

# Dengue in Brazil – Putting the heat on vaccine development and mosquito control

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## SUMMARY KEYWORDS

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## SPEAKERS

Maggie Fox, Dr. André Siqueira, Dr. Ramanan Laxminarayan

### Maggie Fox 00:01

Hello and welcome to One World, One Health where we take a look at some of the biggest problems facing our world. I'm Maggie Fox. This podcast is brought to you by the One Health Trust with bite-sized insights into ways to help address challenges, such as infectious diseases, climate change, and pollution. We take a One Health approach that recognizes that everything on this planet — the animals, plants and people, and the climate and environment — are all linked.

Something's happening in Brazil right now that truly illustrates these links. It's an explosion of the dengue virus. Dengue is carried by mosquitoes, and it can be both painful and deadly. More than a million cases were identified in Brazil in January and February of 2024 alone. That's a record! And that's before Brazil's main Dengue season even started in March. The mosquitoes that carry dengue, *Aedes aegypti* mosquitoes, thrive among people. Part of the problem is urbanization. As people build towns and cities and cut down forests, they make nice living conditions for these mosquitoes. Climate change is also making things worse as conditions get hotter and wetter in many parts of Brazil. So, Brazil started a vaccination campaign. How well and how quickly will it help? Here to chat about that with us is Dr. André Siqueira, an infectious diseases physician who is a principal investigator at the National Institute of Infectious Diseases at the Oswaldo Cruz Foundation, or Fiocruz, for short, in Rio de Janeiro.

Thank you for joining us, André.

### André Siqueira 01:41

My pleasure.

### Maggie Fox 01:43

Can we talk a little bit first about the dengue virus and the symptoms it causes?

### André Siqueira 01:48

Yeah, so the dengue virus is a flavivirus that is transmitted by *Aedes* mosquitoes. And actually, when we are talking about dengue virus, we are talking about four different viruses because there are four serotypes that cause the disease, so one individual can have up to four infections or episodes of disease throughout his lifetime. And the symptoms it causes—it's usually fever, myalgia, they may experience vomiting a lot of the times, and sometimes it can be also severe when it causes hypotension and eventually shock, hemorrhages, and it can be as severe as causing that.

**Maggie Fox 02:26**

Of course, it's the hemorrhages that I think people often think of when they think of dengue because that's such a horrific symptom.

**André Siqueira 02:34**

Yes. A long time ago, dengue was classified as a hemorrhagic fever. And this severe form of dengue was referred to as dengue hemorrhagic fever. But what actually happens — most of the deaths and most of the complications arise from shock. So, it's a lack of blood inside the circulation. So only around 50% of the deaths had visible or noticeable hemorrhages. So, it led the World Health Organization (WHO) to change its nomenclature from dengue hemorrhagic fever to severe dengue in order to comprehend how the different manifestations of severe disease that could lead to death.

**Maggie Fox 03:18**

Is there any treatment for dengue?

**André Siqueira 03:21**

So, we don't have any specific treatment for dengue. It's something that has been researched by many groups. There are now new initiatives, there are new compounds that show some promise, but nothing that we have evidence of being used. So, the clinical management relies on hydration and identification of warning signs of severe signs (symptoms) so people receive the correct amount of fluid to avoid these complications such as shock and bleeding.

**Maggie Fox 03:50**

Things are bad in Brazil this year, especially as there are several factors involved here. Can you talk a little bit about what they are?

**André Siqueira 03:57**

Yeah, so this year, we are still in March, but we have reached up to more than one million confirmed cases. So, it's really a lot. Last year, it was 1,600,000, which was already a lot. Almost every year there are epidemics or outbreaks of dengue in the country, but usually they occur in two or three states of the country. This year, it is more widespread and it's more synchronous. And it began rising much earlier than usual, and it's currently affecting nine states that have declared public health emergencies.

It's much more serious and we don't know for sure all the reasons that explain this increase, but we have climate change, so it's much warmer. Last year was very warm already and there were a very high number of cases. This year seems to be even warmer so, which does contribute to mosquito proliferation. There is increased movement of people, and the fact that dengue is now being transmitted in areas without prior occurrence means that almost all of the population in that area is susceptible to dengue infection.

