

Cost-effectiveness of Prophylactic Zika Vaccine

[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 Dr. Affan Shoukat. He's a mathematical epidemiologist and modeling postdoctoral associate at the Centers for Disease Modeling and Analysis at Yale University. We'll be discussing the cost-effectiveness of providing a vaccine to prevent Zika in the Americas.

Welcome, Dr. Shoukat.

[Affan Shoukat] Hi. Thanks for having me.

[Sarah Gregory] Zika virus started making international headlines in 2016. Tell us a bit about this and what you've learned about it since.

[Affan Shoukat] Well, Zika infection is really...it's caused by a virus which is mainly transmitted by mosquitos, particularly the *Aedes* mosquito family. An infection from Zika mostly just causes Zika fever, which may not have any symptoms or may have symptoms that are relatively mild. But given the recent outbreaks, we've learned that Zika infection can actually cause neurological abnormalities in infants where the mother had been infected with Zika. So, for example, microcephaly was a big outcome of Zika infection. This...it was also linked to miscarriages and stillbirths in a lot of the affected pregnancies, as well.

We also have learned that the virus has been linked to Guillian-Barre syndrome in adults, which is inflammatory autoimmune disorder and it affects the nervous system. GBS, this occurs at a very low frequency—you know, almost two cases per 100,000 individuals—but because of these outbreaks, the World Health Organization showed a 19 percent increase, almost a 20 percent increase in GBS cases in Brazil during 2015.

So, there's also evidence that Zika can have human-to-human transmission—it's not just mosquitos. The virus can spread through sexual interaction through infected males and females and can also have vertical transmission from mother to child. We're still learning quite a bit more about it. We don't know how the specific pathology of the...of the virus works across different ages, across different sexes and medical conditions. So there's still a lot of unanswered questions right now.

[Sarah Gregory] Explain what the economic burden of Zika is. Where do most of the costs come from?

[Affan Shoukat] So, the estimated economic burden is really...is driven by four considerations, right? The first one is just the direct medical costs of detecting and diagnosing and treating the disease, including, you know, the patient follow-up. For the 2015–2017 outbreak in the southern Americas, I think it was estimated around 0.9 to 3.3 billion dollars for the medical costs only, depending on...depending on the country.

The second consideration is just lost time due to work, right? So, it's estimated that if you are a symptomatic individual, someone who's showing symptoms, they'll take an average of five to six days off work, which accounts to lost wages and lost revenue and stuff like that.

The third consideration is a big one: it's the long-term costs associated with microcephaly and other brain abnormalities, right—the medical costs and the indirect costs. So, and when I say *indirect costs*, these could be costs related to the care of children with microcephaly. So, many

parents, often the mothers, will have to either withdraw from the labor force or just not enter the labor force, simply to care for a...for a child with microcephaly.

And the last consideration is just the overall impact in the economy, something called *avoidance behavior* where a country may have lost revenue due to decreased tourism, for example. And so, for the 2015–2017 outbreaks, there was an assessment done by the United Nations Development Program. And overall, they estimated, you know, the total economic burden to be somewhere between 7 to 18 billion for short-term costs and 3.2 to 39 billion for long-term costs for the outbreaks that happened between 2015 and 2017.

[Sarah Gregory] The WHO and the United Nations Children Fund laid out a plan for the implementation of a Zika vaccine. What does this plan say?

[Affan Shoukat] So, in 20...in February 2016, in the midst of the outbreaks and the increasing cases of microcephaly, the World Health Organization, they declared a public health emergency of international concern, and called on, you know, globally...called on global research efforts to control and mitigate the epidemic. And then following that year, in 2017, they laid out a road map to facilitate the development of vaccine candidates and provided a framework for this implementation.

So, one of their strategies was something called the *outbreak response* where, in the context of an ongoing epidemic or an imminent outbreak, they suggested or they recommended a mass vaccination campaign of women of reproductive age, including pregnant women. And they would be the priority for vaccine. And the main objective of the strategy was to prevent the prenatal Zika infections leading to microcephaly. And this was really the strategy that we studied in our...in our model, as well.

They had a second strategy, which was just a routine...a universal vaccination campaign of the general population. That strategy really establishes a population immunity, but there really isn't any evidence right now to say whether Zika is endemic in countries, mostly it's just large outbreaks happen and they fizzle away. So, you know, it's important to protect the women of reproductive age.

