

Cross-Protection of Dengue against Zika

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

[Sarah Gregory] Hi everyone, I'm Sarah Gregory, and today I'm talking to Dr. Felix Drexler. He's calling in from Berlin. Dr. Drexler is an expert in virus discovery and viral ecology at Charité, which is a teaching hospital in Germany. We'll be discussing the ways that dengue infection might protect against Zika syndrome. Welcome, Dr. Drexler.

[Felix Drexler] Hi. Hi, Sarah, nice to meet you.

[Sarah Gregory] So, okay, let's get started. Zika gained international attention a couple of years ago, but we haven't heard much about it since the end of the 2015–16 outbreak. What happened? Is Zika still a problem?

[Felix Drexler] Yeah. Yes, Sarah, I would—I would say it is. And it's actually quite a complex scenario and we don't really fully understand what happened, but a few things are for sure, and one is that Zika has not gone away, simply. We still see cases sporadically from several Latin American countries, but, of course, at a much, much, much lower magnitude compared to the epitome of the outbreak from...from '15–16. But we're still seeing cases and we don't really know for sure why the case numbers, at least of the reported cases, went down so dramatically.

We, of course, have a—a few...we have a few hypotheses and...Zika exists, it's like one serotype. You can have it...probably you can have it once in your life, that we don't know, but for a given time, right, until maybe your immune responses wane sufficiently for you to become infected again. But we don't know that. So, we probably...we can assume that, in those areas that were heavily infected by the Zika outbreak in Brazil, that so many people got infected so quickly, that the population community protective immunity was so, so strong, that there was such a large proportion of the population immune to Zika that they were not...that the number of susceptible individuals dropped too much and the virus couldn't sustain transmission chains. And probably we can assume that at least in several areas—and not many have been studied—but we did a study from...from Salvador, which is in Northeastern Brazil, it's a big city—the third biggest of Brazil—which had about three million inhabitants. And we show that within one year, from 2015 to '16, about 60, 70 percent of the population got infected by Zika. So, this is too much for the virus to maintain itself in that population. And in this population it is probably gone for quite some time. Now whether this applies to all of Latin America, we don't know.

[Sarah Gregory] Does Zika virus infection always lead to birth defects in women's babies?

[Felix Drexler] No, certainly not. I think replying to this, it's—it's good to...to...to...to say where we started, 'cause it's such a great, such an important question. And when...when the Zika outbreak started, the estimates of how frequent a mother's baby or fetus would be damaged upon maternal infection during pregnancy, varied between, like, say 0.05 and 40 percent. And this, of course, is not really helpful. By now there's such a great body of data from several excellent studies and we can say that we are in the range of maybe one or a few percent of defects. But it's important to know, and people sometimes get that wrong, that we are...when we say “birth defects,” we don't just say microcephaly, which is like...the most dramatic and most

visible symptom of a congenital Zika infection. So we are probably seeing much more than just microcephaly. We have—we have to consider hearing impairment in infected kids. And so, there's still a lot to learn from those kids that got infected and that are growing older, so that we are actually still to learn all of the possible sequelae of a congenital Zika infection. But it's definitely much, much less than 40 percent. So that's good.

[Sarah Gregory] That is good news and not what I think, as you said, is the general perception. I think people thought if you got Zika, you had a baby with birth defects.

[Felix Drexler] Yeah, precisely. I mean, we always knew it wasn't going to be that way. It's just that the...the...the symptom was so striking, this is the one thing that you could realize...that people realized that something was going on in Brazil. And it took a long time because, this may sound trivial, but if you don't know what is a normal head circumference in a baby, or in—sorry, in a given population, right? And Brazil has a lot of genetic mixture, the way—so the Brazilian background, the genetic background, is very heterogeneous. And...and so, what is a normal baby's head size in such a population? And it took an incredible amount of time until first we realized that something was going on, and then that we understood how to diagnose—what is too small, so when is a baby's head too small. That took a long time and a lot of work from...from clinicians, gynecologists, pediatricians, and epidemiologists.

[Sarah Gregory] So, dengue and Zika are both considered flaviviruses. What does this mean and how are they similar?

[Felix Drexler] Yeah, they are. Yeah, flaviviruses are called flaviviruses...it comes from Latin, flavus, which means “yellow.” This is because the prototype species is yellow fever virus, which is a virus that affects the liver of those that are infected, and if your liver is not working well, you can get jaundice. And since these people had jaundice, which presents as sort of a yellowish skin color and a yellowish color of your sclera, so your eyes. So, it was sort of such a pathognomonic feature that all these viruses were then called flaviviruses.

