Introduction to COVID-19 Vaccines

Dr. Jill Sells: So, now I'd like to introduce our speaker. Dr. Sean O'Leary is a professor of pediatrics at the University of Colorado School of Medicine and Children's Hospital, Colorado. He's a pediatric infectious disease specialist and a vaccine researcher focusing on strategies for communicating about vaccines. He is vice chair at the American Academy of Pediatrics Committee on Infectious Diseases. For the last six years, he's been a liaison to ACIP, the Advisory Committee on Immunization Practices, which is the committee that makes recommendations about vaccines for the U.S. public, including the childhood immunization schedule that you are familiar with. Since shortly before the pandemic began, he has represented the AAP on ACIP's COVID-19 vaccine work group, helping to advise the CDC on the use of COVID-19 vaccines. So, he has really had a front row seat observing the entire process of the development, testing, and approval of these vaccines. We are delighted to have him join us. And I'll turn this over to Dr. O'Leary.

Dr. Sean O'Leary: Thanks, Dr. Sells. And I'd really like to start by echoing what Dr. Futrell said at the beginning – just thank you all for all the important work you're doing. And I'm going to move into this quickly. We're going to cover a lot of ground here. And to do that, I'm going to start just talking about the very basics of vaccines. I'll talk specifically a little bit about COVID-19 vaccines, what they are and how they work. I'm going to talk a bit about the approval process, and then, also about vaccine safety and safety monitoring.

So, at its most basic level, what is the vaccine? So, a vaccine really trains your immune system to remember what an infectious disease looks like usually by training it to recognize a harmless portion of disease. So often just a very little piece of a virus or a bacteria. A vaccine also helps your immune system create what are called antibodies. So, these are also little proteins. So, when your body comes in contact with the actual infectious disease, your immune system can then recognize that disease and use the antibodies to kill it before it can cause harm. Vaccination, which is a word you see used a lot, is simply the act of giving a vaccine.

So, vaccines protect individual people, but I also want to talk a little bit more about something else they do, which is called herd immunity, sometimes called community immunity. So, this slide just depicts, in a basic level, what is herd immunity. So, you can see over there on the upper left, you've got someone who's got a disease. In this case, we'll say COVID-19. And they can easily transmit that to a susceptible individual who then becomes a transmitting case and can transmit it to others. On the bottom, what you're seeing is when somebody that has a disease, in this case COVID-19, potentially transmits it to another individual. That individual is actually immune and can't get it. So then, when we look at this next slide, what we have here is, at the top, a transmitting case and one that's got COVID-19. But you've got all these people that are around them that are immune. Those people that are around this person are protecting other people in society who are not immune, either because they have not been vaccinated at that point, or because they have some problem with their immune system where vaccines don't

quite work as well. That's very simply kind of what we're talking about when we talk about herd immunity.

So, moving into these COVID-19 vaccines specifically, they can be broken down into three main types. And so, these – and I'll talk a little bit more about each of these – the mRNA vaccines, adenoviral vector vaccines, and recombinant protein vaccines. And three of these are already approved for use in the U.S. And a couple more may be coming soon. So, I'm going to talk about the ones that may be on their way as well. So, this slide really depicts a whole lot of work over the last year around these vaccines. And so, I'm going to summarize briefly what we know from the studies so far. So, the first thing we know is that all of these vaccines produce a very strong immune response in the body, probably, in most cases, actually stronger than what we see from natural infection. So, you get more of a response from the vaccine than you do from actually getting the disease. The safety profiles also look very good at this point. There are some temporary reactions, like fever and fatigue. But overall, these vaccines appear very safe. The companies have also been very successful in enrolling diverse populations in terms of race, ethnicity, age, and underlying conditions. And then, in terms of the three vaccines that are approved for use in the U.S., all of the results we're seeing so far are very, very encouraging – close to 100% protection against hospitalization and death. And I think a lot of us in the field are just – this was beyond our wildest expectations in terms of how well these vaccines are working. We were hoping for something like 50%, 60%, 70% effectiveness. So, 100% protection against hospitalization and death is really reason to celebrate.

Now, I'm going to move into getting a little bit more technical here in terms of how these vaccines actually work. So, the thing that's important to understand is the spike protein. So, coronavirus is called coronavirus. Coronavirus means crown. And so, what you can see on that picture on the left is what looks kind of like a crown, right? And the things that are making it look like a crown are these little things called spike proteins. And the spike protein is important for two reasons. One is that it is the protein on the virus that attaches to our cells to allow the virus to get into our cells and reproduce. It's also – the other reason it's really important is that this particular protein is the target for all of the U.S. vaccines and most of the vaccines that we're using around the world. That's what these vaccines are designed to attack.

