

Alex Trillo

My name is Alex Trillo and I am an assistant professor at Gettysburg College, I'm a professor of animal behavior and tropical biology. I got diagnosed with dengue in the summer of 2016. I do a lot of fieldwork and I work in Panama at the Smithsonian Tropical Research Institute and our work is to set up speakers and playbacks that have frog calls to attract predators and parasites of these frogs. So we attract bats and we attract these very small midges. And so most of our work during the summer at least is in the field all across different field sites in Panama. I was doing this work with some of my students in 2016.

I first started feeling very tired but I thought that it was just cause I wasn't sleeping well cause I had a young baby and I was working at night. On one of the days I was so tired that my husband recalls me just kind of collapsing on the trail going to one of the sites where we had our speakers and he noticed that, I just felt one of those days where I just felt tired. And we kinda let that go. And then a couple of days later I started feeling much more sick. I got a very small fever, I don't really get fevers and I think that that was one of the reasons why it took me so long to realize I had dengue or I had something else than a cold.

I was in an actual moment where I was really stressed out because not only did I need to do all the fieldwork, I had to leave a lot of things set up during the fieldwork for my students because I was traveling to a conference. And so I wasn't really hoping and/or expecting and/or wanting to be sick. I was just trying really hard to power through my cold. I still went on the plane and I remember arriving to the US and I had to walk to my next gate and I just remember sitting on the floor next to the chairs and just calling my husband and saying, 'I just don't know if I can make it to the gate, to the connection, like I'm that tired.'

So at this point what I was feeling mostly was extreme malaise, like super, super tired. What I had was really strong joint pain. I remember very little about the conference, my talk was the second or the third day of the conference so I just worked really hard. The day I gave my talk, that day I started with the fevers. After I finished the talk I came back to my room and I passed out for almost 24 hours. I was fine but I was in a lot of pain. When I came back I got these horrible headaches. It just feels that you have pressure on top of your nose and on the sides of your head but the pressure is from the inside, like someone put a hand inside your brain and tried to pull it from the inside, that's kind of what it feels like.

But on the second day of these really terrible headaches I just said something has to stop, I don't know what it is but we're going to the emergency room cause I wanna literally pull my brain out. The doctor saw me and he at first said, 'Oh it must be a really bad sinusitis infection. And I was like I've had sinus infections before, this is not it, there's something else, it's bigger. And it was actually my husband who was like, 'We're not leaving this place until you test for dengue. You have to test for dengue.' And so they went ahead and they tested and then we were waiting at the waiting room. So I just remember being asleep and then wake up and then the doctor being there and saying yes, you tested positive for dengue. And I just remember both Michael and I actually being happy about it because we finally figured out there was a reason... I was like okay, now we know what to do, like we have a diagnosis and we know what to do about it. But I mean there's not much you can do, right.

I slowly started getting a little bit better. I was weak and tired and feeling malaise for at least two months after that. A lot of people thought that I probably had it from working in Gamboa in the forest but I do remember about 10 days, a week to 10 days before I started feeling sick I was actually with a friend of mine, you guys know him, Sergio, we were sitting at a restaurant outside in the city of Panama. I think that I caught it in the city. And so from then on I told my students and I, we never wear skirts or shorts or short sleeves, we all get long sleeves and pants and shoes every time we go to town cause we're a little bit nervous about that. So yeah, so no more skirts in the city.

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh: You just heard from Dr. Alex Trillo who was nice enough to share her experiences with dengue with us. And if you want to learn more about the awesome research that she does, you can check out her website at [www.alextrillo.com](http://www.alextrillo.com) and you can also follow her on Twitter @trillo\_pa. Thanks again, Alex. Hi, I'm Erin Welsh.

Erin Allmann Updyke: And I'm Erin Allmann Updyke.

Erin Welsh: And this is This Podcast Will Kill You.

Erin Allmann Updyke: Yeah, today we're talking about - do you say 'den-gee- or 'den-gay'?

Erin Welsh: I think I say both.

Erin Allmann Updyke: I think we've done this before, right?

Erin Welsh: We have discussed this.

Erin Allmann Updyke: We have discussed this and we didn't come to a conclusion.

Erin Welsh: Yeah. I'll say 'den-gee', you say 'den-gay'.

Erin Allmann Updyke: Perfect, that sounds excellent.

Erin Welsh: Okay, great.

Erin Allmann Updyke: Cover all our bases.

Erin Welsh: We can irritate everyone that way. (laughs)

Erin Allmann Updyke: Exactly. (laughs) Our favorite thing to do.

Erin Welsh: Yes. So as you might have guessed we are talking about dengue today which is a very fascinating mosquito-borne virus.

Erin Allmann Updyke: Yes.

Erin Welsh: And it is actually an episode or a topic that we have covered once before.

Erin Allmann Updyke: We have.

Erin Welsh: Although only a few of you may have heard it.

Erin Allmann Updyke: Yeah. So in October we got invited - shout out Nick Keiser - to University of Florida to give a little talk and we talked about dengue. So we technically have heard each other talk about dengue before, however I don't remember anything you said, Erin cause I was really nervous during this talk so I was like not actually paying attention.

Erin Welsh: Oh well thank you and same. Also my memory is terrible.

Erin Allmann Updyke: Yeah, there you go.

Erin Welsh: It'll be great.

Erin Allmann Updyke: I'll still learn new things.

Erin Welsh: Apologies to anyone who was in the audience in Florida because if you remember anything then some of this or all of this will be a repeat. But we did add a little bit more to kind of fill in the edges.

Erin Allmann Updyke: We definitely have some new things and some answers to some questions that people asked during that event.

Erin Welsh: Ooh!

Erin Allmann Updyke: So stay tuned.

Erin Welsh: Well.

Erin Allmann Updyke: Is it quarantini time?

Erin Welsh: I think it is.

Erin Allmann Updyke: I think it is too.

Erin Welsh: What are we drinking this week?

Erin Allmann Updyke: We're drinking The Bonebreaker.

Erin Welsh: What's in The Bonebreaker?

Erin Allmann Updyke: It is mezcal preferably, you could use tequila if it's all you've got, passionfruit simple syrup-

Erin Welsh: Oh yeah. So good.

Erin Allmann Updyke: Lime juice, pineapple juice, and you rim it with tajin which is one of our little favorite things.

Erin Welsh: It is. And it's really refreshing and delicious.

Erin Allmann Updyke: So tasty.

Erin Welsh: And hopefully won't make your bones feel like they're breaking.

Erin Allmann Updyke: Let's hope not.

Erin Welsh: Just you head the next day if you have too many.

Erin Allmann Updyke: Exactly. Don't do that, just have one.

Erin Welsh: We will post the recipe for the alcoholic quarantini and the nonalcoholic placeborita on our website and also on our social media which you can follow us @thispodcastwillkillyou on Instagram and @TPWKY on Twitter and you can also find us on Facebook.

Erin Allmann Updyke: Yeah.

Erin Welsh: Cool.

Erin Allmann Updyke: Any other business that we should discuss, Erin?

Erin Welsh: I don't think so.

Erin Allmann Updyke: I don't think so either. Should we jump right into this episode?

Erin Welsh: Let's do it!

TPWKY: (transition theme)

Erin Allmann Updyke: Dengue virus. You already know a lot about it's, it's a virus. This is a Flavivirus so that's in the same group of viruses as yellow fever, West Nile, Zika, a bunch of different encephalitis viruses, etc. Okay. There are 5 serotypes, so that means 5 different strains of this virus. It used to only be 4 but in 2013 they announced a new one.

Erin Welsh: Ooh.

Erin Allmann Updyke: And so this means that if you get infected with one strain of dengue you're not protected against the other strains of dengue.

Erin Welsh: Right.

Erin Allmann Updyke: And as we'll talk about later it's actually a lot worse. Spoilers.