[Sarah Gregory] Well what countries or regions were being most affected by Zika at the end of 2019?

[Affan Shoukat] So, after the large outbreaks from 2017...2015 to 2017, these recent years have been relatively quiet in terms of Zika. There are still a few countries that have a documented presence of Zika, mainly countries in Latin and South America, there are a few countries in Africa, a few countries in Southeast Asia, including Pakistan and India. In the US, in 2016, there were over 41,000 cases, then we had about 1,200 cases in 2017, and 2018, there was only 220 cases. But, you know, that being said, where...countries where the *Aedes* mosquitos are widespread and active, these countries are always at risk of an imminent outbreak if the population isn't sufficiently covered.

[Sarah Gregory] Your study used a model system to simulate different possible patterns of Zika infection. How does a model like this work?

[Affan Shoukat] So, we use something called an *agent-based model*, which is a computational methodology where you have virtual agents interacting together in a virtual world to produce the dynamics of the system we're trying to study. And there's lots of models, there's lots of computational models out there, but the fundamental property in agent-based models is that these

agents are all independent and have their own set of properties and behaviors, and they all work together to produce the dynamics.

So, in our model, the agents (in an agent-based model), where the humans and the mosquitos interacting together to produce the dynamics of Zika infection. And when I say they were independent, I meant...I mean, like, each human was such that they were given an age, they were given a sex at the start of the model simulations. We were easily able to classify pregnant and nonpregnant women. We were able to implement a realistic sexual interaction and virus transmission, we considered a realistic biting process of mosquitos, and how even seasonality affects the mosquitos' lifespan. And so that's where really the advantage of using an agent-based model comes in: it's the ability to incorporate a arbitrary level of detail.

And of course, the more details you add, the more complex and computationally intensive the model becomes. So, as a model...modeler, I have to find that balance where implementing sufficient detail of what I'm trying to study, but also trying to keep it relatively simple. Which, you know, our Zika model was relatively complex, but it actually was controlled enough and it was simple enough that we were able to get good results out of it. And this type of methodology, agent-based modeling, is becoming more and more common in all fields of science, just because of the enormous growth in computer power over the last decade, so we're able to incorporate large amounts of quantitative data.

[Sarah Gregory] Okay, so tell us about the scenarios you ran.

[Affan Shoukat] We implemented vaccination into our model which was very similar to what the World Health Organization recommended in their...in their plan, in their road map. And so, the way we did this was that, at the start of our simulations we said: "Okay, 60 percent of all women of reproductive age were vaccinated." And then for pregnant women, we said 80 percent of all pregnant women, at the start of simulations, would be vaccinated, and that remained throughout the simulation. And for everyone else, you know, males and women of nonreproductive age, we said about 10 percent of them would be vaccinated.

And then we let the model run for one year, doing its thing, capturing the results at the end, which we then analyzed and used in a cost-effect analysis. And this latter analysis, the cost-effectiveness part of it, we considered both the short- and the long-term costs specific to each country. So, when I say short-term costs, these were physician visits, diagnostic tests, and hospitalization. And the long-term costs included costs for microcephaly. So, we considered, you know, hospitalization, treatment, and other factors that are associated with taking care of microcephaly.

[Sarah Gregory] Just to help our listeners kind of understand this model running along for a year, is this kind of like a computer game—you just sort of set up and let it do its own thing?

[Affan Shoukat] Yeah, that's exactly how I would describe it. It's actually a virtual...a virtual world where I set up my agents, my humans and mosquitos, and I let them essentially do their thing. They roam around this virtual world, the mosquitos find humans to bite, they bite them, maybe the disease gets transferred, maybe it doesn't. And so we run this thing for one year, just to kind of replicate a single outbreak, right? So, an outbreak can't really last for more than year because of seasonality, so we ran our model for one year, just to capture one outbreak, to see, you know, the magnitude of the outbreak and what the total costs would be by the end.

[Sarah Gregory] Wow! This is actually really interesting! Okay, so how did you choose what numbers to run in your model for things like risk of infection, survivor rates, and so on.

