Increased Incidence of Invasive Pneumococcal Disease among Children after COVID-19 Pandemic, England

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Shamez Ladhani, a pediatric infectious disease consultant at the UK Health Security Agency in London. We'll be discussing an increase of invasive pneumococcal disease in children after the COVID-19 pandemic in England.

Welcome, Dr. Ladhani.

[Shamez Ladhani] Hi, Sarah. Thank you for having me.

[Sarah Gregory] Let's start with the basics. What is pneumococcal disease?

[Shamez Ladhani] So pneumococcal disease refers to an infection by a bug or a bacteria called *Streptococcus pneumoniae* or pneumococcus. This is a bug that commonly resides in the back of the nose and throats of infants and toddlers without causing any illness. But sometimes they can go on to cause infection and disease in the young ones and in the adults and older adults, which ranges from sore throats to ear infections to sinusitis. But then they can also cause severe disease such as pneumonia, and in rare cases they can cause blood poisoning (septicemia) and meningitis, which is probably the worst possible infection you can get with pneumococcus.

[Sarah Gregory] What kind of vaccinations are there for it and who gets them now?

[Shamez Ladhani] So there are two different types of vaccines against pneumococcus. The earlier vaccines, which have been around since the 1980s, used the sugar capsule of these bugs in a vaccine, which then helped protect against pneumococcus. Now, there are more than 100 different types of pneumococci, each with their own unique sugar capsules. And therefore, these vaccines do not protect against all the pneumococcal infections, only those where we have the sugar capsule vaccine, and this is called a polysaccharide vaccine. And the vaccine that has been available for the last 50 years or so is against 23 different types, and we call it the 23-valent polysaccharide vaccine. The problem with this vaccine is that young children and infants do not recognize the sugar coating of these bacteria, which is how they're able to invade and cause serious illness in young children. And so, to circumvent that, what you can do is take the sugar capsule and attach it to a protein. And then the immune system of the infants will recognize the sugar capsule and the protein that it's connected to. And what you get is a conjugate vaccine that protects young infants against the strains that are in the vaccine.

Unfortunately, the first conjugate vaccines were licensed in the year 2000, and they protected against seven different strains and are known as PCV7. This has evolved over time, so we have a PCV10 that protects against 10 different strains, and a PCV13, which protects against 13 strains.

The newer vaccines that have just come out in the last year protect against 15 and 20 different serotypes, which is very exciting, but they are just starting to be used right now.

[Sarah Gregory] And tell us about the changing vaccination schedule for children. What it was and what it is now, and why we've done this.

[Shamez Ladhani] This is a really exciting field. Usually when the vaccines are licensed, they are licensed on clinical trials based on a very specific schedule. So the earliest pneumococcal conjugate vaccines were licensed at a 3+1 schedule so that infants get three doses at by six months of age, and then a booster at one year of age. But these vaccines are very, very expensive, and countries that implement a national program where the vaccines are bought nationally and distributed to the rest of the population would find such programs very expensive. So the UK initially started really interesting studies where they decided to give only two doses to infants and then a booster at one year of age. And they were able to show that a 2+1 schedule provided a very similar level of protection as the 3+1 schedule. While the UK and many other parts of the world started with the 3+1 schedule for the vaccines in infants, the UK was different because it took a bit longer to implement the vaccine. So we started in 2006 compared to the US, where the vaccine was started to be given in the year 2000. But we implemented a 2+1 schedule, and therefore we reduced the cost of the program by 25% by having one less dose in our schedule.

[Sarah Gregory] Explain the difference from vaccination schedules between the United States and the UK.

[Shamez Ladhani] The United States continues to use a 3+1 schedule, which is given at two months, four months, six months, and then at just after their first birthday. Most other countries around the world, including the UK, use a 2+1 schedule. We give it at two months, four months, and 12 months of age. But what is really interesting is that in 2018, we moved to a 1+1 schedule, which is the first to be done in the world, because we were able to show that when you achieve herd immunity with these vaccines and there's very little disease caused by these vaccine types, then you only need fewer doses of vaccine to maintain a level of herd immunity to protect the whole population compared to trying to eliminate this disease. So in 2019, what we did was we moved to a 1+1 schedule where infants got one dose at three months and then one dose at 12 months.