Erin Welsh: Yeah. I already have a question about that.

Erin Allmann Updyke: Oh excellent.

Erin Welsh: I'm gonna write it down instead of...

Erin Allmann Updyke: (laughs) Write your question down and then ask me later?

Erin Welsh: Yeah!

Erin Allmann Updyke: Okay. You don't wanna ask it now?

Erin Welsh: I mean because it's kind of jumping ahead to...

Erin Allmann Updyke: Okay, all right. Ask it later.

Erin Welsh

Okay.

Erin Allmann Updyke

Okay. So let's talk about how you get infected with dengue. You already mentioned, Erin, this is a mosquito-borne virus so dengue is transmitted by Aedes mosquitoes which we've talked about before because these little buggers transmit a whole number of different diseases including yellow fever, Zika, etc. Chikungunya which we haven't talked about yet. One thing that's different though about dengue than some of these other viruses, although not all of them, is that dengue is pretty specifically often a disease of more urban areas where a lot of other viral hemorrhagic fevers tend to be diseases of more rural areas.

And this is for a couple of different reasons. One is that these Aedes mosquitoes that transmit dengue are very well-adapted to urban environments. They breed in little, tiny containers of water and so anytime you have let's say pots or tires or whatever in your yard that could collect water, Aedes can breed in those small bodies of water. And dengue is a human-specific disease. So unlike something like yellow fever that can spillover from animal populations into human populations, dengue is human-specific. So where you have large populations of humans, you're more likely to get spread of dengue in those areas.

Erin Welsh

I forgot about that aspect of yellow fever.

Erin Allmann Updyke

Yeah.

Erin Welsh

Like why do you think evolutionarily there would be a difference between the two? Like why would dengue be so specific to humans and yellow fever isn't?

Erin Allmann Updyke

Oh that's so interesting, yeah. Well I was hoping you would tell me where dengue came from.

Erin Welsh

I'll tell you that! But I won't be able to answer this question.

Erin Allmann Updyke

But yeah, there's no silvatic wild cycle like there is for yellow fever. It's really interesting.

Erin Welsh

Interesting.

Erin Allmann Updyke

So that also I will say contributes to some of the lack of understanding that we have about dengue fever. We don't fully understand dengue and it's because when we have human-specific diseases it's often really difficult to find good animal models to study these diseases in. So in the case of dengue there are some modified mice that you can infect with dengue and use, you can do it in monkeys in some cases, but we don't have really good animal models for studying dengue.

Erin Welsh

Okay.

Erin Allmann Updyke

The other way that it is possible to get dengue, although this is much more rare than mosquito transmission, is vertical transmission, so across the placenta. So it's possible for this virus to cross the placenta, so during pregnancy if someone is infected especially late in the pregnancy then the fetus can potentially get infected as well. And this can have pretty bad outcomes once the baby is born that we'll talk about a little bit more later.

Erin Welsh

Okay.

Erin Allmann Updyke

But it doesn't seem to cause birth defects the way that something like Zika virus does which I think is very interesting.

Erin Welsh: Right. Yeah.

Erin Allmann Updyke: Yeah. It's not entirely clear if someone gets infected very early in their pregnancy if they might have poor outcomes like maybe a miscarriage or something like that, it's not entirely clear if that happens if you get infected with dengue early in your pregnancy.

Erin Welsh: Okay.

Erin Allmann Updyke: But definitely if you get infected late then the fetus can get infected and then basically when it's born it can either have symptoms of dengue or it might just have antibodies, like it might be born having antibodies against dengue virus.

Erin Welsh: Okay, like having already been infected. Oh!

Erin Allmann Updyke: And then survived the infection, yeah. Yes. Put a pin in that.

Erin Welsh: Oh, okay.

Erin Allmann Updyke: That 'oh' was the perfect 'oh'. (laughs) Okay so that's how you get transmitted or how you get infected rather, that's the transmission cycle. What basically happens, we've talked about a number of mosquito-borne diseases on this podcast by now so what's important to remember about all mosquito-borne diseases is that there's the cycle of the virus in the human and then there's also the cycle of the virus in the mosquito. And so the mosquitoes get infected if they bite a person who's actively febrile for the most part. It's also possible like a couple days before you show symptoms and a couple days after you recover. If a mosquito bites a person infected with dengue during that time period then the mosquito sucks up a bunch of viral particles, those will travel through the gut of the mosquito, and then they have to make it out of the gut and back to the salivary glands of the mosquito. Importantly that whole process in the mosquito takes like 8-10 days.

Erin Welsh: Wow.

Erin Allmann Updyke: Yeah, it's kind of a long time.

Erin Welsh: Okay.

Erin Allmann Updyke: And that means that if you can somehow stop that process in that 8-10 day window, then you could block the transmission of dengue. Right?

Erin Welsh: Right.

Erin Allmann Updyke: So that's really important.

Erin Welsh: Okay.

Erin Allmann Updyke: We'll talk even more about that in the current events section cause what a lot of people are doing.

Erin Welsh: You're dropping all these little hints.

Erin Allmann Updyke

It's all I do, this whole bio section is just gonna be hints for later.

Erin Welsh

Oh my god. Also I just need to have a little point out right now that I remember nothing.

Erin Allmann Updyke

Excellent.

Erin Welsh

I'm like okay yeah, I know it's a Flavivirus, I know this and that. But that was all.

Erin Allmann Updyke

This is great, I think we must've been like nervous blackout when we were presenting.

Erin Welsh

For sure, I remember nothing of that whole trip.

Erin Allmann Updyke

Me neither. Okay so then if that does work properly in the mosquito, then you have a bunch of virus in the mosquito salivary glands, then they're gonna bite another human and spit all of that virus into you essentially. And then that virus will go into usually your lymph system and in the case of dengue virus it will enter your white blood cells and that is where the virus replicates in human bodies. So then after about 4-7 days usually after you get infected with this virus, that's when you'll start to show symptoms.

Erin Welsh

Okay.

Erin Allmann Updyke

Cool? Okay. So now we know the transmission, we know that it's infecting your white blood cells which if you don't recall are part of your immune system. So that's really important because it's directly sort of targeting your immune cells. Okay so what kind of symptoms do we have if you get infected with dengue? If you get infected with dengue for the first time, most people will never have any symptoms.

Erin Welsh

What's most?

Erin Allmann Updyke

80%.

Erin Welsh

Wow!

Erin Allmann Updyke

Yeah. So like 80% of people who are infected for the first time with dengue have either very, very mild symptoms or are entirely asymptomatic which you can imagine makes it even more difficult to understand how many people really do get infected every year and how to actually control this virus.

Erin Welsh

Yeah.

Erin Allmann Updyke

If you do get symptoms from a primary infection it generally starts as all of our favorite diseases do, with a fever. You'll often get a headache and very classically you get severe muscle and joint pain, so that's how it got the name breakbone fever.

Erin Welsh

Right.

Erin Allmann Updyke

And the symptoms can actually be broken down into three main phases but the last two phases tend to only happen if you're getting infected with dengue for the second time.

Erin Welsh

Aha.

Erin Allmann Updyke Okay. So here are the three main phases: febrile, critical - not good - and recovery.

Erin Welsh Oh, great.

Erin Allmann Updyke Asterisk, or death.

Erin Welsh Oh.

Erin Allmann Updyke Yeah, okay. So the febrile phase that we kind of already started talking about, if you get infected for the second time it's much more likely to be symptomatic and this phase will probably start out worse than the first infection. So it starts out with a super high fever, we're talking over 104 Fahrenheit, 40 Celsius.

Erin Welsh Dang!

Erin Allmann Updyke Yeah. Wait is that right? I'm pretty sure that's right.

Erin Welsh That's high.

Erin Allmann Updyke It's very high. And this fever lasts usually between 2-7 days.

