

Erin Allmann Updyke

"Towards the end of September 1827, a disease of a very singular character suddenly made its appearance in the island of St. Thomas and attacked almost every individual in the town which contains a population of about 12,000 souls. The disease appeared so suddenly and spread with such rapidity and the suffering attending it was so great that at first it caused universal alarm and was considered a sort of plague that would probably ravage the whole country. It was soon however discovered that although very painful, it was by no means a dangerous disease and that if the attack was rapid the recovery was no less speedy. This at least was the general belief until longer experience showed the troublesome nature of the secondary pains that constitute the third stage of the disorder.

The most usual mode of attack was the following. A person in perfect health would suddenly feel a stiffness amounting almost to a pain in one of his fingers and most frequently his little finger. The stiffness increased and was accompanied by an intense degree of pain which spread rapidly over the whole hand and up the arm to the shoulder. The fingers of both hands in a few hours became swelled, stiff, and painful, preventing all attempts at bending the joints. This was followed in a short time by restlessness, depression of spirits, and a degree of nausea ending in some cases in vomiting. Then came on shivering succeeded by fever, great heat of skin, intense headache, most acute pain in the back, knees, ankles, and in short in every joint. But perhaps the most distressing symptom of this stage was the intense pain in the eyeballs.

In every case where the first stage was in any degree well marked, patients declared that they had never experienced nor could have conceived pains equal to what they felt in this fever. Not one inch of the body from head to foot was exempt from suffering. An efflorescence was perceived at this time to begin at the palms of the hands and to spread over the whole body. After the eruptive stage the patient began to recover his spirits and his strength but in many cases a complete want of taste remained for some days. Many people did not get rid of the pains in the joints for many weeks. In general however the disease gave a degree of respite for three, four, and even in some cases six weeks and then attacked the joints with more pain and paralysis than at first. I conclude with the hope that I have done my duty in endeavoring to record a disease attended with so many curious symptoms as justly to challenge the attention of every medical man and particularly of those who are destined to practice in tropical countries."

TPWKY

(This Podcast Will Kill You intro theme)

Erin Allmann Updyke

I love these old timey descriptions, Erin, so much.

Erin Welsh

I love that. So that was excerpted from this paper published in 1828 by George Stedman.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. Titled 'Some account of an anomalous disease which raged in the islands of St. Thomas and Santa Cruz in the West Indies during the months of September, October, November, December, and January 1827-1828.' I guess they didn't have character limits in titles back then.

Erin Allmann Updyke

That is the most descriptive and specific title.

Erin Welsh

Yeah. So that whole paper which is available online is an interesting read. There's so much more detail there but I just pulled little excerpts that I thought were most descriptive of the topic of today's episode which is Chikungunya virus.

Erin Allmann Updyke

Chikungunya virus.

Erin Welsh: 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: Welcome to... Is this our first mosquito-borne virus of our whole season?

Erin Welsh: I think so.

Erin Allmann Updyke: Wow.

Erin Welsh: I can't keep track anymore, Erin.

Erin Allmann Updyke: I know, same. I mean we've done some lice and things.

Erin Welsh: Yeah, we've done some vectors.

Erin Allmann Updyke: Yeah. But anyways.

Erin Welsh: But yeah, mosquito-borne virus, I think so.

Erin Allmann Updyke: I'm excited. It's gonna be a good one.

Erin Welsh: It is. I didn't really know anything about Chikungunya besides the name before getting into this. And yeah, I'm very curious to hear how the biology works.

Erin Allmann Updyke: I know. I remember in 2013 and 2014 when the big outbreaks were happening in the Americas and being like what's going to happen with Chikungunya? And then that was it.

Erin Welsh: Yeah.

Erin Allmann Updyke: And I never really learned much more about it. So it was fun to get to research.

Erin Welsh: Yeah.

Erin Allmann Updyke: But first it's quarantini time.

Erin Welsh: It's quarantini time. What are we drinking this week?

Erin Allmann Updyke: We're drinking Head, Shoulders, Knees, & Toes.

Erin Welsh: Yes. And we are drinking Head, Shoulders, Knees, & Toes because one of the hallmark symptoms of Chikungunya virus, as you heard in our firsthand account, is joint pain and headache.

Erin Allmann Updyke: Yep. Pretty severe as we'll discuss.

Erin Welsh: Very severe. Yeah, yeah. So what is in Head, Shoulders, Knees, & Toes?

