weights are sufficiently high that these ... this was felt to be very reasonable, and indeed as you may have read from Pfizer's press release, that does seem like that was a good call. They seem to have, at least by report, good immune responses and good protection. We will be reviewing those data. It makes it relatively simple because we'd be able to roll out as these other vaccines, they will also.

I think for all of the vaccines, not just for Pfizer, but for Moderna and then potentially Janssen. They will be planning on using in that 12- to 15-year-old population, the same adult doses. Makes it reasonably simple, and obviously we feel a sense of urgency of getting through these, and we'll do our best to be reviewing this because we understand that this gets kids. If we can get down to age 12, we can get junior high and high school kids with a good vaccination campaign back to school hopefully in the fall.

**Dr. Bailey:** Any estimates on when we might hear about that EUA for the early adolescence?

**Dr Marks:** Couple of weeks.

**Dr. Bailey:** Okay. Okay. I know the pediatric studies are ongoing as well. I know that the Pfizer, I believe, is ready to move on from the EUA status to actually applying for its biologic license to be approved as opposed to just an emergency authorization. The implications of a vaccine being officially licensed, as opposed to the other ones still being under EUAs, how does that affect availability? ... To me, I would think that that would have a lot of implications in terms of vaccine mandates and things like that. But how long do you think that process is going to take in terms of moving from EUA to BLA?

**Dr Marks:** The best, I can't exactly predict because there are so many moving parts. I can tell you what are the statutory ... what we have as our goal in our commitment letters for a vaccine like this is



that, after it's accepted for filing, we generally have up to six months to review it. Now, obviously, we're going to do our best to get this done faster than that, but I can't say how much faster because there are so many other moving parts here. I came in yesterday not expecting to have this week switched around by safety signals quite the way that it was while I was here over the weekend.

I wasn't expecting this program for this week. We do have to take that into account. That said, I think, Dr. Bailey, your point is very well taken that once there is the most relevant thing here, I don't think it's going to make a big difference on which vaccine becomes dominant because the supply is still the major issue here. But it does make the following differences. Once a vaccine is approved, there is a different legal status in terms of what employers can potentially require, at least what certain employers can require. I mean, it does have a different meaning for the military in terms of required vaccinations. It will make a difference when there is a Biologics License Application that is approved.

**Dr. Bailey:** Do you think that AstraZeneca will be applying for an EUA in the United States, given everything that has happened? Given the discussions around safety signals, what do you think is the likelihood that it would be authorized here?

**Dr. Marks:** You know what? That's one where I can't go there. That's going to be up to the company, and they'll have to ... That's probably a place that I really can't comment on.

**Dr. Bailey:** Understand, had to ask. As far as increasing ... Let's see, I've got so many questions here still to ask. Lots of questions about immunocompromised individuals. There are patients with side common variable immunodeficiency or other types of immune deficiency. I know that we do recommend that most of these patients get vaccinated, should we prefer the two-dose regimen for those patients? Really, what's the current guidance on giving really any of the vaccines in immunocompromised individuals?

**Dr. Marks:** Yeah, I think for immunocompromised, it's really ... This is actually what I think is ... It's actually nice to be on with the AMA because we care about provider-patient relations, right? This is a great place where this is a good time for a conversation between a provider and a patient, and I think you can explain that perhaps what the benefits of the two-dose regimens might be in terms of the highest titers you might achieve, and theoretically perhaps explain that maybe that if you have a lower chance of getting a high titer anyway because of immunocompromised that might be helpful.

Alternatively, if you have somebody that is ... your concern may not come back, you might want to use a one-dose of vaccine. But again, I think this is a really good conversation for a provider and patient to have knowing, exactly as you noted, that the vaccines may not work as well in immunocompromised individuals, but they're probably better than doing nothing.

**Dr. Bailey:** I would think so. I am very concerned about today's announcement fueling vaccine hesitancy and folks that were already hesitant, and it may have engendered some hesitancy in



patients that weren't having much hesitancy before. I know that when, and I've already had some calls from patients when a patient asked me, I remind them the 180 million mRNA vaccines that have been given with really no emerging safety signals. We couldn't have made the trials longer because, like you said, most of the reactions happen within six weeks, and certainly this prothrombotic, thrombocytopenia that we're seeing in these patients, if it's related, is occurring within that window.

So a longer observation may not have made a difference, and it's just to have trials with millions of people in them is just ... There would be so many people that died of COVID while you were waiting for that to happen. I think it would be more than counterproductive because we just can't forget what a frightening, frightening disease this really is. Do you see this changing the shape of vaccine trials in the future in terms of how long we observe people and how large the trial groups are?

**Dr Marks:** Dr. Bailey, it's a great question. The problem is that we could have done a trial that had 100,000 people in it and may never have seen this. It just so happens that we saw it in that trial. I think it's just hard to second guess like this, and that's why we have such good vaccine surveillance systems. I think the best thing we can do to make sure we engender vaccine confidence is to communicate openly we are here ...

Today I've had every epithet hurled at me on my email that we're in one company's pocket or the other company's pocket or against this company, or because this is a nonprofit, supposedly vaccine, we were against it or this and that. No. We're here because the people who work at FDA, everyone comes to work every day because we care whether it's ... or goes to their basement to work every day ... because we care about America's health deeply.

This is not something we undertook lightly, because we really wanted to make sure though that people feel confident that when we say, later in the week, that we've come up with some solution, that they know that we've taken their best interest to heart and that we have something in place that is going to mitigate against this. That's our commitment here. Dr. Bailey, I share your pain about this because it's pain that we all felt, but it's one of those things where you have to weigh doing nothing versus doing something, and then making sure that we explain well why we did it.

I mean, this is a great opportunity to explain that 180 million doses of a vaccine given with remarkably few ... this is remarkably few serious adverse events. Yes, we can say that there are these flu-like symptoms, but by and large in terms of serious things, pretty wonderful rollout. I think, overall, we should be very confident that the systems are working, and the fact that they're picking up rare adverse events is actually the right thing. That's what they were designed to do, and now we just have to deal with them.

**Dr. Bailey:** I think we have to keep everything in perspective and realize that, yes, that this is a sign that the system is working, not that the system is not working, and encourage everyone if they suspect adverse events to report it to VAERS or to the CDC. MedWatch is incredibly important to get this data.

Thanks again to Dr. Marks for his time and his insights into the Janssen vaccine. I know this has been a very busy day for you and everybody at the FDA. Thank you, to all of you, for joining us today and for all of your great questions.

We'll be in touch with the dates and times for future physician webinars. If you're interested in sending this webinar to a friend or colleague or watching past episodes, this "What Physicians Need to Know" web series is available for free on our website at [ama-assn.org/COVID-19-webinars](https://ama-assn.org/COVID-19-webinars), or just visit our main page and search for COVID-19 webinars. Thanks again. We hope you will join us next time. Have a good day.

**Dr Marks:** Thanks so much, Dr. Bailey, and thank you to all the providers watching for all that they do. Thank you.