The Origination and Onslaught of Zika : Dr. Paul Sax Interviews Dr. Duane Gubler

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Text Intro to Accompany Podcast:

In the ninth Open Forum: Infectious Diseases *podcast, OFID Editor in Chief Paul Sax, MD, explores the current Zika virus outbreak with Duane Gubler, ScD, MS, who specializes in vector-borne infectious diseases. Dr. Gubler walks through the epidemiology of Zika, postulates how Zika made its way to Brazil from the South Pacific, and how this disease could impact the United States.*

Dr. Gubler is Professor Emeritus and Founding Director of the Signature Research Program in Emerging Infectious Diseases at Duke-National University of Singapore (NUS) Medical School. He is a fellow of the Infectious Diseases Society of America, fellow of the American Association for the Advancement of Science (AAAS), and is past president of the American Society of Tropical Medicine and Hygiene.

Podcast Transcript to Accompany Podcast:

Hello this is Dr. Paul Sax. I'm the Editor in Chief of *Open Forum: Infectious Diseases*. And welcome to the latest of our ID-related podcasts. Today I'm delighted to welcome Dr. Duane Gubler. He is Professor Emeritus and Founding Director of Signature Research Program in Emerging Infectious Diseases at the Duke-NUS Medical School based in Singapore. And he is also a long-standing expert in vector-borne diseases. Thank you very much for joining us today.

So, for most of us ID doctors, and I confess myself included, Zika was barely known or only kind of a footnote on those talks we go to on Travel Medicine, until last year. And suddenly it emerges. But how about you? You are someone who works in the field of vector-borne diseases. Were you aware of it before last year's outbreak in Brazil?

Well, yes. It was one of those viruses that was isolated back in the '40s as part of the Rockefeller Foundation studies on Yellow Fever and very few human infections had even been known. We actually showed that it was causing a non-specific febrile illness in patients in Indonesia when I started the program in Jakarta in the 1970s. And it was isolated from *Aedes aegypti* mosquitoes, which is a domesticated mosquito that feeds on humans, in Malaysia in 1966. So we knew it was there, we didn't know how widespread it was, but assumed that it was just transmitted sporadically. As it turns out it was transmitted silently and sporadically in a much more widespread geographic area than any of us anticipated.

So I would say it wasn't even a footnote until 2007, when the Yap [Islands] epidemic occurred.

How about that epidemic? Again, for most of us ID doctors, we wouldn't necessarily know about an epidemic of a viral infection in Yap.

Well it was actually reported in *EID* [*Emerging Infectious Diseases*] journal of CDC [Centers for Diseases Control and Infection], but it was a rare and very unexpected outbreak of a virus that had never caused an epidemic in humans in the 50 or 60 years that it had been known. And all of the sudden it pops up in Yap, causes a rather explosive epidemic on that isolated island, and then disappears again. It was sort of a bleep in the history of

epidemic diseases and one of those one-offs that don't get a lot of attention. So most of us just forgot about it again.

Now let's fast-forward to 2014-2015. Can you tell me a bit about how you first heard about the Zika epidemic in Brazil, and what were your initial impressions?

Well there was an epidemic that was initiated in the fall of 2013 in French Polynesia in Tahiti. And that epidemic exploded into a major epidemic – more than 30,000 cases. So that's where I first got involved with it and the reason I got involved was because it is my field and they consulted with me. But also because it was apparently causing Guillain-Barre syndrome in French Tahiti, French Polynesia, and there was a lot of uncertainty, so they were trying to decide if this was really associated with the Zika epidemic. And then in 2014-2015 it was imported into the Americas into Brazil and just exploded. And so we didn't really know about the epidemic in Brazil until the association became apparent with microcephaly.

One thing that I find very interesting and I can't quite figure out is why 2014/2015? Why not several years before? Was there something that happened that just made it suddenly explode in the Americas?

We don't know for sure, but this is my personal opinion that is shared by many others, but Zika virus probably was circulating in many Asian countries. It had been documented after Indonesia in Malaysia, in Thailand, Cambodia, the Philippines, India and Pakistan serologically. But it had been transmitted silently in a cycle similar to the cycle that involves dengue virus – that is *Aedes aegypti* mosquitoes in humans. So my personal feeling is that Zika virus responded to the same societal demographic and technological pressures that were responsible for the pandemic of dengue and that is population growth, unprecedented urbanization, uncontrolled *Aedes aegypti* populations and globalization – the jet airplane moving these viruses. So probably with that kind of pressure, Zika just like dengue mutated and a strain of virus that had greater epidemic potential emerged probably in the Philippines and was imported into Yap first, and then subsequently another strain emerged and was imported into French Polynesia. And the French Polynesian strain of virus then was imported into Brazil. We are quite sure of that, because the sequencing shows they are nearly identical.

What we've seen is the global trends that are responsible for the dengue epidemics, for the chikungunya epidemics, were also responsible for the emergence of Zika as an epidemic virus.