This leads to both a higher number of cases because the number of people that can be infected is very high, and it also leads to higher morbidity and mortality because the health systems of those places were not prepared to deal with the effects of dengue epidemics—that is, an increase in the number of cases, the workload for the health units and for health professionals. And what we need during dengue epidemics is that health professionals and health systems act promptly on the suspicion of dengue, so we don't wait for any blood tests or anything. We have to start hydration orally or intravenously immediately. That's what can change the risk for severe disease.

**Maggie Fox 05:58**

And there is a vaccine can that help solve the problem?

**André Siqueira 06:03**

So now we have a newly approved vaccine called Qdenga. Brazil is the first country that is incorporating this vaccine into the public health system. It was available in the private clinics already, and it is being distributed currently for individuals between the ages of 10 and 14 in areas of high endemicity, so with previous exposure to dengue and preferably where dengue is circulating in an important way.

So why was this decision made? It was highly dependent on the ability of the laboratory to deliver the vaccine, so they could only deliver about six million doses. So, it's about three million individuals that will be vaccinated by the public health system. And they chose this age group because it was based on the analysis of the Minister of Health, the age group that was suffering the highest burden of hospitalization. So that was the rationale guiding that. So, 3 million people will be vaccinated with this three-month interval between the two doses.

We can't expect that to have a huge effect on the epidemics because it's a restricted age group and it's not the whole country, for full immunization we want to be achieved with three months from the initial dose. We will only be able to see the effects of this vaccination in future years because when more vaccine doses will be available, and we can actually strive to see if there is any community-level impact on transmission because we don't expect that with such a restricted group being vaccinated.

**Maggie Fox 07:49**

So why even bother in the first place to try to vaccinate people if you can't stop the spread?

**André Siqueira 07:54**

So they showed vaccinating for dengue this year was controversial because some people said there's no point. Even the Minister of Health said it won't have any impact in this epidemic... so, efforts should be focused on another control measures or even in preparing the health system for the higher load of cases.

The Pro argument would be to use this momentum of people being involved with dengue to start promoting the vaccination, showing that it is safe and it can have an individual impact and then it's curling up in future years.

**Maggie Fox 08:31**

And I think you mentioned something and it's something unusual about at least some of the dengue vaccine research that's been going on. You wanted to find people who might have had previous exposure to dengue.

**André Siqueira 08:42**

Yeah, that's also an important point (when) talking about dengue vaccines, because this (Qdenga) is not the first vaccine to be approved by regulators. We have the dengue vaccine that was produced by Sanofi, which led to major problems in the past, mainly in the Philippines, because this vaccine was shown to increase the risk of hospitalization and severity in individuals who had been exposed to dengue before. And when they were infected with dengue, instead of being protected, they were at higher risk of severe disease. So, this is something that is in the back of all the vaccines that are being developed and evaluated.

The thing that's important to understand is that there's a bit about this dynamic between the four viruses of dengue. So, an individual can have up to four episodes of dengue throughout his lifetime. The antibodies against one serotype will protect against that serotype for the whole life, but they won't protect against the other three serotypes. What can happen, and it's a phenomenon called antibody-dependent enhancement, means that the

antibodies that can protect against some other serotypes can, on the other hand, facilitate the entry of the viruses into the host cells and amplify infection. So, the viral load that's reached in secondary infections is much higher. So, we know that secondary episodes of dengue are usually more severe than primary infections.

**Maggie Fox 10:18**

So, in other words, the goal would be to find a vaccine that protects against all four different strains or serotypes of the virus at once. This is a really hard concept to understand, isn't it?

**André Siqueira 10:30**

Yeah, that is very complicated to understand all this concept and all the science behind the end the challenges of having a vaccine for dengue. That's why in Brazil we have epidemics of dengue every year for the last 40 years. So that's the disease that we want to be protected from, but reaching that goal, it's hard because of that. And the challenge is this: if we think about the current context of the anti-Vax movement, it is to show that the vaccines actually protect individuals and do not cause any harm.

**Maggie Fox 11:05**

Researchers in Brazil are working on a locally made vaccine. When will that one be available and that won't be a better vaccine than the ones that are out there now.

**André Siqueira 11:13**

Yeah, I'm very positive about this new vaccine that is in the clinical trials. It's produced by Butantan, but in collaboration with the United States National Institutes of Health (NIH). It seems very promising because it is a single-dose vaccine. In initial studies, it's shown to produce antibodies generously against the four serotypes. So, the fact that it's a single dose and it's very safe —the initial results are very promising. Recently, the two-year follow-up was published in the New England Journal of Medicine, and we expect the trial to finish in July this year. So each individual following is being followed for five years in the study. So, by the end of the year, we expect to have the results and next year or in the early or late next year to have this vaccine available.