[Sarah Gregory] How vulnerable are the children or people who sort of fell between the cracks here? I mean, this newer vaccine that works better...like people, say, born in 1990, how are they protected?

[Shamez Ladhani] All these vaccines are very new, so a large proportion of our population has never received a pneumococcal vaccine and that's how it has been for a long time. And it's also important to remember that these vaccines only protect against a handful of serotypes, yet there are so many other serotypes that can cause serious infection at the same level that are not protected by the vaccine.

So we know that the highest risk of pneumococcal disease is in infancy (in the first year of life), and then the incidence falls very rapidly so that by three, four years of age, your risk of serious pneumococcal disease is very low until you reach a very old age (probably around 75 years before your risk starts going up again). If you have survived the first years of life without serious pneumococcal disease, then you are probably okay for a very, very long time. What we do have is we have specific programs for risk groups where we give them the 23-valent polysaccharide vaccine. So any person who has underlying conditions that puts them at increased risk of

pneumococcal disease will be given the polysaccharide vaccine. And sometimes they are given a combination of the conjugate vaccine and the polysaccharide vaccine, depending on their risk. But the important thing over here is that the childhood immunization program...when you vaccinate the young children with the conjugate vaccine, they stop carrying those strains at the back of their nose and throat. And therefore, they don't transmit those bacteria to older children and adults and their grandparents, and so on. So what you get is herd immunity from the childhood program, and that's where the conjugate vaccines are very unique.

So by implementing a successful infant program to protect against pneumococcal disease, 80-90% of the reduction in disease is actually in the older children and the adults who are no longer exposed to those strains in the vaccine, and they are protected indirectly through herd immunity. And that is the strength of conjugate vaccines compared to many other vaccines that are out there. In fact, a successful childhood program would protect everybody whether they've been vaccinated before or not.

[Sarah Gregory] Does the UK have the same population level of push back on vaccinations that the United States is seeing more and more of?

[Shamez Ladhani] No, we've been very, very lucky. We've had our share of difficulties with the MMR vaccine and then the false information about autism that did a bit of damage to our immunization program many, many years ago. But I think since then we as a population has learned our mistakes, and we're very careful about making sure that there isn't any false anti-vaccine propaganda in the country and we've built the trust of the population and of parents over the last few decades, and we've maintained a very high vaccine uptake level for the last two decades or so. Saying that, the vaccine uptake has been sort of gradually declining a little bit every year by a percentage point or so.

So there's always clearly room for improvement, and we can do a lot more to get the uptake up by focusing on the minority groups that are less likely to be vaccinated, making the vaccines more accessible, and so on. But in general, we as a country do not really have a lot of antivax activity. We've done really well with maintaining the trust of our vaccine programs.

[Sarah Gregory] Your article talks about immunity debt. What is immunity debt?

[Shamez Ladhani] That's quite a new term, and I'm not sure that there is a technical definition for it, and I think a lot of people interpret it in a different way. What we were trying to do is something we have seen with a few of our vaccine-preventable infections, is to try and explain that when you have lockdowns (such as what we did with the COVID pandemic), you have a whole cohort of children who are not exposed to the bacteria and viruses that they would normally have been exposed to. And so, what happens is when you then come out of lockdown, say, next winter, you have two cohorts of children who are now susceptible to those infections—one that didn't get infected during the pandemic and one that was going to be infected in the next year, anyways. So what we would anticipate to see is that cases would be higher than the pre-pandemic levels because we have double the susceptible populations. But they shouldn't be more than double because the susceptible population is two times, but not all of them will be exposed to the bugs. So if we were to predict what will happen, we would expect the cases to be somewhere between 100 and 200% of the pre-pandemic level. And that is typically what we see with infections as we emerge out of the pandemic.

[Sarah Gregory] Explain a little further how COVID played into infections and vaccinations generally.

