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Pediatric Vaccine Safety: From Clinical Trials to Real-World Care

Announcer:
You're listening to *On the Frontlines of Pediatric Vaccines* on ReachMD. And now, here's your host, Dr. Mary Katherine Cheeley.

Dr. Cheeley:
This is *On the Frontlines of Pediatric Vaccines* on ReachMD. I'm Dr. Mary Katherine Cheeley. Today I'm joined by Dr. Kawsar Talaat to explore how vaccine safety is evaluated, monitored, and communicated to families. Dr. Talaat is an Associate Professor in the Department of International Health at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. She also serves as the Johns Hopkins PI for the CDC Clinical Immunization Safety Assessment Project.

Dr. Talaat, welcome to the program. I'm so glad you're here.

Dr. Talaat:
Thank you very much, Dr. Cheeley. It's my great pleasure.

Dr. Cheeley:
So let's jump in because this is a topic that I think a lot of people have questions about, and I'm so excited that we're getting into today. When people hear the phrase "vaccine safety," they think a lot about side effects. But from a research perspective, what do we actually mean by vaccine safety? What does that encompass?

Dr. Talaat:
It encompasses a tremendous amount, but side effects are a big part of it. When we give somebody a vaccine, we want to know what they're going to feel afterwards. So if you get a shot, you're going to expect that your arm hurts. If your baby gets a shot, you're going to expect their leg might hurt and might be a little bit red or sore. So we're monitoring for the common things, but we're also looking for rare events, such as myocarditis or a seizure or something like that.

Dr. Cheeley:
A lot of parents may not realize how much testing goes into vaccines before it ever even, number one, reaches children, but definitely before it's ever recommended. Can you walk us through how vaccine safety is evaluated during the development of a new vaccine?

Dr. Talaat:
Absolutely. First, before any vaccines go into people, we test them in animals. We want to make sure that the vaccines are safe there before we go into people. Once we take a vaccine into people for the first time, we start in grownups. And the reason we do that is they can give us informed consent. We want to make sure that it's safe before we put them into vulnerable people, like babies, who can't give us their own consent. So we start in grownups. We test to make sure that the vaccine is safe and there's no bad side effects, and then we go down in age until we get to the age where the vaccine is targeted for, either infants, young children, older children, or teenagers. So we start with tens or low hundreds of people in each of those categories as we're marching down.

Once we get into the target age range, we start doing trials in hundreds of children to make sure that it's safe, that it is producing the immune response for the target the way that we expect it to be produced and what we're looking for, and it's a good immune response. And then if it does, then we put it into thousands of children, and the reason to do that is to see if the vaccine works, but also to give us a bigger group where we can monitor safety. These are done in clinical trials, so the parents of these children have to okay our giving their child the vaccine. They're informed about potential risks and potential benefits. They have a lot of opportunities to talk to the doctors who are doing the trial so that they feel comfortable with their child getting these vaccines.

And it's only after all of these trials are done—and it usually takes 10, 20, or even more years—that we know that a vaccine is effective and that it is safe in the population that we want it to be used, that it finally gets licensed by the Food and Drug Administration. And then once it's licensed, then they do another evaluation to look at safety and efficacy and to review whether or not it should be recommended. So there's both the licensure review, and then there's the recommendation review that happens, and that's done by an advisory committee at the CDC.

Dr. Cheeley:
So understandably, adverse effects or questions about them can really raise concerns in families. So how do you as a researcher, or researchers in general, determine whether something is actually causal for the vaccine or just by happenstance after the vaccine was administered?

Dr. Talaat:
That's a really good question. There's a lot of things that go into determining whether a vaccine could potentially cause an adverse event. Things that happen right after a vaccine, like a sore arm or a headache—it makes sense that the vaccine may have contributed to it. If it happens months or years later, it's unlikely that the vaccine contributed to that because the time just doesn't fit.

Other things that we look for are what we call biological plausibility. Is there a mechanism that makes sense that would allow the vaccine to cause that problem? So for example, a sore arm. You would expect that if you're injecting a vaccine into somebody's arm or somebody's leg, a lot of our inflammatory cells are rushing to that area. Our immune system is revving up in that area, and so it makes sense that it hurts. If, you say, "Well, when I got the vaccine in my right leg, my left toe went numb," there's not as much biological plausibility for that.