Now, moving into the specifics of how these different vaccines work – so these are the mRNA vaccines. These are the ones that many of you may have had already. This is the one that I had. My son, actually, just got his first dose yesterday because he works in a restaurant. And where I live in Colorado, we're immunizing people that work in restaurants now. So this is the Pfizer and the Moderna vaccines. And so, down on the bottom here, you see these are RNA vaccines. And the little circle around the RNA is very important. So, the RNA that you see there in the middle – the way you can think of RNA is it simply a set of instructions. So, most of the vaccines we routinely use, as I mentioned, just give you a piece of a virus. In this case, what this vaccine is giving is simply the instructions for how to make this a spike protein. And the reason I said that little thing around the mRNA is important is that mRNA breaks down in our bodies very, very quickly. It's easily broken down by the human immune system. And so, to get it into ourselves to do its work, it needs this thing on the outside what's been called a lipid nanoparticle. So, that

little circle helps it gain entry into our cells. Once it's in our cells, up on the upper right there, what happens is then RNA, our body recognizes it as a set of instructions, and then our body uses our own machinery to turn those instructions into these little proteins. And in this case, it's the spike protein. The spike protein then is released into our system, and our immune system sees it, says, “OK, this doesn't belong here. Let's create an immune response to it.” And so, then our body creates that immune response. And that's basically how these vaccines work.

Now, moving into the viral vector vaccine – so this is the Johnson and Johnson or Janssen and Johnson vaccine. So, these actually in some ways works similarly to the mRNA vaccines in that they are delivering a set of instructions to our body for how to make the spike protein. So, this is what's called a non-replicating viral vector. This is simply a common cold virus that has been engineered in the lab. So, it can't reproduce in our body. And similar to that lipid nanoparticle I described that helps deliver it into our cells, this just uses a virus – a harmless virus – to deliver it into our cells. Once it's in our cells, in a very similar way, it tells our cells how to make the spike protein. Our cells make it. It then shows that spike protein to our immune system and creates our immune response.

Now, moving into the protein subunit vaccine, this one is the Novavax vaccine. And we may be seeing that vaccine approved in the U.S. in the coming months, so, I wanted to mention it briefly. And this is more – this vaccine is similar to some of our more traditional vaccine in that it just gives a very small piece. It actually is giving us the spike protein and the M protein into our immune systems. And then it's digested into our immune system, shown to our immune systems, and then provides the immune response. OK, so that's a fairly general level how these vaccines work. Now, I want to talk a bit about the vaccine approval process. You know, I get this question, not uncommonly, how do these vaccines come to be made so quickly. And so, I want to talk a little bit about how that happens.

So, this slide depicts, sort of, the general way that vaccines come into being used in the U.S. And so, I want to point out that this slide is actually from well before the pandemic. And what I want to point out to you is that these phases, these things that happen in these vaccine trials, all of the same things that happen in vaccines that have been developed over the last several decades happened with the coronavirus vaccines that we're seeing in use already. They just happened on a compressed timeline. And the reason for that, obviously, is because this pandemic is so severe with so much death and suffering that we had to speed this process up. But the process was essentially identical to the way we develop other vaccines, and that was able to happen for a few reasons. One is that instead of having these different phases of vaccine development happen one after the other, they happened more at the same time. And the reason for that, of course, is because we needed vaccines quickly. But also, the other big reason is that development of vaccines from the perspective of manufacturers is a very expensive process, and they don't want to move into a second phase after a first phase unless they know that it's going to be a successful candidate. Less than one out of every 10 vaccines that sort of enters these trials ever makes it out of them. And so, it's a very expensive process for these manufacturers. And so, the U.S. government actually helped with that by taking the risk to these manufacturers away so that these vaccines can be developed safely and

effectively. And so, the thing I want to point out also on this slide is that safety is the first consideration in all of these phases. Safety is the most important thing when we're thinking about developing these vaccines.

Now, I want to move into what happens after these sort of pre-clinical trials that are done. So, up on the top of the slide, you can see the vaccine development and testing and the submission to the FDA. And so, that's what we saw with these vaccines. And then, there's this committee that most people have probably had probably never heard of before this pandemic, and it's been in the news a little bit in the last six months or so. And it's this obscure committee that is actually very important. A lot of people felt like there was kind of a black box around the development of these vaccines, but in fact, it's been a very transparent process. And so, the FDA licenses vaccines. But this is actually a committee that is not part of the U.S. government. It's an external advisory committee that advises the U.S. government on licensing vaccines. And in fact, all of these meetings are publicly available. You can watch them online as they're happening. And I want to tell you a little bit more about them. So, there's 15 voting members. These are primarily experts in vaccines, infectious diseases, and public health. Almost all of them are non-governmental, and these are not political appointees.