Erin Welsh Oh my gosh!

Erin Allmann Updyke I know, it's a long time. You're very, very sick with dengue.

Erin Welsh Does it respond to antipyretics?

Erin Allmann Updyke Good question. Probably. But it's also often biphasic so often you'll get a really high fever and then you'll start to get better and then a couple days later it'll come back again.

Erin Welsh Does the fever intensity correspond to circulating virus? Anything like that?

Erin Allmann Updyke That's a really good question that I don't fully know the answer to. We'll talk a little bit more about viremia, how much virus you have in your body, when we talk about some of the more severe symptoms of it. But definitely the higher the viral load, the more sick you'll probably get.

Erin Welsh Right.

Erin Allmann Updyke And the more likely you are to have symptoms and things like that.

Erin Welsh But is that why the biphasic, like is that part of it?

Erin Allmann Updyke It definitely could be, I mean that's usually when we think of things like malaria and stuff like that, that's usually when you have those biphasic fevers. So it could be like that you get an initial infection and maybe your immune system kicks in, is able to knock it down a bit, but then the viruses just start replicating like crazy and then you get a secondary second wave.

Erin Welsh Interesting.



Erin Allmann Updyke

Yeah.

Erin Welsh

And do we know whether the fever is a defense mechanism, like an immunological response or is it induced by the virus?

Erin Allmann Updyke

Excellent question. Most of the symptoms of dengue are your immune system responding to the virus.

Erin Welsh

Okay.

Erin Allmann Updyke

Great questions, Erin. As always. Other symptoms that you'll see are severe headache and for some reason, don't ask me why on this one cause I won't have an answer, it's often right behind your eyes where you get this severe headache. And then like I mentioned already, muscle and joint pain, nausea and vomiting are really common. And then a rash can often happen after a few days and the rash, unlike other viral illnesses that are really common or that used to be really common, something like measles where you also get a rash, this rash starts on the torso and then spreads to the limbs.

Erin Welsh

Okay.

Erin Allmann Updyke

So a lot of other rashes will start like on the head and go down. So where rashes start can kind of help you figure out what disease it might be. Isn't that weird?

Erin Welsh

Why?

Erin Allmann Updyke

I don't know, Erin. Viruses are just so cool.

Erin Welsh

What did we talk about with the rash on the palms?

Erin Allmann Updyke

Oh so Rickettsia causes that and syphilis causes that.

Erin Welsh

Got it.

Erin Allmann Updyke

And then hand, foot, and mouth disease.

Erin Welsh

Okay, cool.

Erin Allmann Updyke

Yeah.

Erin Welsh

See, I'm remembering things.

Erin Allmann Updyke

Good! So this one starts on the torso, spreads to the limbs but what's really important is that it's often really, really hard to see this rash. So it's not like this really huge scary-looking rash or anything, it's a very light red-pink kind of splotchy rash, so it's not very descriptive. So after those few days, a couple days, 2-7 days of fever, as the fever starts to fade out especially with a secondary infection, dengue can become more severe. This is when we get into two different syndromes called dengue hemorrhagic fever and dengue shock syndrome. Overall across all dengue infections, these two syndromes happen in less than 5% of cases but the vast majority of those are when someone's been infected the second time.

Erin Welsh: You mean the second time with a different strain?

Erin Allmann Updyke: With a different strain, exactly.

Erin Welsh: Okay. And so you cannot get sick again from the same strain. Do you have lifetime immunity or what's the deal?

Erin Allmann Updyke: Pretty much, yeah. From that particular strain. Maybe unless you got infected with a really, really low viral load and you didn't mount a great immune response, then maybe you can be reinfected with the same strain but for the most part in areas where dengue circulates, multiple strains circulate at the same time.

Erin Welsh: Right.

Erin Allmann Updyke: So you're much more likely to get infected with a different strain and that's when you see dengue hemorrhagic fever or dengue shock syndrome.

Erin Welsh: Right.

Erin Allmann Updyke: So what's happening in these two syndromes? Both of them are related to capillary leakage. So your capillaries are the tiny ends where your arteries and veins come together, right? Where gas exchange is happening. And so what happens is the virus and your immune response to the virus both cause damage to these tiny blood vessels and it causes them to leak. And that is going to cause you to not have enough blood essentially in your blood vessels and then you're going to go into shock and potentially die. So whether you have the hemorrhagic form or just the dengue shock form kind of just depends on whether it's damage that's somewhere in your GI tract and the causing massive bleeding or whether it's damage in other areas that just cause plasma leakage, so you're not losing blood volume, you're losing plasma volume.

Erin Welsh: Okay. So the mechanism is the same, it's just the end result that's different.

Erin Allmann Updyke: Yeah, exactly.

Erin Welsh: Okay.

Erin Allmann Updyke: And both of these you can end up with massive organ dysfunction, eventual death. And symptoms, while they're different across the board, you can get severe abdominal pain and especially if you have GI tract involvement, persistent vomiting. If this happens in your lungs then you can have leakage in your lungs which can make it really hard to breathe, so someone might have really rapid breathing which we call tachypnea. You can have bleeding from your gums because your mucus membranes, if those are starting to leak, that's gonna be blood coming out of your gums, etc etc. This phase, the critical phase, usually only lasts a couple of days, like 1-2 days.

Erin Welsh: Only. That's only a couple of days of you bleeding out your gums and your gut.

Erin Allmann Updyke: Yeah. Or you going into shock because all of the plasma has left your bloodstream and you have no blood for your heart to pump, essentially. So if you survive then you'll enter the recovery phase which in theory in itself actually happens relatively quickly. Your blood vessels kind of heal themselves and stop leaking relatively quickly, within 2 or 3 days. But you can imagine that this has caused a lot of damage to your body overall so actual recovery, like you feeling better, can take weeks at a time.

Erin Welsh: Okay. How many people do survive?

Erin Allmann Updyke: So overall for severe dengue, if you get treatment the overall mortality rate is like 1-5% but once a person goes into shock, if they don't have treatment, it's like a 25-30% mortality rate.

Erin Welsh: But if you do receive treatment it's mostly supportive care?

Erin Allmann Updyke: It's entirely supportive care, yeah. So it's a lot of fluid resuscitation to try and combat that fluid leakage. So a lot of IV fluids and things like that to keep your blood vessels full of fluid.

Erin Welsh: Okay.

Erin Allmann Updyke: Yeah.

Erin Welsh: And that's pretty successful?

Erin Allmann Updyke: Yeah I mean it reduces the mortality rate from 25% to 1-5%. So that's pretty dang good.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah. Okay so there's a couple things that we need to talk about when we talk about these severe forms of dengue. First is that there's a lot of differences in the severity not just based on whether or not it was your first or second infection. So comorbidities, like if you already have a number of comorbidities say like diabetes, hypertension, maybe immunocompromise, these things are obviously gonna make it more likely that you might have a more severe dengue, whether or not it's your first or second infection. Also overall viremia, so how much virus you get exposed to overall is also going to help define whether or not you have severe dengue or not. The strain of the virus can also play a part, so some strains are more likely than others. And for some reason I didn't write down which ones those were.

Erin Welsh: I think it's number 2 at least in the Americas that's associated with hemorrhagic fever.

Erin Allmann Updyke: That makes sense, I was gonna guess 2 or 3.

Erin Welsh: But I have a question that's related to this. This is the one I wrote down.

Erin Allmann Updyke: Oh excellent.

Erin Welsh: So dengue hemorrhagic fever happens when you get infected with a second strain or a different strain than you first were infected with. Are there different combinations of strains that will lead to that being more severe or more likely to occur? Maybe that's not known.

Erin Allmann Updyke: It's a good question. Like if you get infected with 1 first and then 2 vs 2 first and then 1?

Erin Welsh: Right.