Dr. Cheeley:
For those of you just tuning in, you're listening to *On the Frontlines of Pediatric Vaccines* on ReachMD. I'm Dr. Mary Katherine Cheeley, and I have the pleasure of speaking with Dr. Kawsar Talaat about the science behind vaccine safety.

So let's jump right back in. Once a vaccine is introduced and licensed in the United States, how do you monitor safety across the total population?

Dr. Talaat:
So between the FDA and the CDC, there's several different vaccine safety monitoring systems. One is called VAERS, or the Vaccine Adverse Event Reporting System, and it's a system database that anybody can report to. So as a doctor, if I see an adverse event after I give somebody a vaccine, I can report it. But I as a patient could also report my own adverse event to VAERS. Or my uncle could report my adverse event to VAERS. So really anybody. The problem with VAERS is it doesn't tell you whether the vaccine caused it. So in VAERS, there's reports of anger after vaccination. Well, it's unlikely that a vaccine caused anger. There's no real biological mechanism for that. But what VAERS does is it detects rare signals. So if you start seeing something rare after a vaccine and it's reported a couple of times, you might want to look in other systems to see if you can find that rare signal appearing in more robust systems.

And so the CDC and the FDA have other systems. One is called the Vaccine Safety Data Network, which is large health systems with computerized health records of their patients, where they can look at people who got the vaccine and people who didn't get the vaccine and see if they have the same number of rare events that are happening to them, or if there's more in those who got the vaccine. Medicare and Medicaid keep a system. The VA keeps this vaccine safety system. There's different vaccine safety systems at different levels, and they all report back to the same agencies to notify them if there's a signal or something that is of concern.

At CISA, we get reports from physicians, pharmacists, and nurses who are taking care of patients and administering vaccines, and if they see an adverse event, they can contact us. And there's experts at several universities and clinics across the country in vaccine science and in different medical specialties who can review the record and determine whether it could be vaccine-related or not.

Dr. Cheeley:
So these very rare adverse events that you're talking about are really important conversations that we need to have with our providers before we give informed consent, like you were talking about. What happens when researchers identify some kind of potential safety signal? How do you guys investigate that?

Dr. Talaat:
So if you see a signal, you can go to one of the big databases and say, "We are worried about this signal," like heart attacks, for example, or seizures in children after they receive this vaccine. And what they do is they look at children in the age range of those who get vaccines, and they can compare them to children who didn't get the vaccine at that age group. But often there's something a little bit

different about the kids who got vaccines and the kids who didn't, so they're not great comparators. So now what we're doing is comparing kids against themselves. We're saying, "In the month or six weeks before they got the vaccine, in a million children, how often are you seeing this rare event? And then “In the month or six weeks after they got the vaccine," or sometimes it's two weeks, or one week, "in a million children, how often are you seeing this rare event?" And if the vaccine had no impact on the rare event, then the two should be equal. But if you see a slightly higher signal in children after they get the vaccine than before, then maybe there's an increased risk.

Dr. Cheeley:
From your perspective, how do you think we can best relay this information about vaccine safety and this rigorous process to caregivers and parents that are concerned?

Dr. Talaat:
I think one of the most important things is to be honest and to say, "Look, vaccines do have some side effects." Everything we do in life has a side effect, and the vast majority of side effects from vaccines—like 99.9 percent—are going to be mild and will happen immediately after you get the vaccine or within the first few days, and they will go away. And you will be protected against this very severe illness after you get the vaccine, or your child will be protected against this very severe illness after they get the vaccine.” They very rarely can cause more severe reactions like seizures and intussusception, but the risk from the disease is much higher.

Dr. Cheeley:
This has been a great discussion. I love everything I learned from you. Thank you so much for taking your time to talk through it with us, Dr. Talaat.

Dr. Talaat:
It's been a pleasure. Thank you very much for inviting me.

Announcer:
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