And, as you say, dengue and Zika are both flaviviruses, so they share a lot of...a lot of different features, actually. They have very similar genomes, structure, and length. So, the nucleic acid that composes the viral genome is very similar. The structure is similar, and that is important because if the structure of the viral protein, the—the viral capsid, is similar, it also translates into something you—you can call antigenicity. So, it means that these structures are so related that...you can have, for example, antibodies that are elicited by an infection with such a virus interact with another virus just 'cause it's structurally so similar.

[Sarah Gregory] With dengue, sometimes the second time someone gets infected, the illness is more severe than the first time? This seems counterintuitive to me. Why would this be?

[Felix Drexler] Basically, we think, and there's now good evidence supporting this hypothesis, that this is due to immune enhancement, and more particularly a process called antibody-dependent enhancement. And this theory was put in place by Scott Halstead in, I think in the 70s, and...and a lot of people didn't agree at that time, and some people still don't agree, but there's very important evidence from large longitudinal studies that support the hypothesis that, indeed, you may have immune enhancement. And in—in principle, this means that the most important feature of antibody-dependent enhancement describes a process where you have dengue once

and your body reacts to the infection by producing...by mounting an immune response, including the production of antibodies that bind with the virus and kill it—simply that. And, so, this antibody is still in a person's blood after the dengue infection has cleared, right? And then dengue, as you said, you can have it more than once because dengue exists differently from Zika, a different...as different serotypes. And...and these serotypes can infect you, despite the infection you had with a prior... before that, with a different serotype. So you can have a second infection with a different serotype.

And now these antibodies that are in your blood from your first infection, again bind to the new dengue virus infecting you at the moment, but instead of neutralizing the virus, they form a complex. So, you have a virus-antibody complex, but it's not killed, it's just floating around. And now there are many cells, like monocytes, that are normally poorly susceptible to dengue virus, but this antibody-virus complex can bind to receptors on these cells, like monocytes, and can be taken up. So, the virus's entry is actually facilitated by these not—or nonneutralizing antibodies. And then you have more virus and the virus is transported around in your body in a...in a facilitated fashion, and you get a more severe infection. So, this is the general principle.

Of course, we now know that it's probably more, a little more complex than this, because we see that, for example, it depends on the amount of antibodies you have. So low antibody titers may be a particularly interesting and relevant risk factor for you to have a severe secondary dengue infection, compared to very high titers that may then rather be protective. So, it's definitely complex and there's a lot of work to do, but...but in principle, we now know that this is definitely happening in dengue.

[Sarah Gregory] Well, that is complicated and seemingly horrifying, frankly. During the outbreak, the number of birth defects caused by Zika was highest in northeastern Brazil. Some scientists theorized that this might have to do with dengue prevalence in that area. Why would they think that?

[Felix Drexler] Well, this is one of the biggest enigmas, I would say, of the Zika outbreak, of the Latin American Zika outbreak, is why we have this incidence of Zika-associated microcephaly cases in Northeastern Brazil, which reported like 95 percent of all cases of microcephaly from that outbreak. So the question is: why is this, why is this regionally happening so much? Is it that no other region in Latin America has seen the same magnitude of Zika infections? Some people think that and...but there's...there's not...that hypothesis is not supported by very solid evidence, but we cannot refute it completely. And others have hypothesized that there may be effect modifiers. So that this population living in Northeastern Brazil, may...there may be a component that aggravates the Zika infection. And many effect modifiers have been discussed. So, people were discussing whether vaccination history would make a difference. For example, if you had a yellow fever shot or not, whether it would protect you or increase the risk for you to have congenital Zika syndrome, if you were a pregnant woman. And others have thought that this is because of toxins that Northeastern Brazilian people who would...you have to know that this is a poor, a relatively poor area of Brazil, right? So it's...the resources are limited. And in some slum areas, people don't have access to...to running water. And so, they have to store water in...in large plastic tanks. And to prevent these—these water supplies from getting full of...yeah, insects, they use some toxins, they add toxins to the water so that it stays clear. And then people

hypothesized that these toxins may actually be causing the...syndrome that people were seeing, instead of the Zika infection, or in addition, or as a component of Zika infection.

But most of these effect modifiers have been ruled out in case-cohort studies, and the one thing that was remaining is—is the question on dengue, because as I said to your earlier question, that you can have a more severe secondary dengue infection than your first dengue infection. So people have thought, well maybe if you have dengue antibodies, they can enhance Zika infection, right—in the same way that they would enhance a secondary dengue infection. And, indeed, one has to say that the data that came out in the early years of the outbreak, so 2016 mostly, were fully supportive of this.