[Affan Shoukat] So, these parameters of the model, like you said the risk of infection, survival rates, the incubation period of Zika, the total infectious period of Zika where, you know, an individual may transmit disease—most of these parameters were actually quantified in other studies and other relevant work on Zika. So that's where we got them. And given that we used an agent-based model, we were easily able to incorporate all of this data that other folks had done. There were some parameters that were...that we were missing, but, you know, given the similarities between Zika and dengue or other vectorborne or other mosquito-borne diseases, we were able to kind of guess or estimate some other parameter values based on these other diseases. But, you know, you have to be careful here. Like, each parameter value is a little bit uncertain, right? So, you know, when I say the total infectious...infectiousness period is 4.7 days, well that's an average number, not everybody is going to be sick for 4.7 days. But again, because our agent-based model works on an individual level, we were able to sample this...you know, if someone did get sick, how long would they be sick for? Well, because everyone was independent, someone would be sick for two to three days and someone could be sick for seven to eight days which, because it's all random, on average you'll come out to the number we're looking for.

[Sarah Gregory] Okay, so you kind of already touched on this, but at the end of all this, did you decide who would be vaccinated? Just pregnant women or everyone, since Zika...?

[Affan Shoukat] Well, in a perfect world, nearly everyone should be vaccinated, right? A sufficiently high vaccine coverage would ensure really no endemic transmission of Zika and will prevent outbreaks. In our model, like I said, we started off at vaccinating 60 percent of all women of reproductive age and 80 percent of all pregnant women. And...I mean, I think these were reasonable assumptions that we used and they kind of...they were...they came from what the World Health Organization suggested.

[Sarah Gregory] How much would it cost to vaccinate a person against Zika? Would the cost be the same in every country or would it vary according to the countries?

[Affan Shoukat] So, because there isn't any available or licensed vaccine on the market, you know, the costs are really unknown. It's unlikely that the costs would be the same in every country and it really depends on the socioeconomic status of that country and then how rich that country is, in a sense. In our study, what we did was we varied the price range in a range, I think it was from one dollar to 100 dollars, which was similar to vaccines for other similar diseases. And then...and then what we tried to do is we tried to find a minimal price under...it would still be considered cost-effective, which is a technical term, in each country in the Latin Americas.

[Sarah Gregory] And I just...We're going to talk quite a bit about vaccines, now, but I just want to be very clear for people listening, there—and you just said it, but I want to say it again—there is actually no real Zika vaccine yet, correct?

[Affan Shoukat] Yes. There is...isn't anything available right now, but there are a few candidates that are under clinical trial.

[Sarah Gregory] Oh, okay, alright, well good. What's the difference between cost-saving and cost-effective? In your simulations you found that whether a vaccine was cost-saving or cost-effective varied by countries, yes?

[Affan Shoukat] So, these are...these are technical terms in health...in the field of health economics. Just to, you know, make it easy, *cost-saving* generally refers to an intervention which provides more benefit and costs less than the status quo. So, of course, why wouldn't you do it, right? It provides more benefit and it costs less, so we consider that intervention to be cost-saving.

But when an intervention, really, it produces more benefit but also costs more than the status quo, well then policymakers have to decide whether to implement the intervention or not. So, you know, let's say it costs X amount of dollars to prevent one case of Zika. Well, policymakers have a threshold value, a *willingness to pay* value, to compare that cost, so "It's going to cost me 10,000 dollars to prevent one case of Zika, is that cost-effective and am I willing to pay 10,000 dollars to do it?" And this threshold value, this willingness to pay, is substantially...is different in every country. It depends on the context of the disease, it depends what they're, you know, the different types of vaccine or whether it's a treatment, it's a new drug. So, the willingness to pay is a...is a number that is somewhat subjective, based on the country that you're dealing with or what the policymaker considers to be cost-effective.

The World Health Organization does suggest that an intervention could be considered cost-effective if it is...if the cost to avert or to prevent an infection is less than the per capita GDP of that country. Now, that's a very standardized number, the per capita GDP, and it's not always the case that the per capita GDP needs to be the threshold value, but that's what we used in our study. We wouldn't know what the threshold values or what the willingness to pay are for the different countries that we studied.

[Sarah Gregory] Okay, so what kind of factors do affect the costs of a vaccination program?

[Affan Shoukat] The biggest cost component of developing a vaccine would be the research and development of it. But assuming that a vaccine is available, is licensed, factors like the number of doses, the efficacy of the vaccine, the duration of the immunity. Is it temporary immunity? Is it lifelong immunity? Safety and potential side effects, reactions—these are all very important factors to consider, and they'll all affect the cost of the vaccination program. Another major factor is the logistics of administering the vaccine, right? So you have to consider the healthcare center, the healthcare workers, storage and the transportation of the vaccine. And even, you know, particular to Zika, because Zika has only had intermittent...intermittent outbreaks, so far, we really also need the ability to store the vaccine stockpiles for long periods of time. We don't know when the next outbreak would be. So, here you have to consider cold chain storage and transportation, and which can significantly increase the costs.

