

# Zika IgM Detection a Year or More after Illness

*[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 Isabel Griffin, an outbreak epidemiologist at Florida Department of Health in Miami-Dade County. We'll be discussing her article about testing for Zika virus infection using the antibody IgM a year or more after illness. Welcome, Isabel.

[Isabel Griffin] Thank you for having me. I appreciate it.

[Sarah Gregory] Let's do some basic biology first. Explain to us what IgM is.

[Isabel Griffin] So, IgM stands for Immunoglobulin M. It's one of five classes of antibodies that your body produces. IgM antibodies are actually the first to appear after an infection. Prior to our study, there was actually very limited data on the length of time that the IgM antibody remains detectable after the onset of Zika symptoms. We knew that the IgM antibodies typically develop about four days after your symptom onset and remain detectable for at least 12 weeks. However, data on other flaviviruses like Zika, such as West Nile virus or yellow fever, suggest that those antibodies can actually remain detectable for a few months to up to years after infection.

[Sarah Gregory] Your study discusses Zika virus IgM and neutralizing antibodies. What's the difference between them?

[Isabel Griffin] So, IgM antibodies are the immune system's first line of defense. Zika virus IgM antibodies actually bind to an antigen, or a protein, that's encoded by the Zika virus genome, on the virus, signaling to the immune system to attack the virus. A Zika neutralizing antibody is one that functionally inhibits the Zika virus. In other words, the neutralizing antibody is preventing Zika virus from infecting the cells in your body. An important distinction for diagnosis between the two is that IgM antibodies eventually will diminish, whereas neutralizing antibodies may actually persist for many years, possibly providing lifelong immunity. Those two antibodies are actually detected by two different tests. So, IgM antibodies are detected using an IgM capture enzyme-linked immunosorbent assay, also known as the MAC-ELISA, and the neutralizing antibodies are detected through what's called plaque-reduction neutralization testing, or PRNT. MAC-ELISA is a pretty common test that most laboratories can perform, whereas the PRNT is a little bit more laborious and very few laboratories actually are able to perform it.

[Sarah Gregory] So, why did you do this study? What were you trying to find out?

[Isabel Griffin] So, we wanted to see if the Zika virus IgM was detectable longer than the previously established 12 weeks. So, in order to do so, we actually reached out to all of our Zika cases from our 2016 outbreak to see if they would be willing to provide us another serum sample to test for the presence of the Zika IgM antibodies, nine to fifteen months after their Zika symptom onset. So, if individuals still had detectable IgM antibodies over a year after onset, this would have significant implications for the interpretation of lab results.

[Sarah Gregory] Did you have a result in mind when you began this study? What did you think you'd find?

[Isabel Griffin] So, based on the literature concerning other flaviviruses, we knew it was plausible that the IgM could remain detectable that far out. Honestly, I thought everybody would be negative or have undetectable levels, given that the previously believed time frame was up to 12 weeks and we were testing a timeframe significantly longer than the 12 weeks.

[Sarah Gregory] And exactly what did you find and what do you consider the most important aspects of these results?

[Isabel Griffin] So, we actually found that almost everybody still had detectable levels of the Zika IgM and all had Zika virus neutralizing antibodies many months after the previously documented antibody response. This means that, if we were to encounter a patient today, for example, an asymptomatic pregnant woman, who tests negative for Zika virus by PCR, or polymerase chain reaction, testing, which is basically just looking for the presence of the virus, rather than the body's antibody response, but is also positive for the Zika IgM antibodies, then we really don't know with certainty whether the exposure to Zika virus was recent or from over a year ago, which has significant implications for a pregnant woman.

[Sarah Gregory] So, this seems pretty challenging. Was...what's the most challenging aspect of your study?

[Isabel Griffin] Definitely the coordination. So, we actually had about 362 potential study participants during our time frame of interest, and it was a lot of coordination between those study participants and our phlebotomists, and coordinating going to the clients' homes or having them come to our clinic. So, it was a lot of work and resources, but obviously it was well worth it, 'cause it now changes how we interpret Zika lab results.

[Sarah Gregory] What does this mean for pregnant women and women of childbearing age, since obviously they are most impacted by getting the Zika virus?

