Global Epidemiology of Diphtheria

[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 to Dr. Kristie Clarke, a medical epidemiologist at CDC. She's also a commander in the U.S. Public Health Service. We'll be discussing trends of diphtheria incidence around the world. Welcome, Commander Clarke.

[Kristie Clarke] Thank you. It's so great to be here.

[Sarah Gregory] To start with, what is diphtheria and what are its symptoms? It's very dangerous, right?

[Kristie Clarke] So, diphtheria is a vaccine-preventable bacterial disease. It's caused by *Corynebacterium diphtheriae*, but specifically, strains of it that produce a dangerous toxin. And, yes, it is very dangerous. About one in 10 patients will die, even with treatment, and even more in populations of young children or older adults. Without treatment, up to half of patients will die. Spread is most often person-to-person—spread by coughing, sneezing, sometimes direct contact with lesions—and the symptoms at first are sore throat, swollen glands in the neck, a low-grade fever, and fatigue. But after two to three days, a patient will develop a thick greyish coating in the throat or nose. And this is called a "pseudomembrane" and it's actually how diphtheria got its name. So, "diphtheria" was derived from the Greek word for "leather" or "hide." And that coating can actually make it very difficult for the patient to breathe or swallow, and for that reason, diphtheria was once known as "the strangling angel," as horrible as that sounds. So, the toxin produced by the bacteria causes cell death which causes that thick coating. And that can also travel throughout the body. That toxin can damage the kidneys, the nerves, can damage the heart muscle, and even cause paralysis and respiratory failure. In order to treat the disease, you need antitoxin, in addition to antibiotics. Now, antitoxin is in limited supply, and it's expensive and time-consuming to produce. So, diphtheria is dangerous because, first, a high proportion of the patients die, and secondly, the treatment is in short supply and difficult to get to where it's needed in time for it to be really the most useful.

[Sarah Gregory] Tell us about the DTP vaccine. I know you need a tetanus booster every ten years, or at least that's what we do in the U.S., and diphtheria is included in that. Is that necessary to have that booster also for diphtheria?

[Kristie Clarke] The DTP vaccine that you mentioned is a combination of protection against diphtheria, tetanus, and pertussis. "Pertussis" is another word for whooping cough. And the diphtheria component of this vaccine was discovered in 1923, so it's one of our oldest vaccines. And three doses of DTP in infancy will protect 95 to a 100 percent of people from diphtheria for at least 10 years. Those three doses are what we refer to as the "primary series," and those are on the vaccination schedule for every country. Now, in order for a country to have good coverage, in order to prevent the spread of an outbreak to getting larger, you need to have 90 percent of the children in that population to have received that primary series. Now, you also asked about the tetanus and the diphtheria boosters that we get in the U.S., and we do get those every 10 years in our U.S. vaccination schedule.

[Sarah Gregory] So, we do need the diphtheria every ten years, as well as the tetanus?

[Kristie Clarke] Yes, yes. If you're going to give a tetanus booster, it's going to have that diphtheria component, and that will help us to maintain our population immunity.

[Sarah Gregory] Okay. The DTP vaccine was actually not really introduced, widely, until after World War II, even though it was discovered in the 1920s, and that helped to reduce the incidence of the disease, as you're saying. But what did diphtheria outbreaks look like before the vaccine? Was it relatively common or was it only a problem in certain parts of the world or at certain times?

[Kristie Clarke] It was very common before vaccine, both in the United States and elsewhere. And it was common among all walks of life. So, when you look back at the history of this disease, everywhere from, in the 1730s, there was an outbreak in the early American colonies that would take the lives of up to half of the children in certain settlements. And then, all the way up to royalty. In the 1800s, Princess Alice of the British royal family passed due to diphtheria. So, it's something that could really affect everyone and we're talking top five causes of childhood death, easily, worldwide. And in 1921, in the United States, there were over 15,500 deaths due to diphtheria, among 206,000 cases. One story that really illustrates how dramatic this disease could be was an outbreak of diphtheria in Nome, Alaska, in 1925. Now, Nome, Alaska in January at that time was only reachable via sled dog. So, there was a huge relay of sled dogs and drivers that was known as the "great race of mercy" that went 24 hours a day, over five and a half days, through blizzard, in minus 60 degrees temperatures, just to get this antitoxin needed to treat diphtheria to this town that had been put on quarantine due to an outbreak of this disease. And if you go to Central Park, the lead sled dog of the final leg of that relay has a statue in his honor, right in the park.

[Sarah Gregory] I actually remember an animated little video…cartoon, whatever…of this.

[Kristie Clarke] Yes, my daughter used to watch it.