Erin Allmann Updyke: Yeah, good question. I don't know based on what I've read about but I'm sure there's some epi studies out there that are looking into that or that have looked into it.

Erin Welsh: Yeah.

Erin Allmann Updyke: It's a really good question.

Erin Welsh: And is there any partial immunity conferred based on yellow fever, if you've been exposed to yellow fever or Zika or other Flaviviruses?

Erin Allmann Updyke: I don't think so.

Erin Welsh: Okay.

Erin Allmann Updyke: Yeah, even though they're all Flaviviruses I don't think they're similar enough to provide any sort of cross immunity or anything like that.

Erin Welsh: Okay.

Erin Allmann Updyke: Yeah. Good questions though. So fun, Erin. Okay and then the other people who are more likely to have severe dengue regardless of number of infection are children and the elderly. And this is for a couple of reasons. Both children and the elderly have kind of a lower threshold for capillary leakage to begin with so they're at increased risk for bleeding in general, like in older people their capillaries are just kind of weak and in children they're not fully formed so they're more likely to have leakage from that. Bleeding especially is more common in older adults and things than in children.

Erin Welsh: Okay.

Erin Allmann Updyke: But we talked briefly about how infants can be born with antibodies to dengue. So a group that's at very, very high risk of severe dengue, dengue hemorrhagic fever or dengue shock syndrome, is infants that have maternal antibodies to dengue still circulating. So if a mom was infected and then the baby is born with those antibodies, if that baby gets infected with another strain of dengue they're at very, very high risk of going on to develop severe symptoms.

Erin Welsh: But if only 20% of people show signs or know that they've been infected with dengue then how do you know?

Erin Allmann Updyke: That's the thing, how do you know?

Erin Welsh: That's scary.

Erin Allmann Updyke: It's really scary, yeah.

Erin Welsh: And there's no screening protocol in any places that's endemic for dengue?

Erin Allmann Updyke: Like during pregnancy?

Erin Welsh: Yeah.

Erin Allmann Updyke: Not that I know of. Not that I know of, yeah.

Erin Welsh: Cool.

Erin Allmann Updyke: So then the question becomes why is it that a secondary infection with dengue is worse than a first infection?

Erin Welsh: Yeah.

Erin Allmann Updyke: That's very bizarre, right?

Erin Welsh: So I can't tell if this is a true guess or a recovered memory but is it something like you know in the 1918 flu where it's like the immune system just goes super ham?

Erin Allmann Updyke: Good question. That's one of the hypotheses that was out there for a long time that it's kind of like a cytokine response that was what happened in the 1918 flu.

Erin Welsh: Yeah. That's what I was looking for.

Erin Allmann Updyke: Cytokine.

Erin Welsh: Maybe not a recovered memory then. (laughs)

Erin Allmann Updyke: Yeah that's one of the hypotheses that are out there. There's a number of different hypotheses out there as to what exactly is the cause of this secondary severe infection. The exact mechanism isn't entirely clear but the most parsimonious and the most well supported hypothesis is called antibody-dependent enhancement. And I will say the fact that infants who are born with antibodies only, to me that provides really good support to this hypothesis cause the idea is basically this.

If you have antibodies against let's say dengue strain number 1, these antibodies are similar to the antibodies that you would make to dengue number 2 but they're not exactly the same. And so for some reason these antibodies bind to dengue number 2 virus, right, and when antibodies bind what they do is they encourage your white blood cells to engulf that virus in order to kill it, right, that's the point of an antibody, it's like a flag that our immune system puts on viruses. So these antibodies that you've made to dengue 1 flag dengue 2 but they don't do it perfectly and for some reason what that does is it causes the virus when it gets into the white blood cells which remember is where dengue wants to be, that's where dengue replicates, it causes a massive amount of replication. So something about the antibodies that are a little bit mismatched binding to that virus enhances their ability to replicate and then increases viremia.

Erin Welsh: Oof.

Erin Allmann Updyke: Right?

Erin Welsh: Also what's really interesting about this is that these strains evolved in isolation cause that's how strains evolve. And so this is like a recent thing, so it just so happens that it turned out to be really, really, really bad for humans.

Erin Allmann Updyke: Yeah. And really good for the virus is it's increasing viremia, right, because the more virus you have circulating then the more likely a mosquito is gonna be able to pick up that virus and transmit it to the next host.

Erin Welsh

That's really fascinating though.

Erin Allmann Updyke

It is. And there's a number of really cool papers out there looking into getting more detail or more support for this hypothesis. So that is dengue. That's the biology, that's how it gets you sick, that's how it kills you. It's a horrible illness and we'll talk later about how many people it kills every year. Erin, where did this thing come from? Why is it here? And why is it so bad?

Erin Welsh

Great questions. Let's take a quick break and then we'll begin.

Erin Allmann Updyke

Excellent.

TPWKY

(transition theme)

Erin Welsh

Dengue virus, all of its types, probably originated in Asia and then kind of exploded out from there. There has been some debate about whether it really originated or diversified in Asia or Africa but most things that I read suggested Asia as the origin.

Erin Allmann Updyke

Okay.

Erin Welsh

So about 2000-4000 years ago the dengue virus, which had been hiding out in the jungle, hitched a ride in a type of mosquito species that likes to hang around human settlements. And these mosquitoes probably transmitted the infection to these small human settlements but then these outbreaks were like little bursts, so they would happen infrequently, everyone would get exposed, and then everyone would gain immunity. And then dengue would retreat and wouldn't be seen again until the number of susceptible people in that settlement would increase to a point where an outbreak could happen again. So then that cycle continued on and on until humans started to live in bigger and bigger groups and then the distance between these settlements or groups shrank and then things like commerce and migrations led to the groups being more and more connected. And so over the course of that time it was kind of a one location, one strain situation. But evolution happens and different strains of dengue start to evolve and they would also make the leap from the sylvatic cycle. So I think originally dengue did circulate in primates, like nonhuman primates, yeah.

Erin Allmann Updyke

Right. It makes sense that it came from nonhuman primates and then just specified onto humans or whatever.

Erin Welsh

Right. And so more and more strains made this leap from just the sylvatic cycle of monkeys and mosquitoes to then this urban cycle or more urban cycle of mosquitoes and humans. But still even though more strains evolved, there was still this geographical isolation among the strains. So one strain would be in this location, one strain would be in that location and there wasn't a whole lot of opportunities for overlap. It did of course happen occasionally but not that often. But it's kind of in a way having these different strains in really interesting because researchers can compare the DNA sequences of these strains and then put a timeline on their emergence and where they emerged as well. Okay so this general pattern that I described, one strain per outbreak, small outbreaks, very sporadic, this continued for hundreds of years, probably thousands of years. And then around the 16th and 17th centuries the slave trade began. And for dengue in particular this meant that A) the world became flat, so the virus could be transmitted or carried all over the world by these ships and introduced to new populations that were full of susceptible humans, and the other thing is that the slave trade also spread the key vector mosquito species, *Aedes aegypti*.

Erin Allmann Updyke

Yeah.

Erin Welsh: Because as you mentioned *Aedes aegypti* lives really well next to humans and it doesn't need a whole lot to continue its life cycle.

Erin Allmann Updyke: Yeah.

Erin Welsh: Basically small bits of water.

Erin Allmann Updyke: They're very hearty.

Erin Welsh: Mm-hmm. And I think this is fascinating because *Aedes aegypti*, it's of African origin. So *Aedes aegypti* is now the primary mosquito.

Erin Allmann Updyke: Yeah but it wasn't the first if it...yeah.

Erin Welsh: No, *Aedes albopictus* was probably what it originated with.

Erin Allmann Updyke: Interesting cause yeah, *Aedes aegypti* and *Aedes albopictus* are both the two main vectors but they talk about *Aedes aegypti* as the primary just because of I think it's distribution and it's a more voracious biter as well.