And I also want to point – so pediatricians are among the most trusted of health care providers. And this committee actually, at this moment in time, has seven pediatricians on the committee right now. I know a number of these folks. There have very high ethical standards, very smart people. Have been working in this space for a long, long time. And I would just want to share a quote with you from one of the pediatricians on that committee. “I'm reassured” the EUA process FDA described was “much, much closer” to the full licensing process than he had thought. So, very reassuring. And then, the other committee I want to point out is the Advisory Committee on Immunization Practices. So, the FDA licenses vaccines and the CDC recommends vaccines for the U.S. public. This committee is similar to the verb pack in that they advise the CDC, and they're also external to the U.S. government. These are non-governmental employees. And ACIP uses a number of different considerations when they recommend vaccines for the U.S. public. But again, the most important is safety. They also, of course, look at effectiveness, they look at burden of disease, and the implementation issues.

So now I want to move into post-licensure safety monitoring because I think this is – there's a lot that goes on behind the scenes all the time to monitor the safety of vaccines for the U.S. population. And this – these systems have really ramped into high gear given the rapid rollout of these vaccines. So, why do we do this? So, one of the things I want to point out is that safety standards, in general, for vaccines are very high. We are giving vaccines, in general, to a large population of people, many of whom are healthy, to prevent disease as opposed to most medicines where we'll tolerate some side effects. So, most medicines we're using to treat a condition, and we'll tolerate side effects with those. In the case of vaccines, we have to have very high safety standards. The other thing I want to point out is that these pre-licensure trials usually are not large enough to detect really rare adverse events, things on the order of one in millions. And you can see that – you probably saw on the news there was some allergic reactions, which it turns out, are actually along the lines of what we see with typical vaccines,

one to two to maybe three in a million doses. All of the people that have had those reactions, by the way, have actually done well, but this is to point out that there are reasons behind having these systems in place. So, going on to this next slide, I want to point out that this is – I'm not going to go through all of these things. I just show you this slide to point out that there's a lot going on behind the scenes all the time to monitor the safety of vaccines.

So, on the left, you can see a lot of different systems that are in place to monitor vaccine safety. And some of these have been in place for several decades, actually. Always working behind the scenes to make sure our vaccines are safe. On the right, are a number of new systems that have been set up to monitor the safety of COVID-19 vaccines specifically. And I'm just going to talk about a couple of these just so you have a sort of a general understanding of some of the things that are going on. So, the first one I'll talk about is the Vaccine Adverse Event Reporting System which was created in 1990, overseen jointly by CDC and FDA. This is a voluntary reporting system. So if you got a vaccine today, and you go out tomorrow, and you get struck by lightning, you can report that to VAERS. It doesn't mean that that vaccine caused you to be struck by lightning, but you could report that. So, each year, VAERS receives about 30,000 reports. About 13% of those are considered serious. Any serious report is then investigated by staff within VAERS. So, VAERS is used to identify rare adverse events. It was helpful with, for example, the allergic reactions that were happening. But it cannot be used to determine if a vaccine did or did not cause a particular event. The point here is that anything that can happen after a vaccine can also happen in the absence of vaccination. And something we say a lot is "association does not equal causation." So, I gave you the example of being struck by lightning. It almost certainly wasn't the vaccine that caused that, right? But there are certain things that some people might say, "Well, it was the vaccine," but really, it was happening – it would have happened in the absence of vaccination.

So, if they find an unusually high number of events after a vaccine, then they look at that in other systems. So that's why I just want to mention this Vaccine Safety Datalink. So, this is a collaboration of many different organizations around the country, monitoring over 12 million children and adults for vaccine safety. The reason that this system is so effective is that these vaccine data are highly accurate. So, these are large populations of people who essentially get all their health care in a single place – their vaccines, their hospitalizations, et cetera. So, this system can actually study if vaccines are related to a specific side effect. And I just show you this slide as an example. So, this is an example from a recent CDC meeting, showing all of these things that the Vaccine Safety Datalink is monitoring in real time to make sure that these COVID-19 vaccines are not causing any of these other things. And so, for example, they're looking to see are there more events of these types of things happening in people who have been recently vaccinated compared to the general population. And so far, all of the things they're finding are very, very reassuring. So, just to finish up, I want to kind of summarize by saying that vaccines to prevent COVID-19 offer a potential to end this pandemic in this really historic moment. The U.S. vaccine candidate at this point appear to be both very safe and highly effective. And although these trials have happened with unprecedented speed, I really believe we have reason to trust the process. And finally, we do have an extensive vaccine safety

monitoring system in place, always working behind the scenes to make sure all vaccines, including COVID-19 vaccines, are safe. And I'll stop there. Thank you.