[Sarah Gregory] It seems that the vaccine efficacy rate that you found could be as low as 60 percent. Is it worth getting vaccinated for such a low rate?

[Affan Shoukat] So, we don't actually know what the true efficacy of the vaccine would be because there isn't a vaccine that's available right now. In our model, we considered a range of the efficacy. We said that the vaccine could be effective between 60 to 90 percent. And we thought...and this is a reasonable number because this is the efficacy of other vaccines for similar diseases or for similar...like dengue, for example.

But just to answer your question, yes, it's absolutely worth getting vaccinated because other studies have shown that it can significantly reduce the risk of microcephaly. Our own study showed that...I think...I think we had over 80 percent reduction in microcephaly cases. And so,

this is substantial. A single averted case of microcephaly can have significant reduction in costs and the wellbeing of that family. You know, so, yes, it's definitely worth getting a vaccine, even if it's 50 to 60 percent efficacy.

[Sarah Gregory] So, the efficacy, even if it's lower, the percentage of preventing microcephaly is higher?

[Affan Shoukat] Yes, yes—it definitely prevents a lot of cases of microcephaly.

[Sarah Gregory] Why should a government consider implementing a vaccination program, even if in some cases it might not necessarily save costs?

[Affan Shoukat] Yes, so in some cases this is true, right? It may not save costs, it might actually cost the government a lot of money to implement a vaccine program. But it's important to consider that, you know, one, we're all connected at a global level, right? So, preventing a case in one country may prevent an entire outbreak in another country, because, you know, people travel. And that's how these large outbreaks in southern America and in the US, that you were...actually started, because someone imported the disease in.

Yeah, so, so we have to consider the ethics of it, right? The quality of life for someone who's going through microcephaly or is suffering with microcephaly, so even though it might cost more, it may be still worth it to have a vaccination program.

[Sarah Gregory] Another clarification here—and it's really not relevant to Zika—but did you just say that there is a dengue vaccine?

[Affan Shoukat] Yes, there is a dengue vaccine. That was announced, actually, very recently. And it does exist and it's licensed.

[Sarah Gregory] Okay, well, that's good news. Do you know the efficacy of that one?

[Affan Shoukat] I don't know the efficacy of that one.

[Sarah Gregory] Okay. Are you optimistic about the future of Zika prevention or do you think we might be at risk for another huge outbreak?

[Affan Shoukat] There are a lot of countries that are suitable for the mosquito populations that transmit Zika, so a sizable portion of the world's population remains at risk. In the US alone, 22 million people live in areas where the *Aedes aegypti* mosquito is active year-round. And so it does set the stage for possible outbreaks. But based on our knowledge that we...you know, from our studies from 2015 to 2017, the outbreaks during that time, we now have knowledge on how microcephaly works, how it gets transmitted. We've learned that Zika can also be transmitted sexually. And so, I'm optimistic in the sense that we are definitely more prepared if another outbreak happens.

[Sarah Gregory] Where are some of these areas where these 22 million people in the US live?

[Affan Shoukat] This would be in the southern area of US—Florida and the surrounding states.

[Sarah Gregory] Like Louisiana, Texas?

[Affan Shoukat] Right.

[Sarah Gregory] Well, tell us about yourself and what do you do and what you love most about your job.

[Affan Shoukat] I recently got my PhD in applied math at York University in Toronto and I'm currently a postdoc research associate at Yale University. And my research really is about biomathematics and mathematical epidemiology, but also health economics and public health decision making and policy. What I like most about my job is just developing these models and the ability to integrate data from other studies. And then just to be able to answer questions that need answers.

[Sarah Gregory] I don't have the mathematical chops to do what you do, but it absolutely sounds so fascinating.

Well, thank you so much for taking the time to talk with me today, Dr. Shoukat.

[Affan Shoukat] Yeah, thank you for having me.

[Sarah Gregory] And thanks for joining me out there. You can read the December 2019 article, "Cost-effectiveness of Prophylactic Zika Virus Vaccine in the Americas," online at [cdc.gov/eid](https://www.cdc.gov/eid).

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

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