[Sarah Gregory] Wow! Okay. Alright, after the vaccine was introduced, what happened? Did that pretty much get rid of diphtheria?

[Kristie Clarke] The vaccine worked really well and there was a rapid decline, although recently, we'll talk about how we have been seeing some increasing number of cases due to falling vaccination rates in some areas. So, when it was first put out, there was a rapid decline in industrialized nations that had access. Then, in 1974, the World Health Organization, or WHO, started its expanded program on immunization. And that primary series was in that original recommendations worldwide. And that caused a rapid decline then in lower-income nations, as well. And reported cases hovered around a low point of about 5,000 reported cases a year worldwide from 2006 to 2013. So, that's great if you think about 208,000 cases, just in the U.S. in a single year in the 1920s, right? However, there have been recent increases, and there were over 16,000 cases reported worldwide in 2018, and that's the highest number since 1996, and those were in areas of poor vaccination coverage. Now, here in the U.S. the last confirmed case by a toxin-producing strain was in 1997. However, as we've learned from recent outbreaks of measles outbreaks, for example, there're lots of diseases that are just a plane ride away, so we can't let our guard down.

[Sarah Gregory] Your study examines the occurrence of diphtheria around the world in the years 2000 through 2017, as you sort of just talked about. Why did you decide to investigate this?

[Kristie Clarke] Well, there really hadn't been any analysis of the worldwide epidemiology of diphtheria since the year 2000. There was a lot of attention to this disease in the 1990s, and that was due to a big outbreak of diphtheria in the former Soviet republics during that time. So, there

were several summary articles done at that time. However, since then, there really hadn't been anything published. And, like I said, we are in a time when we're seeing an increase in cases. And, in accordance with all of this, the WHO was in the process of deciding, "Should we recommend booster doses in the schedule worldwide?," and they also were interested in this analysis, so this paper grew out of an analysis that was presented to the Strategic Advisory group of Experts on Immunization of the World Health Organization, for that purpose, as well.

[Sarah Gregory] Well, go ahead and tell us about your study then.

[Kristie Clarke] Absolutely! So, I was particularly interested in looking at the ages and vaccination status of the cases of diphtheria that had been diagnosed in different countries. And our objective was to analyze the epidemiology of respiratory diphtheria since 2000 and also look at the vaccination rates within those countries and incorporate that into the analysis. So, epidemiology is the study of disease distribution and factors that can change the health status of a population, and we use it to help prevent and control public health problems. In order to do that, we needed data. So, we gathered the data from published papers, from the grey literature, which means reports that were disseminated, but not published in peer-reviewed journals, as well as requested any available data we were able to obtain from surveillance systems. Our final dataset included over 15,000 cases from 34 countries.

[Sarah Gregory] What did you find? Were your findings the same around the world?

[Kristie Clarke] So, in all countries, most cases were in people who were unvaccinated or incompletely vaccinated. And the biggest difference was in the age of the cases in different settings. Countries with more cases had a higher proportion of cases in young children, and that was due to lower childhood vaccination rates. So, in countries with endemic disease, that is, countries where diphtheria has a constant presence or countries that have more frequent and larger outbreaks, almost two in three cases were in children under 15. In countries with less frequent, smaller outbreaks, two in three cases were in people 15 and older. In both settings, about eight in 10 patients had never received a vaccine against diphtheria or had not received the full three-dose series. In countries with the endemic disease, two in three casesvhad no vaccines against diphtheria at all, whereas incomplete vaccination was more common in the countries with just a few cases.

[Sarah Gregory] Well, what was the most challenging part of doing this study?

[Kristie Clarke] Well, the most challenging part of doing this study was putting together the data to be able to do the study. So, there is no worldwide database of the age and vaccination status of people with diphtheria. What we have are how many cases were in a certain country in a certain year, but we don't know which ones had been vaccinated, how many vaccines, or how old they were. So, in order to get that, myself and my coauthors had to review over a thousand abstracts, dig through the disseminated reports, or grey literature, from the ministries of health from many different countries, look through presentations, and then we had to figure out how to put that all together in a database where these data from different sources could really all be combined to look at some of the factors that we were interested in, in a valid way. Now, this presented a limitation. The same data weren't available for each case in every single country or region. And we addressed that by doing several sub-analyses, or they're called sensitivity analyses technically, to test our conclusions. So, what if we take out this group, then do we have the same trend? What if we take out this other group? So, we looked at, you know, the strength of the data

that we had and used that to decide how to divide up our analysis to do the best that we could with the data that are available on the age and vaccination status of cases of this disease.

[Sarah Gregory] How long did all that take you?