Erin Welsh: Apparently yeah, it's more efficient at transmitting the virus as well.

Erin Allmann Updyke: Wow! Interesting.

Erin Welsh: And so this is kind of what caused this debate as to the geographical origin of dengue because it would make more sense that this virus and this mosquito species fit so well together and work so well together that that would be the origin, that they would've evolved together as well.

Erin Allmann Updyke: Yeah. Right.

Erin Welsh: But it seems that actually *albopictus* is where it came from.

Erin Allmann Updyke: Fascinating.

Erin Welsh: I don't know. Anyway, so *Aedes aegypti* being this super cosmopolitan mosquito species really helped the distribution of dengue. And so probably by the 18th century the dengue virus was all over the global tropics and also its distribution could creep northwards during the warmer months, especially in port cities, thanks to the widespread distribution of *Aedes aegypti*. And even in those more northern or more southern places like a little bit outside of the mosquito's yearlong environmental requirements, it would just be reintroduced.

Erin Allmann Updyke: Yeah.

Erin Welsh: It'd be like, 'Oh it's warm enough in the summer. I'll die off in the winter and then be reintroduced.'

Erin Allmann Updyke: Yep.

Erin Welsh: Knowing the evolutionary origins of dengue is one thing but when did humans actually first recognize the disease?

Erin Allmann Updyke: Yeah.

Erin Welsh: So it's around the late 18th century, 1779 to be exact, that we see what is considered to be the first dengue pandemic.

Erin Allmann Updyke: Ooh.

Erin Welsh: In 1779 there are descriptions of a dengue-like illness in Jaffa in Egypt and the following year we see it pop up in Philadelphia. And this is actually when it gets its colloquial name, breakbone fever which was coined by Benjamin Rush. And he was also a physician and so to give you an idea of the scale of this epidemic in Philadelphia, he saw over the course of 2 months around 1000 people, he treated them for dengue.

Erin Allmann Updyke: 2 months, 1000 people in Philadelphia.

Erin Welsh: Yeah. He alone.

Erin Allmann Updyke: He alone.

Erin Welsh: Yeah.

Erin Allmann Updyke: Wow.

Erin Welsh: Yeah. I couldn't find an exact estimate of the total number of people likely infected but probably it was pretty high.

Erin Allmann Updyke: Wait a second, this is the one recovered memory I have from the time that we talked about dengue in Florida. Benjamin Rush is one of the Founding Fathers?

Erin Welsh: Yeah! He is.

Erin Allmann Updyke: I learned that from you. (laughs)

Erin Welsh: (laughs) I'm so glad that's the one bit of trivia.

Erin Allmann Updyke: All right.

Erin Welsh: Next time you go to trivia at The Blind Pig.

Erin Allmann Updyke: Mm-hmm, Benjamin Rush.

Erin Welsh: Benjamin Rush. Name three Founding Fathers.

Erin Allmann Updyke: That's the only one I know now. Oh god. Moving on.



Erin Welsh: Anyway. So the epidemic in Philadelphia from Benjamin Rush's description was pretty likely dengue.

Erin Allmann Updyke: Okay.

Erin Welsh: Egypt and Jaffa may have been chikungunya, there's been a lot of recent debate over whether these early descriptions are actually chikungunya virus as opposed to dengue virus.

Erin Allmann Updyke: Okay, cool.

Erin Welsh: In any case it seems that Philadelphia was pretty likely and that's the earliest most convincing instance. There are descriptions of a dengue-like disease in a Chinese encyclopedia dating back to the year 992.

Erin Allmann Updyke: Whoa.

Erin Welsh: Yeah. And in this encyclopedia this disease is referred to as 'water poison' and was known to be associated with flying insects that live near the water, so mosquitoes.

Erin Allmann Updyke: Okay, fascinating.

Erin Welsh: And the symptoms of this disease sound a lot like dengue. So you've got the fever, rash, eye pain, bleeding, sometimes high mortality, and this also lends further support to the hypothesis that the virus originated in Asia. But anyway the virus was circulating throughout much of the world during the 18th and 19th centuries with an estimated 8 pandemics each lasting 3-7 years from 1779-1916.

Erin Allmann Updyke: Whoa! Wow.

Erin Welsh: Yeah. With a disease that is as old and particularly as wide ranging as dengue, it makes sense that it would accumulate a few names over its lifetime.

Erin Allmann Updyke: Yes! I love the names.

Erin Welsh: Yes. I hope that there's another one that you remember because I did a little more digging.

Erin Allmann Updyke: Oh okay.

Erin Welsh: So the word 'dengue' first seems to pop up in Spain around 1801 and researchers think that the most likely origin of that was actually from the Swahili name for the disease 'kidingapopo' meaning a disease characterized by a sudden cramp-like seizure caused by an evil spirit.

Erin Allmann Updyke: That sounds familiar, okay.

Erin Welsh: Yeah so it was called 'dinga' or 'denga' from the early 19th century on. But it had a lot of other names. We've already heard water poison, we've already heard breakbone fever, breakheart fever-

Erin Allmann Updyke: Oh yeah!

Erin Welsh: You remember that one?

Erin Allmann Updyke: I do remember that one.

Erin Welsh: Cause all the women that Benjamin Rush treated were crying.

Erin Allmann Updyke: They were crying women, yeah. And old Ben was like, 'Well these poor ladies and their heartbreak'.

Erin Welsh: No, one of the supposed patients was like, 'You should call it breakheart fever cause I'm just broken-hearted'.

Erin Allmann Updyke: Oh gracious.

Erin Welsh: Scarletina rheumatic, polka fever, ephemeral fever, and the most baffling one at the time, dandy fever.

Erin Allmann Updyke: Dandy fever, yes!

Erin Welsh: You remember this?

Erin Allmann Updyke: We were like what the heck is a dandy? And I was thinking of that character in American Horror Story, that's who I think of.

Erin Welsh: And I still haven't seen that so...

Erin Allmann Updyke: Well everyone else, you know the circus season? It's the guy who is a really horrible person but he's like a dandy. I think he's a dandy. Tell me what's a dandy.

Erin Welsh: Okay so I did a little sleuthing which basically means that I went to the Wikipedia article for 'dandy' which is pretty lengthy actually.

Erin Allmann Updyke: Cool.

Erin Welsh: All right. So according to Wikipedia, quote: "A dandy, historically, is a man who places particular importance upon physical appearance, refined language, and leisurely hobbies, pursued with the appearance of nonchalance in a cult of self." Like Yankee Doodle Dandy.

Erin Allmann Updyke: Mm-hmm, Yankee Doodle Dandy. He puts a feather in his cap cause he's concerned about his appearance.

Erin Welsh: He called it Macaroni, he wanted to stand out.

Erin Allmann Updyke: Exactly.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah, okay. So that's a dandy.

Erin Welsh: That's a dandy. I still don't understand what this means in terms of dandy fever.

Erin Allmann Updyke: Dandy fever. It doesn't make any sense.

Erin Welsh: Any hypotheses? Send them our way.

Erin Allmann Updyke: Yep.

Erin Welsh: Okay so that's dengue etymology and also hopefully a little bit more about dandy fever than we knew before.

Erin Allmann Updyke: Yeah. Although still not an answer.

Erin Welsh: Still unanswered. Okay so anyway the disease dengue was known by at least the late 1700s but it would take a bit before some of its biological characteristics were discovered. So once scientists made the link between mosquitoes and yellow fever which was in the late 1800s, they kind of got the feeling that dengue was also transmitted by mosquitoes and that took a little bit longer to show but they did show it. Let's have these infected mosquitoes bite humans, human "volunteers" quote unquote. And then right after that researchers discovered that dengue was caused by a filterable, transmissible agent which back then before microscopy and microbiology advanced pretty much meant that it was a virus. The viruses wouldn't be isolated until 1943, this was during or right after the Nagasaki dengue epidemic of 1942 which had over 23,000 reported cases.