Erin Allmann Updyke Oh it's a perfect little fall concoction. You've got some apple cider, some orange, and some mezcal for smokiness.

Erin Welsh Yeah. And also as a callback to dengue, our dengue episode and our dengue quarantini which had mezcal in it.

Erin Allmann Updyke Yeah.

Erin Welsh Because you're going to hear a lot about dengue.

Erin Allmann Updyke I know, there'll be a lot of compare/contrast dengue, Chikungunya, etc. So it makes sense. So we called back to it. We'll post the full recipe for our quarantini as well as our nonalcoholic placeborita on our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com) and all of our social media channels.

Erin Welsh Before we dive into the episode, of course the routine check out our website, etc, etc, there's a lot of stuff there. But also this is our second to last episode of Season 5.

Erin Allmann Updyke What?

Erin Welsh Yeah. There's just one more coming out after this. But don't worry, we will be back. We're just going to take a break and not read about disease stuff for a minute.

Erin Allmann Updyke I mean we'll probably still read about disease stuff but just quietly to ourselves.

Erin Welsh Actually that's true. And then we'll just text each other.

Erin Allmann Updyke Exactly.

Erin Welsh Well in any case we will be back and so make sure you follow us on all of our social media accounts so that you know when we are on our way back. And if you have suggestions that you really want to hear for next season, send them our way.

Erin Allmann Updyke Well with that Erin, shall we get into Chikungunya virus?

Erin Welsh Let's do it.

Erin Allmann Updyke Right after this break.

TPWKY (transition theme)

Erin Allmann Updyke Chikungunya virus is an arbovirus which means a virus transmitted by arthropod vectors. And in this case like we said mosquitoes. I'm probably going to end up talking about the two main mosquito vectors more than anyone bargained for, it's going to be fun.

Erin Welsh I'm so glad because I did a little bit of diving into the ecology and I was like I don't know where this goes in the history section, hopefully Erin will talk about it.

Erin Allmann Updyke

Well I found myself thinking so much of Ally and Allison in our old lab and being like I wish I could call and be like can you tell me about their ecology? Anyways. So let's get into it, shall we? Chikungunya virus is in the genus Alphavirus in the family Togaviridae. And these viruses, they're RNA viruses, the majority of which are arboviruses, they are transmitted by mosquitoes and other vectors. A few that people may have heard of include Ross River virus and Western and Eastern Equine Encephalitis viruses. One thing I thought was interesting about Alphaviruses in general is that at least one of the papers that I was reading was talking about how for a lot of Alphaviruses, humans and our domestic animals are often considered dead end hosts.

So we aren't necessarily the evolutionary hosts for these pathogens which is I think very interesting especially because I'm going to end up comparing and contrasting Chikungunya virus in this episode because it's compared a lot in the literature to a few other arboviruses like dengue, Zika virus, yellow fever virus. All of those viruses are not in the Alphavirus family, those are all Flaviviruses, so a completely different family of viruses, some of which are very human specific like yellow fever or can cause disease in animals and humans kind of equally.

Erin Welsh

That's interesting that humans are considered the dead end host for Alphaviruses. Is that because of viremia and mosquitoes not being able to get enough virus? Or is it because mosquitoes aren't biting as much?

Erin Allmann Updyke

Yeah, I think both from what I could tell.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah, yeah. But as we'll see that's not the case for Chikungunya. So the two major vector species of Chikungunya virus are mosquitoes that might be familiar to longtime listeners, they are mosquitoes in the genus Aedes, particularly Aedes albopictus and Aedes aegypti. These are the same mosquitoes that are responsible for the transmission of dengue fever, or yellow fever, and of Zika virus among many others. There are a lot of other species of Aedes mosquitoes that can also transmit Chikungunya as well as perhaps some species of Culex that have been found to be infected. But predominantly, especially for humans, it's albopictus and aegypti and that's probably how I'll refer to them throughout this episode.

And like many of our mosquito-borne viral and other pathogens, this life cycle can be a little bit complicated but it goes a little something like this. The mosquito takes a bite of an infected blood meal from an animal or a human in the case of Chikungunya, the virus has to travel through the guts of that mosquito, disseminate through the gut wall of the mosquito, travel through the hemolymph and invade the salivary glands where they can replicate. And this process for Chikungunya virus within the mosquito takes between 2-5 days to happen.

Erin Welsh

Okay.