There was an incredibly strong amount of data raised in vitro, so in cell culture or on placental tissues, that was showing that, in the presence of dengue antibodies, you had a much more intense Zika virus infection. So, it all made sense, in many ways, and this was a clear call for further epidemiological studies. Because, at some time point, you have to go for...for epidemiological investigation—you can't just resolve everything in vitro. The data from the animal models was contradictory in many ways. For example, you could confirm the enhancement of Zika virus infection by dengue immunity in some mouse models, but not in nonhuman primate models. So, as I said, it got complex, and we needed epidemiological studies like ours.

[Sarah Gregory] Okay, so what was the goal of your study?

[Felix Drexler] Yeah, so we looked precisely at that. We wanted to know if Northeastern Brazil had seen different dengue viruses in the past. 'Cause, hypothetically, you could argue, "So, why Northeastern Brazil only?" You could say, well, maybe Northeastern Brazil saw different dengue viruses than, let's say, Rio de Janeiro or São Paulo, right, which are more to the south. And so, we wanted to find out about dengue infection histories in Northeastern Brazil, in that city that I was mentioning earlier, in Salvador.

[Sarah Gregory] Okay, so tell us about this study. Who was involved, when did it take place, and what were your methods?

[Felix Drexler] We...well we...first of all we did a case-cohort design. So, this means that we enrolled women who were giving birth during the epitome of the—of the outbreak, 2015-'16, and we offered them to participate in our study. And virtually every single woman deliberated giving birth in the university hospital's maternity ward in Salvador was happy to be enrolled, to participate in the study, because everybody was so scared, and people were happy to get additional support from that study.

So, we enrolled the mothers, and then we followed them up. And some of the mothers gave birth to a child with a neurological problem, like microcephaly, and other babies were apparently healthy. And we just...we followed them up a bit, as well, a few more months, so that we could know something...if everything was going fine the first few months after birth. These are...these are the patients, the study participants.

And then in the lab...so, we took blood from those mothers at delivery, and we tested it for antibodies against all four dengue viruses, so that we could find out if they had been infected with dengue, and if so, with which serotype. Dengue has four serotypes and we tested all four of

them. And, finally, we checked all the dengue genomes that are in public databases and sorted them by their origin, so that we could say, “Okay, this is a dengue virus that has—has been obtained from somebody in Northeastern Brazil or in any other region of Brazil. And eventually we did some mathematical modeling to quantify the impact of some of the variables we have—had been studying on the development of congenital Zika syndrome. So, this is pretty much our study design.

[Sarah Gregory] And you had some pretty striking results. What were they? You were pretty surprised, right?

[Felix Drexler] Yeah, you could say so. I mean, basically the opposite of what we thought would be true came out. So, what our data showed is that, instead of dengue infection *increasing* the risk of a mother’s baby to have Zika-associated problems, it protected against it. So, what we saw is that, strikingly, the cases—so the cases of the mothers whose babies had problems, and...and these people had seen less dengue infection than the controls. So, dengue was much more frequent in the...in the lives of those mothers whose babies were healthy than in the cases. And this was pretty striking and alerting at the same time. And I have to say that I was extremely pleased that our data were completely consistent with two important studies that came out around about the same time as our article in EID, from Albert Ko’s group at Yale and Eva Harris’ group in Berkeley, who were investigating other populations and found similar things. So, we are...I think that the picture is now pretty consistent, I’d say.

[Sarah Gregory] And what’s the explanation for this?

[Felix Drexler] Well, I’m...I will have to hypothesize. What we are seeing here is probably, again, a complex pattern, where probably what is happening is if you have dengue over and over and over, and recently, then your immune response against dengue virus is very strong and probably this strong immune response is rather protective than enhancing. And in comparison, if you had dengue maybe just once and it was 10 years ago or 20 years ago, then maybe your immune responses against that past infection are so weak that they...that they do not protect you anymore.

And I think, because we investigated whether the magnitude of the antibody titers would make a difference, and it did not, so what I think is...what is probably happening is that you see a strong component of cellular immune response that protect the baby of those mothers that are...that got infected by dengue before. And...the... it’s—it’s not easy for a pathogen to cross the placental barrier, right? So the, all of the, all of the contact, all of the blood that is circulating to the fetus has to cross the placenta, and the placental barrier, the maternal side of the placenta is full of T-cells that...that are exactly there to protect the fetus from...from pathogens...for example, among other things, from pathogens infecting the mother during pregnancy. And probably, if these women had been infected repeatedly by dengue viruses, then probably these T-cells were so active, they were so active...there was such a strong cellular immune response at the placental level that it protected the fetuses of those women. That’s my best guess, at least.