Erin Allmann Updyke: Wow.

Erin Welsh: And so at this time researchers isolated some serum from someone who was infected and then they injected it into the brains of suckling mice.

Erin Allmann Updyke: Oh.

Erin Welsh: And it gave them dengue.

Erin Allmann Updyke: Okay, weird.

Erin Welsh: But the important thing about this was that this was that this isolation of this virus allowed researchers to also look at the different strains and which strains were causing which outbreaks. So that was pretty important. So speaking of strains, up to this point this history is mostly about the history of dengue viruses but not specifically dengue hemorrhagic fever.

Erin Allmann Updyke: Right.

Erin Welsh: And that's because that's really its own part of the story. So let's go to the 1940s for that. So I've talked before many times, every episode probably about how important war is in terms of disease transmission.

Erin Allmann Updyke: Oh yeah.

Erin Welsh

Dengue and dengue hemorrhagic fever are no exceptions to that. During WWII especially in the Pacific and Asian theaters of war there was massive destruction of everything, the landscape both natural and urban was just destroyed. And so in urban areas in particular the infrastructure for water supplies or draining and plumbing essentially collapsed and people had to store water in large containers and a lot of water pools would form rather than drain.

Erin Allmann Updyke

Oh dear.

Erin Welsh

The mosquito populations grew enormously and they found plenty of hosts as people were also on the move both during and following the war with a huge influx into urban centers. And the urban centers couldn't keep up with the growth in terms of infrastructure and so you just have all of a sudden these mosquitoes are like, 'Well we have plenty of hosts here to be able to do our thing.'

Erin Allmann Updyke

Right. And collapsing infrastructure with plenty of places for water to collect.

Erin Welsh

Exactly.

Erin Allmann Updyke

Yep.

Erin Welsh

It's sort of a perfect storm of bad things happening. So the other thing is that during the 1940s, both during the war and after, you have massive movement of people not just like from the rural centers to urban centers, you have movement across the entire world. What this turned into was no longer a one strain, one city situation. Suddenly there were 2 or 3 or 4 dengue virus strains mixing in the same location.

Erin Allmann Updyke

Right.

Erin Welsh

And that as we know is how you get dengue hemorrhagic fever. Of course this had been described before but it was really sporadic and the exception. But in the years after WWII there were epidemics of dengue hemorrhagic fever of very large scales and since then they have pretty much only - correct me if I'm wrong - but only increased in frequency and geographic spread and size in many cases.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah. So we see the first epidemics of dengue hemorrhagic fever in Southeast Asia in the 1950s and 60s, starting in 1953 in Manila in the Philippines. And then these epidemics at first were sporadic, every few years but then they grew in size as trade and urbanization and populations increased. Epidemics of dengue hemorrhagic fever in the Americas lagged a bit behind these epidemics in Southeast Asia, popping up only in the late 1970s, early 1980s. And this delay was possibly due to simple geography but also probably had something to do with the widespread mosquito eradication campaigns throughout the Americas in the 20th century. I wanna talk a little bit about these campaigns because I think they're important not only in understanding the current landscape of mosquito-borne disease risk across the Americas but also I think it's a really good example of why it's so important to work interdisciplinarily and how quickly things can be undone.

Erin Allmann Updyke

Oh yeah.

Erin Welsh: Yeah. The anti-mosquito campaigns in the Americas were initially spurred on by a desire to get rid of pest mosquitoes. It was before the true extent of the disease-causing capabilities of the mosquitoes were known and so mostly it was just like-

Erin Allmann Updyke: These are annoying.

Erin Welsh: These are horribly annoying. And to read some of these quotes, I can't really blame them. Like it sounds like madness. Here's one, this is from an English settler.

Erin Allmann Updyke: Okay.

Erin Welsh: They said, "The noise they make in flying can not be conceived by persons who have only heard gnats in England." That's one. And a Catholic priest said, "The greatest torment in comparison with which all the rest would be but sport is the mosquitoes. The cruel persecution of the mosquitoes. The plague of Egypt I think was no more cruel. This little insect has caused more swearing since the French have been in Mississippi than had previously taken place in all the world."

Erin Allmann Updyke: (laughs) More swearing in Mississippi than in all the world.

Erin Welsh: Yeah! What a strange sentence.

Erin Allmann Updyke: That is a really weird sentence.

Erin Welsh: But it does seem that mosquitoes were like unheard of.

Erin Allmann Updyke: Super annoying?

Erin Welsh: Super annoying, yeah. And they did drive people out of towns, they slowed tourism, and they reduced property values. And so people, particularly landowners, wanted something to be done. Even though it started out as this like let's get rid of nuisance mosquitoes angle, it soon took on public health motivations as well once the links between yellow fever and mosquitoes and dengue, mosquitoes and malaria, once those were all uncovered.

Erin Allmann Updyke: Right.

Erin Welsh: In the yellow fever episode we talked about the elimination of mosquitoes and reduction of yellow fever in the predominantly white Panama Canal zone.

Erin Allmann Updyke: Exactly.

Erin Welsh: So that kind of was like oh, it can be done, so maybe we should try it. And it started in New Jersey of all places.

Erin Allmann Updyke: New Jersey?

Erin Welsh: New Jersey.

Erin Allmann Updyke: Okay.

Erin Welsh They were one of the most vocal about their mosquito problem and so that's where this began. Basically the first strategy of this campaign was to essentially use oil as they did in Panama to dump it in mosquito breeding grounds like standing water and then this would be like a larvicide and whatever. But it's really bad for the environment to just dump oil in. So a bunch of fish died, a bunch of other animals like any aquatic animals, plants also died.

Erin Allmann Updyke Did they use castor oil? Just kidding.

Erin Welsh Throwback to two weeks ago. (laughs) and also only a subset of mosquitoes were affected by the oil and so they were like, 'We need another solution.'

Erin Allmann Updyke Yeah.

Erin Welsh The fishermen were like, We're not standing for this'.

Erin Allmann Updyke Yeah.

Erin Welsh So they were like let's drain these marshes and swamps and wetlands.

Erin Allmann Updyke Great plan, guys.

Erin Welsh Great plan.

Erin Allmann Updyke Excellent.

Erin Welsh And they were like well no matter that there are hundreds of thousands of acres of this, let's do it anyway. And they did run into some problems, one was just the sheer size of the project that they were trying to undertake, one was funding, and the other was that not everyone wanted to have their land be drained. So then there were laws put in place starting in New Jersey, then California followed suit, saying that any standing water is a public nuisance and the person would either be fined or agree to comply to have their land be drained. Mosquito engineering is what it was called. By the 1920s, anti-mosquito campaigns were pretty much set up across the US with one exception being Florida, like Florida seemed to be strangely resistant.

Erin Allmann Updyke They love their mosquitoes down there, it's always mosquito season.

Erin Welsh (laughs) As we learned.

Erin Allmann Updyke As we learned when we were there.

Erin Welsh But mosquito control cost money and it wasn't exactly promising results because it would be like oh yeah, New Jersey was doing great and then there would be heavy rains one year and all their work would be undone.

Erin Allmann Updyke Shocking.

Erin Welsh And everything else dies. So yeah. But then some unexpected and unasked for good PR for the anti-mosquito campaigns came to Florida in 1921 in the form of a dengue outbreak. About 500 diagnosed cases and hundreds more that went unreported. And then the following year there was a massive dengue epidemic across the southeast in Texas, Georgia, Florida, 200,000 people infected.

Erin Allmann Updyke: Whoa!

Erin Welsh: Yeah.

Erin Allmann Updyke: Wow!

Erin Welsh: In 1922.