Erin Allmann Updyke

So what that means is that the adult mosquito, after it takes its first blood meal, has to live at least 2-5 days to then be infectious to another person.

Erin Welsh

I have a question about mosquito longevity.

Erin Allmann Updyke

Okay, so glad Erin, I have so many fun facts about these mosquitoes.

Erin Welsh

Yes. Okay, excellent. How long on average do the different species, albopictus and aegypti, live?

Erin Allmann Updyke

So these mosquitoes take about a week to develop from egg into adult but once they are adults they can live for 4-6 weeks.

Erin Welsh

Okay.

Erin Allmann Updyke

Which is a very long time.

Erin Welsh

That's a lot of biting potential.

Erin Allmann Updyke

It sure is. And it's only female mosquitoes that bite, they have to take a blood meal in order to make eggs, in order to lay a brood. And Aedes mosquitoes, if they are able to take an entire blood meal and there are differences between Aedes aegypti and albopictus in terms of how often they lay eggs and things like that, but if they took a whole entire blood meal they might be able to go several days between feedings. But what often happens is that they get interrupted really frequently during their feedings so they don't get a whole blood meal at once, so they might bite and then bite and then bite and then bite in order to get enough blood to be able to make an egg brood.

Erin Welsh

So it's not like one blood meal or one feeding sesh, one infected person, it could be five feeding sessions to get your stomach full and you infect five people. So is there viral load, infectious dose? Does that play a role in it as well?

Erin Allmann Updyke

Great question. I totally don't have answers for you on that, like how many viral particles does the mosquito have in their salivary glands and how many are they injecting with each feed? I have no idea. But at least in theory if this mosquito is biting many different hosts, not only is that many opportunities to become infected but it's also many opportunities to transmit that pathogen.

Erin Welsh

Makes sense. Wow.

Erin Allmann Updyke

But going back to the timeline of it. So 2-5 days for that process of dissemination through the guts before a mosquito becomes infectious. Here we start to compare/contrast something like Chikungunya with something like dengue virus. Dengue virus takes 8-10 days before it's transmissible in the adult mosquito. So already you have a mosquito that doesn't have to live nearly as long before it can start infecting other people.

Erin Welsh

Interesting. So I guess that would probably play a big role in how fast an epidemic or an outbreak happens.

Erin Allmann Updyke

Sure could.

Erin Welsh

All right.

Erin Allmann Updyke

So continuing on in our life cycle. Once that mosquito is infectious, it takes another blood meal and then those viruses are injected from the salivary glands into our subcutaneous tissues. Those viruses make their way into our bloodstream, they infect a number of different cells. They infect our fibroblast cells, they can replicate in our skin cells, they make their way into our liver and into our joints where they infect a variety of cells. I'm going to pause in the life cycle here because I want to talk a little bit more about these two species of mosquito, even though we've already kind of dove into some of the fun bits. These two species of mosquito, Aedes albopictus and Aedes aegypti, we've talked about them a lot because we've done Zika, we've done yellow fever, we've done dengue.

These mosquitoes are particularly good, particularly well adapted to rural, urban, and human-built environments. Especially *Aedes aegypti*. This is a mosquito that just loves humans and our urban environments. These two mosquito species are generally both container breeding mosquitoes so they do really well in things like old tires or that pot you forgot about, that one pothole in your street that absolutely never drains, your neighbor's pool that they drained three years ago but they never filled it so there's just like an inch of water in there. Also tree holes in more suburban or rural environments, etc. Any tiny amount of standing water is enough for *Aedes aegypti* and *albopictus* both to be able to breed and survive.

These two mosquitoes are also very aggressive. They're really aggressive biters, especially for humans, they really like humans. And especially *Aedes albopictus* tend to be more diurnal than most mosquito species. So they can primarily bite during the daytime in the mornings and in the evenings. So they're really difficult to avoid and things like bed nets that are often used to protect against other mosquito species that bite at night don't do anything to prevent the bites of *Aedes albopictus* and *Aedes aegypti*.

Erin Welsh

Right.

Erin Allmann Updyke

And like I said, they can complete their entire initial life cycle in as little as a week from egg all the way to adult. So in times of plenty in terms of rainfall, like the rainy season, you have many, many broods of mosquitoes over and over hatching and going out in search of new blood meals. But at the same time, like many mosquito species, these eggs can dry out completely and then survive until the next rainfall season. That's why they can do so well in these small containers of water that might dry out completely. They can just hang on.