[Sarah Gregory] That’s really interesting, especially since dengue doesn’t protect against itself.

[Felix Drexler] Well, against the same serotype, right?

[Sarah Gregory] Yeah. Some people noticed that there were very little dengue infection going on at the time of the Zika outbreak. Is this related?

[Felix Drexler] Yeah, that's a good question. If...I guess it is. Again, the data are not so solid, but what...what may be happening is that this is a two-sided process. So, at the same time that dengue may protect or may induce cross-protection against Zika, Zika, in turn, may cross-protect against dengue. 'Cause hypothetically, we can assume that, as I said, 60 to 70 percent of people, at least in some areas of Latin America, got infected quite fast, right? So, these people were so full of Zika-induced immunity that, probably, it's the other flaviviruses, like dengue, probably didn't stand a chance to actually replicate and infect those people. So this is what we can assume, but we definitely...we probably need more data, epidemiological data, to really have solid data proving this.

[Sarah Gregory] Can these findings be used to protect people?

[Felix Drexler] Oh certainly. Maybe not on the short run, but this whole game of having cross-protection on the one hand, but enhancement on the other hand, right? So that, prior flavivirus infection can protect you or it can make you more sick in a secondary flavivirus infection. So, the more we understand that, the better we can design our vaccine strategies.

You know that there is a dengue vaccine now and that it's being used in several countries, including Brazil and the Philippines, and that we have a lot of problems over the last, well, two years or so, in that, exactly in the context of enhancement that we're—that we are discussing today, it was observed that people who had never seen dengue got a dengue shot, and then got the real dengue infection were actually...were at higher risk to be...to have severe disease than...than those people that got infected that had already seen dengue before, right? So it's the same game of cross-protection versus enhancement; it's really exactly the same thing.

And we need to understand the flaviviral immune interplay much better so that we can design safe vaccines. Which we clearly need to do. I mean, the whole dengue vaccine uproar has really had a massive impact on vaccine—on how people perceive vaccines. And we need vaccines, we definitely need vaccines, we need dengue vaccines, but we need safe vaccines that people actually accept, and that do not cause immune enhancement. Because, I'm not sure if you've seen the data from the Philippines, for example, is quite dramatic in that people were so unhappy with what they thought would be a safe vaccine, that they stopped taking *all* vaccines, or many. And they are now...they just recently had the largest measles virus outbreak in a long time, and that's not good. We need to understand this...this interplay, this immune interplay, so that we can produce vaccines that are safe and that people are happy in taking, so we can protect them.

[Sarah Gregory] Yes, this is very unfortunate in this whole climate of vaccine fear, to have this happen.

[Felix Drexler] Yeah, exactly. Now we clearly... I mean, we need vaccines, and we need good vaccines, and we need to have people believe that these vaccines are actually really protecting them. And this is exactly... and flavivirus, that's not an easy topic. You don't just make an easy...easily make a flavivirus vaccine, exactly because of the context of what we are discussing today.

[Sarah Gregory] Right. But I do want to take a moment here to reaffirm that...that this was a rare exception, that most vaccines are very safe and people do need be taking them, right?

[Felix Drexler] Absolutely. No, I completely agree. It's very unfortunate that people who actually don't really understand vaccines and vaccinology make expressions that they shouldn't be doing and—and raising fears. Vaccines are the single most effective solution...I mean nothing has saved more lives than vaccines. I mean, vaccines are, like, together with antibiotics, and...it is the thing that has saved us in the last decades or hundred years. And we do need vaccines and need people to take vaccines and understand the benefit that they all bring. And they are really quite safe and, as you say, the dengue vaccination story is very recent and very...a very rare exception and a lot of people are working to actually to find better ways to apply these vaccines. I'm not saying—I apologize if I was not clear—I'm not saying that the—the dengue vaccine is not to be taken, it's just that we need to have better ways to make it safe and to know who we should be giving it to, right?

[Sarah Gregory] Right. Should we be worried about Zika making a comeback? I understand that herd immunity protected that whole region rather quickly, but can it sneak into other areas that don't have such an overwhelming reaction and sort of start up again?