[Shamez Ladhani] More than COVID itself, really. It was the restrictions that were put in place that reduced the amount of interactions between people, which then reduced the infection and transmission of various viruses and bacteria. So it's not just the bacteria, such as the pneumococcus that we've talked about. The viruses play a very important part because a lot of these bacterial infections are secondary to viral infections, and normally what you see is you see influenza season and then they get a secondary pneumococcal infection, and we see other viruses and you get secondary pneumonia because of the viruses. And all that disappears during the lockdown period (the one year of the pandemic). And so, we saw very large reductions in many, many infections during that time. And with viruses, what we've learned is they've started coming up at very odd times. We had peaks in the summer when they should have been in the winter, with a peak in the spring when it should have been in the autumn. And it's going to take a few years before this settles down back to the pre-pandemic seasonality that we were seeing. But a consequence of that is that the bacterial infections that usually superimpose on many of these viruses have also changed. We have seen great shifts in the risk of infections due to this bacteria because of the changes in the viral seasonality in the background.

[Sarah Gregory] What time period did your study look at?

[Shamez Ladhani] The study that we're talking about is actually part of the national surveillance that the UK HSA undertakes. So England, we are constantly monitoring vaccine-preventable diseases through multiple sources. And this particular surveillance that we're talking about is invasive pneumococcal disease across all age groups in England since the start of the vaccine program two decades ago. But what we were focusing specifically on is changes in infections due to the pneumococcus in the different age groups as we went into the lockdown. But more importantly, what was happening to infection rates as we came out of the lockdown period.

So we were particularly interested in the last six months of 2021 compared to the previous year when we were in lockdown, and then compare that to the three pre-pandemic years to see how case numbers have changed over time.

[Sarah Gregory] Did you see something particular happening that you were looking at this from a different viewpoint?

[Shamez Ladhani] That's a really important question, because a few months before then, we had reported that we were seeing huge reductions in pneumococcal disease across all age groups because of the lockdown, and these reductions were consistently seen from birth all the way to old age. And we were convinced that these reductions were almost entirely because of the lockdown measures that were implemented (the social distancing, the masking, and so on), which reduced the ability of the pneumococcus to be transmitted from person to person. And what we wanted to do is, having said that these infections were going down, we wanted to report a small but significant increase that we were seeing in the young toddlers who were developing severe pneumococcal disease as we were coming out of the pandemic lockdowns.

[Sarah Gregory] How did you conduct this study?

[Shamez Ladhani] The UK has a very exciting surveillance program that is already in place and has been in place for many decades where we basically kept reports of every single confirmed

infection across the country by all the hospital laboratories around England which have electronic notifications in real time that allow us to monitor various different infections, including pneumococcus. We then have a system where we actually ask the hospitals to submit their strains to our reference laboratory so we can try and look at the strains that are responsible, so we know whether they are vaccine strains or non-vaccine strains and how much of the infection could potentially be preventable.

So by monitoring these case numbers, collecting a bit of data from the primary care providers and the hospitals and looking at the outcomes of the infection, we get a very good picture of how pneumococcal disease evolved during the pandemic, the lockdown, and as we emerged from the lockdown.

[Sarah Gregory] So just briefly, you want to tell us more specifically about the study?

[Shamez Ladhani] The reason for writing this paper was that we noticed a higher-than-expected increase in pneumococcal disease in toddlers (these are the one- to four-year-old age groups), though this is not surprising because this is the group that has the highest carriage rate of the pneumococcus at the back of the nose and throat. But what you would anticipate is that as the children got together in their nursery and caregivers and so on, they were interacting with each other a lot more and passing the bug a lot more. So if you are going to see any increase in cases, you would see it in the group with the highest carriage rates because that's where the bugs move around. And what we were trying to do with this paper is to raise awareness that, look, now that we're coming out of the lockdown, we need to be aware because we've already seen an increase in the toddlers (an increase, as expected, higher than the pre-pandemic levels). And this is usually the first sign that the rest of the population will also see an increase in cases because this is what we would expect as part of the ecological transmission of this bug in a community.

[Sarah Gregory] What exactly did you find with the study?