And I gather that it turns out not to be soccer or football, but another sporting event that turned out to be the precipitating event in Brazil.

Again, we don't know for sure. There's one paper that was published in *Science* that speculates that the virus was introduced as early as 2013. But my colleagues in French Polynesia think that it was a paddling event in 2014 and there were something like five South Pacific countries involved in that event, and it was in Brazil. And Zika was being transmitted in most of those countries. So that was the likely source of introduction.

That might be the first time there's been a major epidemic that started with a canoe race.

I would guess. Well who can say? In the old days, mosquitoes were transmitted between islands in the Pacific in canoes. They would lay their eggs in canoes where the water accumulated, rain water. They would get in their canoe and paddle to another island and mosquitoes would emerge. So who knows? It's definitely the first documented case.

Shows how much I know. I will say though it was very interesting as an ID doctor to watch the community of both infectious disease doctors and also just commentators. There seemed to be quite a bit of skepticism at

first about the association between Zika virus infection and microcephaly. Why do you think that was the case?

Well, the perception was that it was a viscerotropic virus transmitted by *Aedes*, and while these viruses can cause rarely neurologic infection, it's not a common event. The fact that this virus was associated with microcephaly was looked on with some skepticism. But, the temporal distribution, the ultimate isolation of the virus from amniotic fluid and amniotic tissues showing that the virus was actually in the brain cells essentially convinced people that there was an association.

I sat on the World Health Organization emergency committee as a technical expert, and we weren't really sure that there was a cause and effect, but the fact that it could be was enough to declare it an emergency and the emergency was actually declared because of microcephaly and not because of the Zika epidemic. But the *MMWR* [*Morbidity and Mortality Weekly Report*] article and the papers in the last week have shown pretty conclusively that there is cause and effect there. But the original skepticism was based on the fact that this virus was not considered to be a neurotropic virus, it was considered to be a viscerotropic virus.

Interesting. I have to say that I have some colleagues from Brazil who are infectious disease doctors and they historically have not struck me as alarmists. The fact that they were so concerned about this certainly made me concerned myself.

It seems from what happened in French Polynesia and Yap that the epidemics would peak and then dissipate. Why did that happen and can we expect the same in countries that are experiencing outbreaks now?

Well in Yap it was a rare, very small and limited population and to a certain extent in French Polynesia as well, all of those South Pacific islands. It's very typical of epidemics to go through and cause a rather explosive epidemic and then go silent for several years. The virus doesn't necessarily disappear. A lot of times it does. In Brazil, and in Latin America, all of tropical America with a much larger population it's uncertain because I doubt that all of us susceptible are going to be used up. Normally what happens with viruses like dengue and chikungunya, for example, is the virus could mutate again and become somewhat attenuated so that it goes back into a silent transmission. So we don't really fully understand why these viruses emerge periodically as epidemics. Clearly immunity is one of the factors, but it's only one of the factors.

The strain of the virus is also important. And we've documented, at least with dengue, which is a related virus, that epidemic strains of virus can actually mutate and become more attenuated, or they can mutate and become more virulent or have greater epidemic potential. The same thing happens with chikungunya so there's no reason why it won't happen with Zika. So I would say that Zika is going to be around for a long time, at least if our assumption that *Aedes aegypti* human transmission cycle is the main mode of transmission. Probably the epidemic will dissipate, but the viruses are not going to go away and we will see periodic epidemics over time. There's only one Zika virus and so it may act more like chikungunya, and there will be longer intervals between epidemics than we see with dengue, which has four serotypes with no cross-protective immunity. I think we'll see Zika being transmitted in large urban areas for some time to come.

And I'm sure you've been asked this question multiple times but I have to ask it. What do you think is going to happen in the United States?

I think we'll see maybe sporadic transmission. You'll see something just like we've seen with dengue. The United States has both vectors that we think transmit these viruses in the peri-domestic and urban environment. But our demographic and societal conditions are very different. We don't have really dense populations in areas where we have large populations of mosquitoes. We live in essentially closed houses with air conditioning and we are usually inside the houses during peak biting periods of these mosquitoes. *Aedes albopictus*, which is the

most dominant mosquito in the United States, is not an efficient epidemic vector. *Aedes aegypti* is an efficient epidemic vector, but it has very limited distribution in the U.S. or in very limited populations. I think we'll see some sporadic transmission. We may see some of that associated with sexual transmission, but I don't think we're going to see major epidemics.

So for us non-entomologists, what is the difference between these *Aedes* mosquitoes that accounts for the difference in efficiency of transmission, or is that not known?

Well there are several factors involved. Number one, and most important, is the feeding behavior of the mosquito. *Aedes aegypti*, which is the efficient epidemic vector, is highly adapted to humans. It likes to live with humans. It likes to rest inside their houses. It feeds almost exclusively on humans in most situations, there are exceptions of course. It lays its eggs in water containers in the domestic environment. In the U.S. it's mainly outdoors, but in a lot of tropical countries it's both. Because it's been associated with humans for so many years, it's very flighty and the slightest movement will make it disrupt its feeding and jump to another host. And so it has the unusual behavior of feeding on multiple persons during a single egg-laying cycle. In other words to get enough blood to support the development of its eggs, it may feed on four, five or six people. If the mosquito is infectious, if it has salivary gland infection at that time, every one of the people that it bites, that it probes, will become infected with dengue, or with Zika, or chikungunya. So it's that multiple feeding that makes it so efficient.

