Pneumococcal Disease in Refugee Children in Germany

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

[Sarah Gregory] Hi, I'm Sarah Gregory, and today I'm talking with Stephanie Perniciaro about her study on invasive pneumococcal disease in refugee children in Germany. She's a doctoral candidate at the German National Reference Center and she's calling from Aachen, Germany. Welcome, Stephanie.

[Stephanie Perniciaro] Hi. Thank you so much for having me.

[Sarah Gregory] Would you begin by explaining what invasive pneumococcal disease is?

[Stephanie Perniciaro] Sure. Invasive Pneumococcal Disease, or IPD, is an umbrella term for serious disease caused by the bacteria *Streptococcus pneumonia,* or pneumococcus. When we talk about IPD, we usually think about three main clinical presentations: sepsis, bacteremic pneumonia, and meningitis. There are also lots of noninvasive pneumococcal diseases, like ear infections, skin infections, and so forth, but IPD is the really dangerous one.

[Sarah Gregory] Okay, so what kind of symptoms does it cause?

[Stephanie Perniciaro] It depends on the clinical presentation, really. For example, meningitis often causes a severe headache and a neck stiffness, as well as a high fever, because meningitis is when bacteria get into the tissues surrounding your brain, so all of the symptoms are sort of localized there. A high fever is also common in sepsis and bacteremic pneumonia, but obviously those have different symptoms that aren't focused around your head and neck. All IPD, though, is severe illness. This is not something that you're going to get over with extra rest or grandma's soup, unless your version of grandma's soup is intravenous antibiotics. IPD requires hospitalization, and even that is not a guarantee of recovery, since mortality rates can range between 10 and 50 percent, depending on the population.

[Sarah Gregory] Pneumococcal conjugate vaccine, or PCV, can help prevent this illness, and in some countries, the vaccine is given routinely. Why don't children get vaccinated in every country?

[Stephanie Perniciaro] So, that's a great question, and the answer's a little complicated. Some children are unvaccinated because the vaccine is not available or it's too expensive and this is hard to change. And some children are unvaccinated because their caregivers *choose* not to vaccinate and that is also hard to change. A lot of excellent organizations are working to improve access and uptake of vaccines throughout the world, so, hopefully, with some more education and cooperation, we can provide better levels of protection against infectious diseases. But it is a very complicated problem.

[Sarah Gregory] Tell us a little bit about the refugee situation in Germany. I understand Germany has taken in more than a million refugees since 2015, and more than a third of them were children under the age of 18.

[Stephanie Perniciaro] Yes, that's right. So, this was because of a few reasons. One was the civil war in Syria, which started in late 2012, and then the expansion of the Islamic State in 2014 and

15. The number of asylum seekers entering Germany increased tenfold. A peak of over 700,000 people arrived in 2016—that's one percent of the whole population of Germany. And, since then, numbers have decreased, with over 200,000 applicants arriving in 2017, and so far in 2018, over 96,000 people have applied for asylum in Germany, almost half of whom were under 18 years old. The refugee crisis is by no means over and will likely not be over until the events precipitating it are fully resolved. We're in it for the long haul.

Having so many young people arrive is a special challenge, especially from a public health perspective. In addition to all of the housing, healthcare, financial, integration hurdles from an adult population, children are at higher risk for many infectious diseases. So, the European Center for Disease Control and Prevention developed a list of high-priority diseases which refugees should be vaccinated against on arrival. In practice, however, this didn't happen with every arriving refugee. There was a lot of confusion stemming from overwhelmed resources and a lack of personnel at the refugee intake centers, and the rate of successful vaccination varied a lot, with a range of six percent to 89 percent of people receiving the vaccination. A big problem for us was that PCVs weren't on this list in the first place, so I think IPD and noninvasive pneumococcal disease weren't really on the radar here, at all. By the way, these numbers came from the German Federal Office for Migration and Refugees, which are freely available online.

[Sarah Gregory] Of the 10 countries that most of the refugees come from, six do have the national vaccination program. The programs, again, are supposed to ensure that children are routinely vaccinated, so why aren't all the children from these countries vaccinated?

[Stephanie Perniciaro] So, these vaccination programs are designed to work when the countries' governments and healthcare delivery infrastructure is in place. When there's widespread conflict, society ceases to function, and especially when there's violent conflict, short-term survival gets prioritized over any preventative treatments. Workers from international relief organizations can sometimes help with vaccinations in these situations, but they are also often understaffed and overwhelmed. And the desperate conditions that led people to flee their homelands were not conducive to regular doctor's visits.

[Sarah Gregory] Okay, so why are refugees at greater risk for infectious diseases and, particularly, why do they have more antibiotic-resistant infections?

[Stephanie Perniciaro] Okay, so many refugees had not been vaccinated at all before arrival in Germany. So, for the first case, there's no prevention and no protection. So, people are more likely to carry infectious disease microbes in this situation. Also, the conditions in which refugees lived before and often shortly after arrival, are frequently overcrowded, which makes it very easy for germs to spread. One cough, one sneeze, one unwashed hand—this all matters a lot more when living conditions are cramped. Now, for antibiotic resistance, resistance typically develops when bacteria and the people who carry them are exposed to antibiotics. So, refugees tend to have more antibiotic-resistant infections because the bacteria carried in their countries of origin have been exposed to more antibiotics. And, how do you get exposed to more antibiotics? That just means that, if antibiotics are freely available for purchase or if people share prescriptions, there's a lot more opportunities for bacteria to come in contact with these chemicals and to survive the presence of these chemicals.