[Shamez Ladhani] What we saw was an increase in pneumococcal disease in one- to four-year-olds. There were more children being admitted to hospitals with severe pneumococcal disease—I'm talking about meningitis, which is inflammation of the lining of the brain, and septicemia, which is blood poisoning—and children can get very sick with it and develop very long-term complications out of the illness, or they could potentially die from the infection as well. These serious infections, if they are not treated quickly in a hospital, can be fatal very quickly. And what we were starting to see is young children having very severe presentations with this bug. And we wanted to raise awareness among the clinicians that you need to be more careful with the children coming in because it is possible that they have a serious underlying bacterial infection that needs to be treated very quickly.

For the epidemiologists and for public health policy, we had a separate lesson, which was that this increase in cases in the toddlers who have the highest carriage rates is probably the first signal of the bacteria coming back into the population, and if we see an increase in the toddlers, we are likely to see an increase in other age groups as well. What we did report, actually, is an increase in cases in adults as well, that was likely behind the toddlers as we expected. But we were still running at 50% of the pre-pandemic level. So overall, we were still seeing huge reductions in pneumococcal disease compared to the pre-pandemic year. It just happened that the cases we were seeing were disproportionately higher in the younger children, who are more likely to get more severe illness than the older children and the adults.

[Sarah Gregory] Do you have any further thoughts on why all of this occurred?

[Shamez Ladhani] It can be predicted from first principle, simply because the toddlers are the group that are most likely to carry the pneumococcus at the back of their nose and throats. And when they start interacting with each other, there's a lot more transmission in that group. And there will be the odd child who will be susceptible to pneumococcal disease, and therefore, that's where you will see it. We see a very similar phenomenon with meningococcal disease, which causes meningitis and the characteristic rash that you see which doesn't fade with the glass test. With meningococcal disease, it's the teenagers who are the main carriers of the meningococcus at the back of the nose and throat. And as we came out of the pandemic lockdowns, what we saw was an increase in meningococcal disease in teenagers, because again, that's the group that we expected a lot of transmission to occur between themselves. And then a few children who are susceptible will then get infected and get meningococcal disease. And that, again, was the first sign to us that meningococcal disease is also likely to increase because we are already seeing activity in the age group that has the highest carriage rate.

[Sarah Gregory] There's a vaccine for that one?

[Shamez Ladhani] There are different meningococcal serogroups, five of them are the ones that cause the most infection in Europe and in North America. There is an excellent vaccine called the ACWY vaccine that we offer to all our teenagers in this country. The US has a very similar program. So ACWY disease is very uncommon because of the program that we have in place. The increase that was also seen was due to meningococcal group B. There is a vaccine for group B meningococcus. But the highest incidence of group B disease is in infants. The UK has a national program for infants with the MenB vaccine, but not for teenagers because their risk is very low (we're talking about a handful of cases across the country). But what we are seeing is a definite increase in cases.

Interestingly, the US doesn't have a program for MenB disease because group B disease is really uncommon in the United States for reasons that we don't know. But nowhere in the United States is group B a problem in any age group at all.

[Sarah Gregory] So back to the study, were there surprises?

[Shamez Ladhani] There were no surprises with this study. There was nothing unusual that we didn't expect as part of this study. Perhaps the most interesting thing is we didn't expect this increase to occur so quickly after coming out of lockdown and having seen it within a year of the lockdown was a little surprising. We anticipated it will take a few years before we start seeing increases in all these infections as they reach their equilibrium. So that was a bit of a surprise. But I think that we were also very reassured that total number of cases were still running at 50%, which is excellent news because the vast majority of cases that we see are in adults and the older adults, and there was still very little infection in that age group, which overall was a reassuring message. I think what was important about this paper was really to raise awareness among clinicians that we are seeing an increase in cases among toddlers. If they are more aware that this is happening, then they will look out for the signs and treat the infection early, which then gives the child a better chance of full recovery.

[Sarah Gregory] I mean, you had this wonderful surveillance system, so I'm sure that helped enormously. But outside of that, were there challenges?