[Kristie Clarke] Overall, I've worked on this about three years, combined with other projects, so it took a good amount of time.

[Sarah Gregory] Why doesn't every country submit this kind of data to the WHO?

[Kristie Clarke] Well, I have great news. There are new surveillance guidelines that have been released by the WHO for diphtheria and these are guidelines for collecting, analyzing, and distributing data about the people who have contracted this disease to help them keep track of where the disease is happening, what are the trends, and how can we take public health action. And those new guidelines do recommend case-based information which would include age and vaccination status. So putting these guidelines into action will improve the evidence that's available for public health action and for future research like this, and in the meantime, you know, this study does show a methodology that people can use if they're trying to look at the epidemiology of a disease for which there is less information available.

[Sarah Gregory] As you mentioned earlier, you talked briefly about the over 15 and under 15 people that got diphtheria, and you looked at the ages of people who were diagnosed with diphtheria in your study, why is this important? Did age have an impact on disease risk?

[Kristie Clarke] So, age was really important in our analysis because it was designed to answer the question whether booster doses at older ages should be added to the worldwide recommended vaccination schedule. Now, when you look at the proportion of cases in people aged 15 and over in a country and then you also look at how many people are getting the primary series of diphtheria vaccine in that country, you can see that, in countries with strong childhood vaccination coverage, there are fewer young people that are getting diphtheria, specifically in countries with the coverage over that 90 percent benchmark I mentioned, more than half of diphtheria cases are occurring among people aged 15 and over and when good coverage is achieved in that primary series the older people represent a high proportion of cases and that did suggest that the addition of booster does to the globally recommended schedule would be beneficial.

[Sarah Gregory] Ok, so it makes sense that as more children are vaccinated fewer of them will catch diphtheria but why are adults getting sick, especially in countries that don't have a lot of diphtheria outbreaks?

[Kristie Clarke] So this is something that we see in a lot of vaccine preventable diseases. There are increasing proportion of older patients as there's more children getting a vaccine and it's not because more adults are getting sick it's that fewer children are getting sick so therefore adults make up a larger proportion of the total cases. So that could be for a few reasons. Adults might have grown up during a time when the vaccination schedule in their country was different, when they had few or no booster doses; they could have grown up when coverage was lower so lower protection in their age group; it also could be due to waning immunity from that primary series, combined with a lack of exposure because, fortunately, the disease isn't circulating in that environment. So this is where booster doses can really help and after weighing this evidence combined with other presentations during the session, eventually, the strategic advisory group of

experts and the World Health Organization did update the recommended schedule worldwide to include booster doses for diphtheria.

[Sarah Gregory] Tell us how vaccines work. Give us a rundown on why they're so effective and not dangerous as so many people seem to believe that they are.

[Kristie Clarke] I'm really glad that you asked that question because it's a really important question and I'm going to answer from two different perspectives, which are both really core to who I am and the first is as a pediatrician and the second is as a parent. So, as a pediatrician, I've seen children suffer unnecessarily because they weren't vaccinated against a disease that made them sick and that's really heartbreaking to see. Vaccines are like self-defense training for your body. They train the cells in your body to know what to do if they do encounter a real germ or toxin and that way your cells are ready and by getting the vaccine you don't have to get really sick when you're exposed to a deadly disease like diphtheria. That's really important because, as I mentioned, about one out of 10 people who get diphtheria will die. Now, as a parent, and actually having seen what vaccine-preventable diseases can do, I was so relieved when I got my daughter her first set of vaccines. I mean all parents want nothing more than to protect their children, especially against dangerous diseases like diphtheria, and vaccination is the best way to prevent this disease. And as I mentioned, in our interconnected world, diseases like diphtheria are just a plane ride away and children are at greater risk if they are unvaccinated. That's not something—that's not a risk that I would ever be willing to take and, as a pediatrician, it's certainly not a risk that I would ever advise anyone to take.

[Sarah Gregory] Can you just tell us real briefly how a vaccine works? What actually happens in your body with vaccine? You're not introducing a medicine, this is a different process, right?

[Kristie Clarke] Right. So it is different. It's being exposed to usually a certain component, or in the case of diphtheria, a toxoid, which is an inactivated version of the toxin so that your body can learn how to defend itself if it were to ever encounter the real thing. So, basically being in a situation where there is a safe component that it can react to so that it can protect itself in the future.

[Sarah Gregory] All right. What does the DTP vaccination schedule look like and why did experts pick that specific timeframe?