[Isabel Griffin] Yes. So, our results really emphasize the importance of diagnosing Zika virus infection in pregnant women using the PCR. So, that test that's looking for the presence of the virus, which can confirm a recent infection. PCR can be positive for a short period, usually about a week or two after infection, but when using the serological test results, such as the IgM, it's important to consider the current epidemiology of the disease, whether the pregnant woman has had an exposure to Zika virus, her symptoms she may be having, so is she having those cardinal symptoms of the fever, the rash, the joint pain, or the conjunctivitis, which may help determine the timing of infection?

[Sarah Gregory] So, just help me understand here. If they've got these...this IgM or neutralizing antibodies that you find much later, they're really not still carrying a virus that could hurt a fetus then?

[Isabel Griffin] Exactly. So, it's just showing that at one point in time they were exposed, but it may not show that it's a recent infection. So, it's really the presence of the virus that's having the greater impact on the fetus versus the presence of the antibodies.

[Sarah Gregory] So, can you clarify this crossover infection result? Does it mean that people have had multiple types of infection or that somehow the body reacts the same to all these flaviviruses?

[Isabel Griffin] Mmm hmm. So, the cross-reactivity refers to a limitation of the testing, where serologic tests are unable to differentiate between flaviviruses, specifically Zika and dengue. Primary Zika infection, so people that have never had another flavivirus infection, so they've only had Zika, typically generate a highly specific neutralizing antibody. Whereas, secondary flavivirus infections, so perhaps someone that has had dengue previous to their Zika infection, show a high degree of cross-reactivity. Our convalescent study, or specimens, all had neutralizing antibodies to Zika virus, and 63 percent also had neutralizing antibodies to dengue virus. So, our findings indicate that there's pretty significant cross-reactivity that is happening months to years after symptom onset. This particular cross-reactivity really limits our ability to make a definitive diagnosis, especially for diseases that have similar clinical presentations.

[Sarah Gregory] So, that does not mean that they've actually had both viruses?

[Isabel Griffin] Exactly. The lab results will look like they did, but they didn't. So it's cross-reacting.

[Sarah Gregory] Why do you think EID chose to publish this study? What good is this information for public health and how can it improve things?

[Isabel Griffin] So, our findings have significant implications for both healthcare providers, as well as public health officials. For healthcare providers, the findings affect how laboratory results are interpreted when diagnosing Zika virus. And for public health officials, like myself, this changes how we actually conduct investigations of Zika virus, including those that would be looking at possible local transmission of the virus. So, during our 2016 outbreak, if we had an asymptomatic individual who was PCR negative, so didn't have the presence of the virus in their urine or their serum, but was IgM positive, we assumed that that individual was actually exposed in the prior 12 weeks, because of what we believed the duration of the IgM to be. Based on our study findings now, we do not know, actually, if this individual was exposed up to a year ago or possibly longer. So, our findings will hopefully improve both the diagnostic of Zika virus, as well as the characterization of local transmission.

[Sarah Gregory] And you...think you've touched on this earlier, but if you...if people have antibodies to flaviviruses, does that mean they can't get the same one again? And if you are immune to, say, Zika, will that also protect you from dengue or chikungunya or one of the others?

[Isabel Griffin] Yes. So, based on our experiences with other flaviviruses, we believe that individuals who have had Zika infection will be protected from future infections. To date, there hasn't been a report of reinfection with Zika virus, and there are studies in animal models which show that prior infection will provide protection against future infections. However, if the virus strain were to mutate, we really don't know if that could impact long-term immunity. We also don't know if previous infection with Zika virus provides any sort of protection from dengue or other flaviviruses. There was actually a recent study that was just published last month in *Science* that suggests prior dengue infection lowers the risk of having a symptomatic Zika infection, but much more research is needed to address all of those questions.

[Sarah Gregory] And what do you think are the future studies that should be done to help understand the Zika virus more?

[Isabel Griffin] So, the surprising results of this study, our study, actually prompted us to ask whether these antibodies extend even further beyond 15 months in which we were able to detect them. And I'm happy to say we actually just recently completed our final follow-up to the study, to determine whether individuals remain positive 18 to 25 months after symptom onset. We're also examining how the PRNT titer value changes over time to better understand how to interpret Zika virus and dengue virus PRNT titers. We still don't know if someone is protected from reinfection or from other flaviviruses. So, looking forward, we hope that those questions will be answered by colleagues.

[Sarah Gregory] And what are the best ways for individuals to protect themselves from flaviviruses?