Erin Allmann Updyke: Wow.

Erin Welsh: So then people got behind these anti-mosquito campaigns pretty quickly after that.

Erin Allmann Updyke: Okay.

Erin Welsh: So I think it's important to point out that this blanket hatred for mosquitoes and full steam ahead approach wasn't necessarily unanimous among the people in charge. It's easy to look back and assume that's the case because that's what actually did happen, there was a lot of 'let's kill all the mosquitoes'. But there were dissenting voices early on, so there were people who worked directly in the mosquito control business were suspicious that these poisonous gases were also toxic to fish and birds and others saw right through some of the efforts as a monkey-making scheme for real estate developers. But because there was more money to be made in complete mosquito eradication than in ecologically balanced approach, these dissenting voices were drowned out.

Erin Allmann Updyke: Yeah, in the swamps that they drained.

Erin Welsh: Exactly. The 1930s saw even a larger expansion in mosquito control efforts at the US scale and then the following decade PAHO, Pan American Health Organization got involved and their campaign was to eliminate *Aedes aegypti* across the Americas.

Erin Allmann Updyke: How'd that work out for them?

Erin Welsh: Well great actually, for a very short time.

Erin Allmann Updyke: Okay, all right.

Erin Welsh: Yeah. So in general these projects were developed or carried out by engineers, not ecologists and so that led to some major problems. In some of these marshy areas there was diverse habitat, rich with plant and animal life, a few years later it was just destruction.

Erin Allmann Updyke: Yeah.

Erin Welsh: And this led to a pretty big rift actually between mosquito control advocates and conservationists even though it seems like they should both be on the same side of things. But this rift would only grow larger because in the 1940s a new pesticide called dichloro-diphenyl-trichloroethane...

Erin Allmann Updyke: DDT.

Erin Welsh	You got it. And that was found to be an extremely cheap and really effective way to control or kill both adult mosquito populations and larvae.
Erin Allmann Updyke	And like everything else, it's great. Just kill everything.
Erin Welsh	Just kill everything. And it was great also because it persisted in the environment.
Erin Allmann Updyke	Excellent!
Erin Welsh	You just needed one treatment.
Erin Allmann Updyke	And then you can kill everything for years to come!
Erin Welsh	Just for decades and decades and decades.
Erin Allmann Updyke	No potential downside to this whatsoever.
Erin Welsh	Nope. And so the 1940s, 50s, 60s all saw widespread use of DDT. It also saw the emergence of DDT resistance.
Erin Allmann Updyke	Shocking.
Erin Welsh	And it also saw the widespread destruction and population declines in a host of other animals. And so in 1962 is sort of when things started to turn against the tide of mosquito campaigns. Rachel Carson's book 'Silent Spring' was published and in effect that was the birth of the modern environmentalist movement. The first Earth Day was celebrated in 1970 and by 1972 DDT was banned in the US. And around this time also is when PAHO kind of stopped or slowed its efforts for mosquito elimination campaigns and a lot of that was just a loss of funding and another was they no longer felt it was necessary because yellow fever and dengue was no longer an issue in so many of the places. Aedes aegypti was successfully eliminated in Mexico, Guatemala, Belize, Honduras, El Salvador, Nicaragua, Costa Rica, Panama, Colombia, Ecuador, Peru, Chile, Bolivia, Paraguay, Argentina, Uruguay, Brazil, the Cayman Islands, and Bermuda.
Erin Allmann Updyke	Wow.
Erin Welsh	It was eliminated, done.
Erin Allmann Updyke	That's a lot of countries.
Erin Welsh	Not everywhere, it wasn't successful everywhere.
Erin Allmann Updyke	Right. But a lot of them.
Erin Welsh	But when these campaigns stopped, within a few years all the mosquitoes came back as you might expect.
Erin Allmann Updyke	I would expect.



Erin Welsh: This is when you see the first cases of dengue hemorrhagic fever in the late 1970s. Within a couple decades after that the levels of mosquitoes that we have in all of those places are at pre-eradication levels, like before any of these campaigns ever got started.

Erin Allmann Updyke: Wow. Man, mosquitoes are hearty little bugs, I'll tell you what.

Erin Welsh: Yeah. So we're back to where we started essentially.

Erin Allmann Updyke: Yeah.

Erin Welsh: Or actually in a worse situation.

Erin Allmann Updyke: Right because now it's everywhere.

Erin Welsh: Now it's everywhere. The first decade of the 21st century saw huge increases in dengue incidents in the Americas including two Pan American epidemics with over a million reported cases as well as local transmission within different places. I found an article that said there are 5 major reasons for dengue's emergence as a public health problem.

Erin Allmann Updyke: Excellent.

Erin Welsh: 1) Unprecedented global population growth.

Erin Allmann Updyke: Okay.

Erin Welsh: 2) Uncontrolled urbanization and all that goes with it including substandard water treatment, sewer and waste management infrastructure, etc. 3) Lack of effective mosquito control in places where the disease is endemic. 4) increased air travel. And 5) decay in public health infrastructure meaning that there was more of a focus on epidemic response rather than prevention. So Erin, now that dengue is around us everywhere at all times, well not here in Chicago in the middle of January. (laughs) How worried should we be? Tell us about the vaccine, tell us about the latest epidemics. What's going on?

Erin Allmann Updyke: All right, let's talk all about it. We'll take one quick break first.

TPWKY: (transition theme)

Erin Allmann Updyke: Erin, it's not good news.

Erin Welsh: Cool.

Erin Allmann Updyke: Worldwide dengue is, I don't know if you would say endemic but certainly circulates in over 100 countries.

Erin Welsh: Okay.

Erin Allmann Updyke: We don't as per usual have a good handle on how many cases there actually are every year. However, do you wanna hear some terrifying estimates?

Erin Welsh: Mm-hmm.

Erin Allmann Updyke A modeling study in 2013 that was published in Nature which we'll link on our website estimated, and this is now the estimates that WHO has on their website, etc, it's a good modeling study. They estimated 390 million dengue virus infections per year.

Erin Welsh What?

Erin Allmann Updyke 390 million infections, remember the vast majority are asymptomatic. So it's estimated that 96 million of those will manifest clinically at some level of severity. So yeah.

Erin Welsh Hold on, okay. This is every year?

Erin Allmann Updyke Every year.

Erin Welsh But how are there even that many susceptible people?

Erin Allmann Updyke Another study estimated that 3.9 billion people are at risk of infection with dengue.

Erin Welsh That's half of the world.

Erin Allmann Updyke Yep. Exactly.

Erin Welsh Hold on. But how does that mathematically... Every year we would all be...

Erin Allmann Updyke I mean how many people are born every year?

Erin Welsh Hey Google. How many people are born every year?

Google Here is some information from the web that might possibly help. On the website theguardian.com they say, "There are on average about 250 babies born every minute, more than 130 million in a year." To find out more, look for the link in your Google Home or Google-assisted app.

Erin Welsh There you go. 130 million babies born every year.

Erin Allmann Updyke Okay so then at a certain point everyone is going to be infected with dengue is what that means.

Erin Welsh Yeah, it's only a matter of time.

Erin Allmann Updyke It's only a matter of time. Fascinating. Wow. Way to go, Google. Okay. Now here's where it gets even more interesting. Like you kind of mentioned, the number of dengue cases has been increasing. Now we have to balance the fact that it's being reported more often, etc etc but there is no doubt that dengue is growing in its number of cases, it's not just because we're reporting it more often.

Erin Welsh Right.

Erin Allmann Updyke But for example between 2010 and 2016 the number of cases reported to WHO increased from less than half a million to 3.3 million in only 6 years.

Erin Welsh

What?

Erin Allmann Updyke

Right. And that's just what's reported, you know. So that's a lot less than what it's estimated that people are actually infected.