[Sarah Gregory] So, antibiotic-resistant infections become resistant because of more antibiotic use. Is this a across-the-board thing or is it an individual thing, like if…if seven people have had lots of antibiotics, then they will be resistant, and, say, one person hasn't had antibiotics much, will they be less likely to be resistant, or is it more just that the infection itself is resistant?

[Stephanie Perniciaro] Right, it's the microbes themselves that are resistant. It doesn't so much matter on an individual level. If we're talking about a group population exposure to antibiotics, though, this will directly cause more antibiotic-resistant infections. But, say, if you personally have never taken antibiotics, you could still get a strongly antibiotic-resistant infection.

[Sarah Gregory] That's too bad.

[Stephanie Perniciaro] Yeah!

[Sarah Gregory] Your study compared isolates from German children with IPD and refugee children with IPD. What specifically were you looking for?

[Stephanie Perniciaro] Okay, so a little background to explain this a little better. First, pneumococci, or *Streptococcus pneumoniae*, have a lot of different serotypes. And a serotype is a name for the kind of capsules that surrounds the bacteria and lets it grow and spread inside a person. And only a few of these serotypes are included in PCVs—7, 10, or 13. Serotypes that are included in PCVs were chosen for a few reasons. How common they are, how good they are at causing serious disease, and their levels of resistance to antibiotics.

So, one of our main tasks, as the national reference center for streptococci, is to track which pneumococcal serotypes are making people sick in Germany. We have a vaccinations program for children in place and we want to make sure that it's working. So, for this study, we wanted to see if German-born children with IPD were getting sick with different serotypes than refugee children with IPD. We know that refugee children are almost always PCV naïve, that is, they've never gotten a dose of PCV, because PCV was not on that list of high-priority vaccines for refugees arriving in Germany. So, essentially, we wanted to see if refugee children who have no exposure to PCVs were getting the same kinds of IPD as German children who have benefitted from a PCV program since July 2006.

[Sarah Gregory] Okay, and what did you find?

[Stephanie Perniciaro] We found that refugee children had IPD caused by serotypes covered by the vaccine that is currently used most often in Germany. This vaccine is PCV-13; it protects against 13 common disease-causing serotypes. And for the three years that we studied, refugee children had significantly higher odds, six times higher, of having vaccine-type IPDs than German-born children. And, additionally, when it came to antibiotic resistance, refugee children were over 23 times more likely to have multiple antibiotic resistant IPD than German-born children. Now, multiple antibiotic resistance, or we call it a lot, multiple drug resistance, we defined it as three or more classes of antibiotics are resisted by the bacteria. So, these infections are particularly difficult to treat and particularly dangerous. Any time that a child has IPD, it is a life-threatening situation. But, when the first-line treatments are not effective, it is even harder to treat the infection. So, combining the two steps, having vaccine-type IPD and having multiple drug resistant IPD, refugee children were, again, significantly more likely, over eight times more

likely, to have vaccine-type IPD that was also antibiotic resistant. So, all-in-all, our study found that refugee children did, for the most part, have different IPDs than German-born children.

[Sarah Gregory] Do you have any suggested next steps for all of this?

[Stephanie Perniciaro] Definitely. So, some of our recent work shows that most German children with IPD, over 80 percent of them, have received one dose of PCV, but that compliance with the full vaccination schedule, which is two primary doses and one booster dose, is pretty shaky, more like 10 percent of them. So, as far as public health practice goes, I would say we should work on improving that number. Providing more information to caregivers and pediatricians about PCV might help. And expanding the PCV program to also cover newly arriving refugee children, that would also help. As far as additional research in this area, I want to do a comparison that also separates German-born children by vaccination status, and compares IPD cases from fully protected, correctly vaccinated German-born children to refugee children. I think that this analysis will show an even more dramatic difference between the two populations and give a good illustration of why vaccination is beneficial.

[Sarah Gregory] Alright, Stephanie, and, finally, why are you interested in refugee health?

[Stephanie Perniciaro] Refugees have survived horrible circumstances and risked their lives to come to a completely unfamiliar place with the hope of providing a better future for themselves and their children. I think that these people, whose bravery in leaving their homeland and whose belief in the stability of a new country led them here, should inspire us to earn their trust and to also believe in our country's ability to do something good and unselfish and humane. Caring for refugees and ensuring that they're supported after their arrival, in healthcare, education, housing, and other basic needs, is a good thing. Protecting a vulnerable group in our society doesn't only benefit that group, it benefits all of us. If we can prevent serious illness, like IPD, with a vaccine, especially one that has been shown to be highly effective and cost effective, we should do it.

[Sarah Gregory] Thank you, Stephanie, for taking the time to talk with us today. I've been talking with Stephanie Perniciaro about her October 2018 article, Invasive pneumococcal disease in refugee children in Germany, a potential niche for vaccine type and antibiotic-resistant isolates. You can read the entire article online at CDC.gov/EID.

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

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