[Isabel Griffin] Definitely mosquito repellent. The silver lining to mosquito-borne diseases is that we can mostly prevent them as long as we avoid or reduce mosquito exposures, and of course, with Zika, unprotected sex with individuals with Zika virus. So, if individuals are living in an area with mosquitos, chances are they can spread disease, so it's always best to take precautions—wearing appropriate clothing and EPA-registered mosquito repellent.

[Sarah Gregory] Is Zika unique in the fact that it can be sexually transmitted in flaviviruses?

[Isabel Griffin] As far as I know, it is one of the only ones that can be sexually transmitted.

[Sarah Gregory] What's your personal "why"? Why are you interested in this topic?

[Isabel Griffin] So, at the beginning of the outbreak, which just kind of appeared in Miami, we really didn't fully understand Zika virus, its transmission, and the risks associated with infection. So, as the outbreak progressed in Miami, I actually oversaw the local investigations in my immediate county. So, myself and countless other epidemiologists volunteered, so a lot of us—government officials and mosquito control specialists—worked many, many hours to identify areas of transmission and reduce the mosquito vector, in order to prevent the future spread of the virus. For me, I didn't want a pregnant woman to have to worry about being bit by an infected mosquito, and I didn't want for other people, you know, people living in the same community as myself, to have the same concerns that I did, that an infected mosquito would bite them. And basically all that hard work paid off, because we were able to stop Zika in Miami-Dade County.

The outbreak also really served as an opportunity to learn more about the virus, and kind of fill that gap in knowledge that was present at the beginning of the outbreak. So, since then, we, as a county, have been able to write several reports describing how we identified the first outbreak in Wynwood, which we wouldn't have been able to do if those first cases and the affected businesses involved hadn't welcomed us during the investigation. We were able to look at clinical manifestations of Zika virus in children, which was actually a population that was often forgotten during the outbreak, as a lot of our efforts primarily targeted pregnant women. We were able to look at things like HIV and Zika coinfection. So, we received an incredible number of calls from healthcare providers that were really concerned about their HIV-positive patients and whether they were at greater risk of complications due to Zika with their HIV. And so, because Miami is uniquely positioned, in that we have a high burden of HIV in our county, we were actually able to look into that. And then now, it's the duration of the Zika virus IgM antibodies.

[Sarah Gregory] What did you find with the Zika and the HIV?

[Isabel Griffin] So, our sample size was pretty small—it's more of a case series of about nine. But we didn't find any significant differences between having HIV and being HIV-negative and being coinfecting, which is good.

[Sarah Gregory] Very good, yes.

[Isabel Griffin] But that's definitely one that you...we need to continue looking into in future outbreaks.

[Sarah Gregory] Future studies.

[Isabel Griffin] Mmm hmm—exactly.

[Sarah Gregory] If you personally could fix one thing in public health for all time, what would you choose?

[Isabel Griffin] Probably that we, as public health professionals, would practice maybe more primary prevention—that is, preventing diseases before they occur, rather than responding once it has already occurred. There's a lot of significant, you know, emerging infectious disease threats now, you know, such as healthcare-associated infections, that we could be preventing and containing before they become the next epidemic.

[Sarah Gregory] And, finally, would you like to tell us a little bit about yourself—where you work now, and your career, and what you're most passionate about?

[Isabel Griffin] Sure. So, I've been working with the Florida Department of Health in Miami-Dade County, since 2014, and I currently serve as an outbreak epidemiologist in the Applied Epidemiology and Research Unit. I actually obtained my Master of Public Health degree, or MPH, from the University of Miami in 2014, and I'm currently pursuing my PhD in epidemiology at Florida International University. In recent years, I've been most involved with our county's response to chikungunya, Ebola, measles, and most recently, Zika. But if you were to ask my friends and my colleagues, they'd probably unanimously say that I am overly enthusiastic about public health, going as...so far as to nickname me the “Leslie Knope of epidemiology.”

[Sarah Gregory] Well, thank you so much for taking the time to talk with me today, Isabel.

[Isabel Griffin] Thank you. I appreciate that *Emerging Infectious Diseases* decided to publish the paper because these findings truly do impact diagnosing pregnant women and conducting future investigations of outbreaks in the future. So, I really do appreciate you taking the time to discuss their findings with me.

[Sarah Gregory] You listeners out there can read the February 2019 article, “Zika Virus IgM Detection and Neutralizing Antibody Profiles 12–19 Months after Illness Onset,” online at [cdc.gov/eid](http://cdc.gov/eid).

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

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