[Kristie Clarke] So previously, the global schedule included three doses in the first year, but now, after all that evidence was presented, it includes three booster doses. So one at 12 to 23 months of age, one at four to seven years of age, and one to nine to 15 years of age. And many studies have indicated that these are the ages to continue to increase protection and that, in countries that have followed a booster schedule, the disease had been better controlled. So we've had booster doses in the U.S. for a long time but this is a new recommendation in terms of worldwide.

[Sarah Gregory] Since your study ended in 2017 have there been any major diphtheria outbreaks around the globe and if so what caused these?

[Kristie Clarke] Unfortunately, yes. So, as I mentioned, there were over 16,000 case in 2018 that were reported and large outbreaks have recently been reported largely in countries that are experiencing conflict, social disruption, or there are areas maybe of security or disruptions in the supply chain, that make, basically any circumstance that makes routine vaccination difficult,

makes it more possible for there to be an outbreak of diphtheria and that's something that we have seen. So you may have heard of the major outbreak among Rohingya refugees in Bangladesh. Yemen, Nigeria, and Venezuela are also among countries reporting high numbers of cases last year.

[Sarah Gregory] Based on your results, what steps do you think the international communities should take to keep fighting diphtheria?

[Kristie Clarke] Well, I think that the actions fall into three categories: vaccination, surveillance, and treatment. So in terms of vaccination, the U.S. Centers for Disease Control and Prevention, CDC, recommends that children do receive all their vaccinations on schedule and it's particularly important for children to receive the primary series on time. Global coverage with the primary series is 86 percent and it's plateaued near that level since 2010. So the primary series is still really important to get right but also to start the recommended booster dose schedule and monitor coverage rates with those booster doses to be able to make them the most effective. Now secondly with surveillance, we need to have effective surveillance systems in place in areas of conflict, refugee settings, etc., to be able to detect diphtheria outbreaks from the earliest stages and keep them from spreading in these vulnerable populations where we've tended to see some of the recent outbreaks. And for all countries to use the new WHO surveillance recommendations that include that important information, like age and vaccination status. Now lastly, in terms of treatment, to improve the availability of diphtheria antitoxins so patients can be treated as quickly as possible and how fast they get that antitoxin definitely is important in terms of their risk of dying or serious complications from the disease.

[Sarah Gregory] In your opinion, what's today's greatest public health challenge?

[Kristie Clarke] Well, of course, CDC's work in addressing public health challenges is informed by the evidence-based science, not anyone's personal opinion and the evidence, both globally and domestically, tells us that addressing the health of young children remains a challenge and a top global health priority for CDC. And certainly, of course, having spent all those years training as a pediatrician, the health of young children is a top priority, you know, for me and when you look at this multi-faceted challenge, the health of children is not just addressing barriers to childhood vaccination, which we've talked about being important, but it also involves nutrition, and the fact that children, you know, have developing lungs, they have lower body mass and are more sensitive to anything in their environment. We're even learning more about how traumatic experiences early in life can impact chronic disease risk into adulthood. So the challenge of trying to make the next generation healthier than ourselves is really one that is multi-faceted and, even though CDC is known as the public health agency and there are public health departments in all of our states which are important partners, really improving the health of children is a team effort—it's parents, it's families, it's teachers, it's everyone in our community and I just am amazed if I imagine what our world could look like in forty or fifty years, if we were able to meet this challenge because, globally, children are about a third of our population but they're all of our future.

[Sarah Gregory] On that note, tell us a little bit about your job at CDC. What excites you about it the most?

[Kristie Clarke] Sure. I'm a medical epidemiologist, so I'm a physician who can treat individual patients but I also study patterns of disease at a population level and I love that for two main

reasons. First, it's so multi-disciplinary. I loved my pre-med courses, but I was a Spanish major and an international politics minor and what I love about public health is that it's where science intersects with sociology, with economics, political science, psychology, communication, all of these things and that's really fascinating to me. And secondly, I love the variety of challenges that we're confronted with. So they're always changing and I've done deployments for polio eradication, for Zika virus, for Ebola virus disease several times and I'm able to help people out which is a true honor. And I'm always learning and I've had the opportunity to work in areas with infectious disease, as well as nutrition, reproductive health, birth defects so I like to envision addressing childhood health challenges but I love that, through my work, I'm able to be a part of that change and meeting that challenge.

[Sarah Gregory] Well thank you for joining us today, Commander Clarke.

[Kristie Clarke] It's my pleasure. It was really wonderful to be here with you.

[Sarah Gregory] And thank you out there for joining us. You can read the October 2019 article, Global Epidemiology of Diphtheria, 2000-2017, online at CDC.gov/eid

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

[Announcer] For the most accurate health information, visit cdc.gov or call 1-800-CDC-INFO.