Aedes albopictus on the other hand usually takes blood from a single host during a particular egg-laying cycle. *Aedes albopictus* will feed readily on humans if they're available, but it also feeds readily on a lot of other different animals. So it dilutes the effects, so if you've got an *Aedes albopictus* infected with Zika or dengue or chikungunya, the probability of it infecting one person is reduced because of its catholic feeding behavior. It's definitely much lower than *Aedes aegypti* that may feed on five or six people.

That's a fascinating and very clear summary. The ID nerds listening right now will definitely appreciate that. So back to the epidemiology for a moment, the sexual transmission of Zika has understandably received lots of attention, in particular for young couples who are trying to conceive. And there have been various estimates about what proportion of cases are linked to sexual transmission versus mosquito transmission. Is there any way to get a sense of which is the dominant transmission factor?

Not at this point. We have to assume, and I think correctly, that the dominant mode of transmission is by mosquitoes. But we don't fully understand how important epidemiologically sexual transmission is, how efficient it is, and in a large urban setting, how frequently it occurs. We don't know how long infectious virus stays in the semen, for example. RNA has been detected as long as 60 days after the active infection, but RNA doesn't mean that the infectious virus is there, it just means that it's been there. So I think what we need to do is have more detailed clinical epidemiologic studies, case-controlled studies, where we actually try and measure this before we can answer that question.

If you had to put your money down, what do you think will be the most effective prevention strategy for Zika, or do you think it's going to be a multi-pronged approach? How do you think that will play out?

If we could control the vector effectively, that would be the most effective. Because it would not only control Zika, it would control dengue, it would control chikungunya, it would control Yellow Fever. But we've essentially failed at controlling these diseases in the last 40 years by vector control. It doesn't mean vector control doesn't work, it has worked in the past, it's just in today's world, cities with 20 million people and our democratic society, so to speak, where you can't implement a top-down paramilitary type of control program, makes it very difficult.

Number one we need to develop mosquito control tools that can be used in these large urban areas. Number two we are going to have to develop vaccines that can be used effectively in those same populations and we're going to have to develop better management in drugs that will inhibit viral replication. All of those are being developed in various institutions around the world, and many of them show promise, but none of them are really online as of yet. At the end of the day effective control is going to use a multi-pronged, integrated approach using different methods in different urban situations. In other words, no single method is going to fit all.

Let me just add one thing that you might encourage your audience to consider. Yellow Fever is sort of waiting in the wings. It has the same epidemiology, the same transmission cycle as Zika, as dengue and chikungunya. We have a very good vaccine for Yellow Fever; we don't have enough of it. In fact we don't have anywhere near enough of it. And, sort of like a time bomb, we've got an epidemic of Yellow Fever occurring in Angola right now. There are tens of thousands of Chinese there working in Angola; none of them are immunized. Many of them are returning back to China carrying the virus with them. That could be our next major global public health emergency. So keep your eyes open for Yellow Fever or as the old saying, I think it was C.J. Peters that said, "If you hear hoof beats, think of zebras as well as horses."

And as well as Yellow Fever. Thank you very much for that reminder. And on to one area of tremendous frustration for us even here in Boston and I'm sure in other cities around the United States, is the diagnostic test is so bad right now. Where do we stand with diagnostics – both antibody, antigen, PCR [Polymerase Chain Reaction], etc.?

Well the PCR tests are right now the most sensitive and most reliable. They're certainly the most specific. Serology is problematic simply because of the cross-reactivity between all of these flaviviruses. And there appears to be a one-way crossing that we don't fully understand yet among the different flaviviruses. What we need to deal with especially things like sexual transmission, microcephaly, etc. is a point-of-care diagnostic test that can be used in a clinical setting. We don't have that right now. The best thing we have is PCR. A lot of people are looking at what we call an NF1 test that could be as specific as the PCR, whether or not it will be as sensitive is questionable.

A lot of this depends on clinical diagnosis and management of the clinical symptoms. And we're going to have to rely on that as well as the epidemiology and the tests that we have. Having said that, there's a lot of people out there right now working on new diagnostic technology. Some of the systems biology approaches, where we can look at the chemical signature that may be able to identify the infecting agent, is the way to go in the future, but we don't have it yet.

I'm an optimist by nature, and because there are so many people working on diagnostic strategies, I feel like that's some place we will see a lot of progress pretty soon. Dr. Gubler I want to thank you for joining us today. This has been a really fascinating discussion about Zika. And if we have some more questions about it in the future, I hope I get to speak to you again.

It's been my pleasure.