[Shamez Ladhani] The challenges are more the long-term surveillance program. It's trying to maintain a surveillance program that can pick up the cases at such low levels that we are seeing during the pandemic and after the pandemic. Some of the other challenges, especially during the pandemic, was actually getting the laboratory to submit their strains to the reference laboratory so we could look at the serotypes that are causing disease. This is critical for pneumococcal disease surveillance because there are only certain serotypes that are protected by the vaccine. And so, one, we wanted to know whether these vaccine serotypes were starting to emerge, and we were not aware of it; the second one was if it wasn't the vaccine serotypes, is there any specific nasty virulent strain that has come up that we're not aware of that has suddenly taken hold? Which we wouldn't have been able to do if every hospital in the country didn't submit their isolates to the reference laboratory. And for the UK, what was actually very challenging was that we had just moved to that 1+1 reduced schedule, and the whole world's eyes were on our program because we were the only country to implement such a reduced schedule and there was concern that we would have rebound infections because we weren't providing enough protection with this reduced schedule. And the problem was that the pandemic started literally when we moved to the 1+1 schedule. So we weren't able to assess the effect of the new program because case numbers just disappeared because of the lockdowns. So one of our concerns with this increase in cases was that perhaps the 1+1 schedule wasn't enough, and we were particularly worried because we knew we weren't getting the high vaccine uptake that we wanted because of the pandemic and the lockdowns, and we knew that vaccine uptake had fallen. We were trying very hard to catch up with our vaccine programs, and we've done pretty well with it. But there was always the concern that if we hadn't vaccinated enough children, we couldn't maintain that herd immunity that we needed to protect the rest of the population. So rather than challenges, it was more like getting the information quickly and in real time so we can try and mitigate any potential adverse outcomes that we were not expecting. The good news is that actually everything that we saw was as predicted. The serotypes were nearly all due to those that have not gotten the vaccine, so it has nothing to do with the vaccine. The case numbers have remained very low, and the overall disease burden remains below the pandemic level. So we are actually in a good place now compared to the pre-pandemic period.

[Sarah Gregory] How do you hope this information will be used?

[Shamez Ladhani] There are several really important messages that need to be got out there as quickly as possible, and I think this paper helps with the data to support this. The first one is that we are seeing an increase in pneumococcal disease in the toddlers, where we know that pneumococcal disease can be very severe because they present at the more severe end of the disease spectrum with meningitis and septicemia. So by raising awareness that we are seeing an increase in these age groups, we hope that clinicians will take note and be more aware of the condition and hopefully diagnose it early so that treatment can be implemented early.

The second bit is the public health awareness, to say that if we are starting to see it in the age group that we're monitoring very carefully, then we will start in the other age groups and we should be preparing ourselves to go back to pre-pandemic levels and make sure that we have the healthcare resources to deal with the situation whilst we are trying to come out of the pandemic.

And the third most important thing is that it's just a good reminder for everyone to get their children vaccinated to give them the best protection against these diseases. And it's not just pneumococcal, as I hope the messaging is for all vaccinations so we can maintain a very high

level of vaccine uptake for all vaccine-preventable diseases because the last thing we need is other problems after we come out of the pandemic.

[Sarah Gregory] Like we're seeing with polio now, right?

[Shamez Ladhani] Polio is definitely a case. And even though we don't think it's directly related to the childhood vaccine program or uptake in children, it is that type of concern that we do have. What we don't need is, we're still dealing with COVID, we still have a massive immunization program in place, we are still trying to protect our children from COVID, the COVID vaccines in children are taking up a lot of time and resources, and what we have to do is make sure that we don't compromise on our routine vaccinations, because we do not need any more problems. Polio is definitely one of that, it was completely out of the blue and unexpected. The UK has taken very big decisions about monitoring and dealing with the polio outbreak. We are vaccinating for all our one- to nine-year-olds to give them added protection against polio, which will add to the resources. Other countries have got measles problems because their MMR uptake fell during the pandemic, and they started seeing measles outbreaks. So there are many of these vaccine-preventable conditions that have the potential to explode as we come out of the pandemic, and we need to try and do everything we can to optimize our vaccinations that are available and known to be highly effective.

[Sarah Gregory] Are there ways people can protect their children, besides getting these very important vaccines?