[Felix Drexler] Yeah, absolutely. I mean the extent of Zika spread all across Latin America is unknown. We know it for some areas, but not for many. So, hypothetically, it probably can come back in many of these areas and we simply don't know. So, this is one thing. But at the same time, of course, I don't want to raise unwarranted fears about Zika is lurking around the corner, I'm not saying that. It's just that it could reemerge, that's one thing.

And at the same time, Zika is an arbovirus, right? So it's transmitted by the bite of an arthropod, a mosquito. And usually these viruses—which we call arthropod-borne viruses or in short arboviruses—infect...they can infect other vertebrates than humans, as well, say, in the jungle, or you know, like monkeys or maybe other animals, so we can talk about animal reservoirs. It may reside in the mosquito, per se; it may be in... sustained in...it may be circulating amongst nonhuman primates, such as monkeys. Now we simply don't know at all.

And the point is, if Zika...if Zika virus made it into what we call a sylvatic cycle in Latin America, then it may simply never go away. And if what we have seen—there's other arboviruses, like chikungunya virus and dengue virus itself, which used to be a sylvatic virus before it made its way out of the jungle to just be sustained among people. Chikungunya, for example, is a good example, which just stays somewhere in the bush, we don't really know in which animals, and it reemerges once the pool of susceptible human individuals has replenished, either because people are migrating or because simply enough...enough babies are born who are immunologically naïve, so they are susceptible to the virus. And the virus, as soon as it has a population that is big enough to sustain it and it is introduced, so of course you have a stochastic element here, right? You have to ...the virus has to be lucky enough to get into that population, like Zika into Latin America. And as soon as that happens, it may all begin again, but we simply don't know if Zika virus made it into a sylvatic cycle. So, we need to know that and what we...finally, what we have also seen is that we have seen...that those countries that maintain close commercial interactions with Latin American countries, such as Angola and Cape Verde, who are Portuguese-speaking countries, such as Brazil, or like Brazil, and we have seen

Brazilian-type Zika infecting people now in Africa. And Zika used to—this is—this is actually really interesting because Zika virus is an African virus, right? Zika is named after a forest that is in Uganda, the Zika Forest—and it made its way out of Africa over all...all these years, and now it's coming back to Africa in a form that caused the outbreak in Latin America. And we don't know at all what they may...what that may cause—we really have no clue.

[Sarah Gregory] So, what's the best way for our listeners to protect themselves from Zika or any other mosquito-borne diseases?

[Felix Drexler] Don't get bitten!

[Sarah Gregory] [laughs] Oh great!

[Felix Drexler] [laughs] Yeah, use repellants, you know, long sleeves and that's really the basics: don't get bitten. And then we talked about vaccines. If we are talking about a flavivirus that...for which a good vaccine exists, such as yellow fever virus or tickborne encephalitis virus in Europe, take the vaccine. Brazil has seen the largest yellow fever outbreak in decades immediately after Zika, and it's such a great vaccine, it's an old vaccine, the yellow fever vaccine is an established vaccine, but it's extremely efficient and it protects people from a disease that otherwise kills almost one in two that are infected. So, don't get bitten, use vaccines where possible.

[Sarah Gregory] Okay. Alright. So, tell us about your job and how you became interested in this subject.

[Felix Drexler] Well, I'm an MD and after med school I worked in Brazil for almost 10 years. And I was seeing patients in a tropical medicine unit, and I was interested to also do research into these infections. And so I started a scientific career and went back and forth to different institutes in different countries, and still working in Brazil. I really enjoy developing new tools to diagnose those infections in a setting like Brazil where, you know, you don't—you can't just do anything you want because the resources are somehow limited. And we developed new tools to diagnose HIV, hepatitis C virus, yellow fever virus. And I'm very pleased still that some of these tools have made their way into public health laboratories in Brazil, for example, and are actually being used. So, this is really great. And so, I got interested and I still am interested because I think it's a great way to do this...to do research that really helps people deal with these emerging infections.

[Sarah Gregory] Are you...are you from Germany originally?

[Felix Drexler] Yep.

[Sarah Gregory] Yeah.

[Felix Drexler] Yeah, I was born here.

[Sarah Gregory] OK. In Berlin?

[Felix Drexler] No, in Frankfurt.

[Sarah Gregory] Okay, well thank you so much for joining us today, Dr. Drexler.

[Felix Drexler] My pleasure. Thanks for having me.

[Sarah Gregory] And thank you, my listeners, for joining us as well. You can read the full August 2019 article, “Cross-Protection of Dengue Virus Infection against Congenital Zika Syndrome, Northeastern Brazil,” online at [cdc.gov/eid](https://www.cdc.gov/eid).

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

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