Erin Welsh

So is it pretty easy to get screened for dengue? Like is the test expensive or is it fast?

Erin Allmann Updyke

So that's one of the limitations in dengue research is that we don't have perfect screening methods. You can screen for it, you use seroprevalence tests, so you'll look for antibodies to dengue just like we do for a lot of other diseases. It's usually I think a PCR test, so those aren't super cheap but they're not super expensive or very cost-prohibitive or anything. But it is a limitation that we don't have screening everywhere, not every clinic is going to be able to test for dengue. So in 2017 and 2018 cases were actually down, it was looking good for dengue, there were fewer cases than the past few years. 2019 not so much. Especially in the Americas. So PAHO reported over 2.7 million cases and over 1200 deaths between January and October of 2019.

Erin Welsh

Oof.

Erin Allmann Updyke

Yeah, right? That's a lot.

Erin Welsh

Wow.

Erin Allmann Updyke

So PAHO is the Pan American Health Organization, that's just the Americas. Across the globe there was also increases kind of across the board. So there were outbreaks in 2019 across Australia, Cambodia, China, Malaysia, Philippines, Singapore, Vietnam, Brazil, Colombia, Tanzania, Congo, French Polynesia, everywhere. So overall it's estimated that at least 500,000 people every year are hospitalized with severe dengue and across the globe this has on average about 2.5% case fatality rate, so that's a lot of people dying every year from dengue.

Erin Welsh

That is so many people. What is our hope?

Erin Allmann Updyke

Well there are a few. There are kind of a number.

Erin Welsh

Cool.

Erin Allmann Updyke

Let's end this episode on a positive note for once in our lives.

Erin Welsh

Great.

Erin Allmann Updyke

So there is a vaccine and there's more than one, there are I think four or five vaccines under study, that are undergoing phase 3 trials and there's one called Dengvaxia that was licensed in 2015. So currently you can get this vaccine in a number of different countries. It was actually approved by the FDA for the US in May of 2019. The only problem, not the only problem, one of the problems with this vaccine is that when they first did studies on it, it's protective against all four serotypes, all four strains of virus which is really important because remember, if you get infected with a different strain then you're more likely to have dengue hemorrhagic fever or dengue shock syndrome. So any vaccine has to protect against all of the serotypes of dengue.

Erin Welsh

Aren't there five?

Erin Allmann Updyke

There are but the newest one, I don't know if it only circulates in really small areas or if we just didn't know enough about it, it's not in any of these vaccines. But the four are the ones that are really prevalent.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah. So from initial trials the overall efficacy of this vaccine was around 60% for dengue infection overall but 80% protective against severe dengue, so that's really good. However when they went back and over time did some longer term studies, what they realized is that if you give this vaccine to people who have never been infected with dengue, so who are seronegative when they get the vaccine, over time they're actually more likely to get severe dengue infection.

Erin Welsh

Okay.

Erin Allmann Updyke

So what that suggests is that this vaccine isn't providing complete immunity against all four strains.

Erin Welsh

Okay.

Erin Allmann Updyke

Okay? So the current recommendation right now is that if countries are going to start introducing the dengue vaccine, they should screen people for previous infection before they give them the vaccine. Cause in people who have been exposed to at least one strain, the vaccine is very protective and doesn't increase your risk of severe dengue.

Erin Welsh

Gotcha.

Erin Allmann Updyke

Okay. So yeah, so that's kind of the preferred option at this point, it's pre-vaccination screening and you only give the vaccine to people who have previously been infected with dengue. Here's where I'm gonna answer a question. Shout out to Kobe from University of South Florida who first of all drove all the way from Tampa to Gainesville to come and see us talk.

Erin Welsh

Oh my gosh. The sweetest.

Erin Allmann Updyke

I still can't believe that people drove to see us.

Erin Welsh

I know.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah.

Erin Allmann Updyke

So he asked an amazing question after the talk that I wanna make sure that I touch on. He asked why is it that if you give somebody the dengue vaccine after they've been exposed to dengue, why doesn't the vaccine cause dengue hemorrhagic fever or dengue shock syndrome in those people?

Erin Welsh

Ooh, yeah. I remember this question.

Erin Allmann Updyke

Right, it's a really good question. And my thought at the time was well maybe the vaccines are only component vaccines. Turns out they're not. So the vaccine that's licensed and most of the ones that are in trials are live-attenuated vaccines which means they are live virus of the four different serotypes.

Erin Welsh

Okay.

Erin Allmann Updyke

But the viral strains have been grown in the lab until they're no longer very virulent, so they don't make us sick. All they do is stimulate an immune response. But your immune system has a lot to do with the dengue hemorrhagic fever and dengue shock syndrome manifestations so why is it that we don't see this in the vaccine? And the answer I think from what I can tell just turns out to be because these strains are not virulent they don't induce that response. But theoretically they could. Yeah, isn't that fascinating?

Erin Welsh

That's really interesting.

Erin Allmann Updyke

So Kobe, that was a really good question.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah. And there's a couple of cool papers that I found looking at the current status of vaccine research cause again this isn't the only vaccine that's out there, there's other vaccines under trials. So we'll post all of those on our website as usual. So that's the good news about the vaccine. What's really cool about dengue too though is there's a ton of research going on in better mosquito control but not the way that we've done it in the past. So for dengue there's a lot of research going on in genetically modifying mosquitoes to no longer be able to transmit dengue virus.

Erin Welsh

Very cool.

Erin Allmann Updyke

I absolutely love this. So one of the main strategies that people are using is a bacteria called Wolbachia.

Erin Welsh

Oh yeah.

Erin Allmann Updyke

So mosquitoes in general, tons of different species of mosquitoes are naturally infected with a species of bacteria called Wolbachia and in Aedes mosquitoes it turns out that infection with Wolbachia reduces the ability of the mosquito to transmit dengue and other arboviruses like yellow fever, chikungunya, Zika, etc. So what they've been doing and we don't have time to really get into the nitty gritty details of this but what they're basically doing is engineering Wolbachia to be able to transmit it between mosquitoes so that a whole population of mosquitoes could end up infected with this Wolbachia bacteria and that can then make it so that that population of mosquitoes can't transmit the dengue virus. Isn't that cool?

Erin Welsh

That's really cool.

Erin Allmann Updyke

Yeah. So we'll end this one on a happy note, it's not all doom and gloom and hundreds of thousands of people dying every year.

Erin Welsh

It's just hundreds of millions of people getting infected with dengue, that's it.

Erin Allmann Updyke

That's all. Oh dear.

Erin Welsh

Sources?

Erin Allmann Updyke

Sources?

Erin Welsh

So I have several and I wanna shout out a few. One is called 'The Mosquito Crusades' and this is a book by Gordon Patterson. And then another great source was a book by Duane Gubler called 'Dengue and Dengue Hemorrhagic Fever'. And a paper by Dick et al, 'The History of Dengue Outbreaks in the Americas'. And a few more that I'll post on the website.

Erin Allmann Updyke

That paper from Nature 2013 that estimated 'The global distribution and burden of dengue', that was the title, was by Samir Bhatt et al. And there was an also very great paper titled 'The pathogenesis of dengue: dawn of a new era' in F1000 Research in 2015. And then a number of textbooks and other papers that we will post on our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com).

Erin Welsh

Cool. Well thank you to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Allmann Updyke

And thank you all for listening and allowing us to make this podcast. And if you were at our Florida show, thank you so much for coming to see us.

Erin Welsh

Oh my gosh, thank you. It was the most fun.

Erin Allmann Updyke

It was so fun.

Erin Welsh

And thanks again of course to Dr. Alex Trillo for providing the firsthand account for this episode. We'll post her website and her Twitter information in our shownotes. Okay well with that, wash your hands.

Erin Allmann Updyke

You filthy animals!