[Shamez Ladhani] It's difficult to think of anything apart from vaccines that will help prevent these infections. Overall, it's to do with maintaining a good general health and making sure that children are healthy overall so that even if they do get an illness, they are able to cope with it and deal with it as we're supposed to. And the other side of the coin is if they do become unwell and if parents are concerned, we hope that parents get the message that they should seek medical advice early if they are worried about their children so that they can get the medical treatment that they need quickly, because we know that early treatment is the mainstay of good outcomes from these infections.

And that message is really important, especially in the COVID pandemic era, because there are many parents who are still reluctant to take their children to doctors because they're worried about COVID. And we need to change that messaging. Early in the pandemic, we saw a lot of children coming in with very serious illnesses because their parents were too scared to bring them into a hospital. And that wasn't a good idea. We had to change our messaging to let parents know that if their child is not well, they should seek medical advice as quickly as possible so that they can get the right treatment as soon as possible.

[Sarah Gregory] Dr. Ladhani, tell us about your job and your career path.

[Shamez Ladhani] So I have a very unique job, which I had to create myself because of my interests. I'm a pediatric infectious diseases specialist. I am a practicing clinician; I look after children with complex infectious diseases in a pediatric hospital in south London. I'm also a professor of pediatric infectious diseases and vaccine-preventable diseases at the university that's affiliated to the hospital where we do a lot of clinical trials on vaccines and other therapeutics for infections in children. But half of my job is working as an epidemiologist at the UK Health Security Agency, where I am responsible for a number of vaccine-preventable infections,

including meningococcal disease, *Haemophilus* disease, and pneumococcal disease. But being part of the pediatric public health system is very unique because it gives you the opportunity to work on a whole range of different infections, because it is such a unique position.

So in the last couple of years, COVID in children has taken up a lot of my time. It has been very exciting working with COVID in kids. We had the recent hepatitis outbreak in children which we had to deal with nationally, and more recently we're dealing with monkeypox outbreaks. And children are often neglected in these outbreaks because they are not considered to be affected, yet they are always part of the system and if you don't look after them, then you end up with having problems. So we are constantly developing guidelines and studies to make sure that children are protected in all these different outbreaks that we are witnessing.

[Sarah Gregory] What's your favorite project or area that you work on or have worked on?

[Shamez Ladhani] I think the most exciting thing about my job is not knowing what's going to come around the corner. And over the last few years, there's always something that's either directly or indirectly related to children. And there aren't many of us in pediatrics who work in public health, and so you are kept on your toes about the next event that might arise. Typically, as I just said with COVID, there was so much attention going to adults at the time because they were overwhelming the healthcare system. And there was so many fatalities in older adults that really very little was done with children, and we had to set up a national surveillance program. We went into schools to take blood samples to look at whether children are infecting everybody, whether they are developing immunity, and what their role was in transmission. All that had to be set up from scratch and literally working with colleagues around the country to go into schools and getting the samples that we need.

So COVID has probably been the busiest time of my life, but just when you think you were coming out, we had this big hepatitis outbreak that we had to deal with because we didn't really understand why it suddenly happened after the pandemic and what the causes were. So that needed setting up a national study to understand it. And recently the monkeypox outbreak, everybody was concentrating on the high-risk groups, but there are always going to be kids exposed to the virus, either in the house or in schools. We had a few staff that came in, and children were exposed to the virus in classrooms, and we had no idea what the risks were. There is a vaccine against monkeypox, but it has never been used in children, so we had to make judgement calls on when to use the vaccine, when not to use the vaccine. And those are the types of decisions that you make at the national level that clearly have major impact, and they do rely on you knowing your stuff and being able to respond in real time. So all very exciting, and I think all these new diseases come with their own exciting questions that we try and answer.

[Sarah Gregory] Well, thank you so much for taking the time to talk with me...taking the time out of your astoundingly busy schedule, Dr. Ladhani.

[Shamez Ladhani] Thank you very much. And thank you for having me again.

[Sarah Gregory] And thanks for joining me out there. You can read the August 2022 article, Increased Incidence of Invasive Pneumococcal Disease among Children after COVID-19 Pandemic, England, online at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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