**Maggie Fox 12:06**

This one sounds like it might solve a lot of the problems. It's one vaccine that protects against all four types of dengue. So, you don't have this problem with the more serious disease. Can Brazil produce enough doses to cover the population?

**André Siqueira 12:20**

So now that is in the discussion, there have been some conversations on collaboration with other laboratories to produce it together with them and make it available. There will be some discussions on the possibility of having 20 million doses per year, which is a considerable increase. But these conversations are flowing, and we expect that in one or two years' time, we will have a good quantity of vaccine for improving the coverage of the population. And then there's a challenge of whether people will take it or not.

**Maggie Fox 12:54**

Now this virus is spread by *Aedes aegypti* mosquitoes, and they're really super hard to control. Can you tell us a little bit about how difficult it is to control the spread in the first place?

**André Siqueira 13:05**

*Aedes aegypti* is a very effective vector of viruses. It transmits dengue, but also transmits Chikungunya and Zika, which are also part of arboviruses. And *Aedes aegypti* has adapted perfectly to the environment, so it doesn't

need a lot of water to breed in very high numbers; it needs a droplet of clean water, which can be enough. Sometimes, no one even realizes it's there.

It has developed resistance to most insecticides. Unfortunately, in many of Brazil's biggest city centers, there are a lot of problems with urbanization, meaning that there are a lot of breeding sites for the mosquitoes. So, it's very resilient to most of the control measures we have.

**Maggie Fox 13:55**

But there are some new scientific methods and new technologies such as genetic modification, and there's this other special mosquito that's infected with bacteria called Wolbachia. Can you talk about those a little bit?

**André Siqueira 13:05**

The genetically modified mosquitoes, what they do is that the genetically modified male mosquitoes, when they copulate with the female ones, they don't cause fertile fecundation, so they don't generate eggs and new mosquitoes. Only if they can be released in good numbers and in a sustained way. So, that's the challenge – we have to keep releasing these genetically modified mosquitoes in big numbers. But it can reduce the number of mosquitoes in the environment.

The mosquitoes infected with Wolbachia - So Wolbachia is a bacteria that's common in other mosquitoes and flies in the wild. But what happens is that mosquitoes which have Wolbachia in their intestines, they don't get infected by the viruses and therefore, they don't transmit the virus. So, despite them being in the community, they are not transmitting the disease. So, it's like a perfect scenario if we can eliminate the mosquitoes.

And the advantage of these Wolbachia-infected mosquitoes is that if we reach good numbers of these mosquitoes in a certain geographical area, it starts transmitting to the wild mosquitoes. The challenge with Wolbachia is having to produce mosquitoes. We have to invest in mosquito factories or mosquito farms in fact. Then we go back and release them for a period of time. The mosquitoes that will be sustaining these Wolbachia infection, they come in.

And the challenge is also the community engagement. People have been accustomed to hearing that they need to combat mosquitoes, and where Wolbachia was implemented, they had to work with the communities that have been told to avoid and mosquitoes not to use insecticide and kill mosquitoes for a while. And Wolbachia, where it has been applied with success, has led to a decrease in the risk of infection with dengue by 70%. So it seems to be feasible and effective at the same time.

**Maggie Fox 16:13**

So, it sounds like you're fighting on a lot of fronts. You're fighting the virus, you're fighting the mosquitoes that spread it, you're fighting human behavior that helps spread it, and you're fighting the doubt around the science of vaccination, the science of genetic modification, and even the use of pesticides.

**André Siqueira 16:33**

So, a lot of discussions are currently underway because maybe it's human nature; we try to have this magic bullet. So either we will have a vaccine or have something that will control the mosquitoes. But what we actually need and what can be more effective is to have an integrated approach: so we have mosquito control measures, we will have the vaccine, we will have desirable drugs to treat dengue (if people catch it, even though we are trying to prevent it), we will have drugs to treat it if necessary, and we need community engagement and we need the public understanding and engagement for these tools to be affected.

**Maggie Fox 17:15**

André, thank you so much for spending some time with us.

**André Siqueira 17:19**

It's been my pleasure, and I'm here anytime you need.

**Maggie Fox 13:52**

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**Dr Ramanan Laxminarayan 14:13**

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