Erin Welsh

It's amazing and I respect it but I also hate it.

Erin Allmann Updyke

I know, I know, I know. So that's just kind of some fun facts about *Aedes aegypti* and *albopictus*. I'll probably talk more about them in the current events section because they're also really important invasive species worldwide, especially *Aedes albopictus*.

Erin Welsh

Yeah.

Erin Allmann Updyke

And they spread so many different diseases that they're an incredibly important source of vector-borne disease. But if that isn't enough, Chikungunya virus can also be spread via vertical transmission within the mosquito, meaning it can pass into the eggs and result in larvae and therefore adults that are already infected.

Erin Welsh

It's horrible.

Erin Allmann Updyke

It's terrible. I don't know the rate at which this happens but it definitely happens. And just to make it even worse, males who become infected at birth, males do not blood feed so they can't become infected as adults but they can be born infected and can infect females during the mating process. So this virus is just really good at spreading through these mosquitoes.

Erin Welsh

And that's just for *Aedes aegypti*, right, the vertical transmission?

Erin Allmann Updyke

I saw it primarily for *Aedes aegypti*.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah. And like I said, Chikungunya virus is more than just a human virus. So these mosquitoes can become infected by biting a huge variety of mammals including rodents, bats, nonhuman primates, but also even birds and reptiles that can become infected and harbor Chikungunya virus. I didn't get a sense and I think that because this disease has largely been an outbreak disease, the outbreak patterns in humans tend to be from human to vector to human transmission, so humans being the primary reservoir, largely because these two species of mosquitoes do really like to bite humans. So I didn't get a sense of what the natural reservoirs likely are across the globe but it probably varies in different parts of the world.

Erin Welsh

Yeah. It seems like historically they found it in nonhuman primates.

Erin Allmann Updyke

Yeah.

Erin Welsh

And then the more sampling they did, the more they found in other species as as often happens.

Erin Allmann Updyke

As tends to.

Erin Welsh

Yeah.

Erin Allmann Updyke

So all of that is just the virus, the mosquitoes, and the transmission. Let's get into the disease that Chikungunya causes, shall we?

Erin Welsh

Let's do it.

Erin Allmann Updyke

So once a person gets bitten and this mosquito injects you full of virus, the incubation period tends to be about 2-4 days. Different papers report slightly different ranges but that's about the average.

Erin Welsh

I feel like that's a pretty tight range.

Erin Allmann Updyke

It is. I mean it does range from 1-12 but I think...

Erin Welsh

Okay, nevermind. I take it back.

Erin Allmann Updyke

I know, I know. But in general most papers consensus 2-4, some like to say 3-7 just to hedge their bets.

Erin Welsh

Okay.

Erin Allmann Updyke

But symptom onset tends to be abrupt and severe. The firsthand account that we read was actually a pretty decent description of what I'm about to talk about, especially when you consider that was from the 1800s. So love that. The symptoms tend to start with a fever of course, headache, back pain, very, very severe joint pain and in potentially any joint, ankles, wrists, fingers, hips, knees, large joints, small joints. And it does tend to be so severe that it is difficult to bear and people often will have rigors and be bent over and just in an excruciating amount of pain. About 50% of people will also have some kind of skin involvement. The most common rash is a very itchy, red, splotchy kind of what I think of as just a very generic viral-looking rash. So little red splotches with bumps in the middle, what we call maculopapular.

Erin Welsh

Okay.

Erin Allmann Updyke

And this can be across the chest, the stomach, the back. I know the firsthand account mentioned the palms but I don't think that we tend to see that very commonly. What's interesting is that in children the rash can often be quite different with more of a blistering appearance, like very large blisters across the whole skin or even with petechiae which are those tiny little purple spots that mean that you're having little tiny pinpoint bleeds underneath your skin.

Erin Welsh

Why is it different? Just immune system stuff?

Erin Allmann Updyke

Yeah, great question.

Erin Welsh

Okay.

Erin Allmann Updyke

No clue. And in general Chikungunya fever tends to be considered a self limited condition. Usually these symptoms are going to resolve in 7-10 days which is a long time to be this sick. However this incredibly painful arthritis can in some cases persist for months or even years afterwards.

Erin Welsh

Oh my gosh.

Erin Allmann Updyke

Yeah, it's horrible. And what's truly awful is that this happens in up to 30-40% of people who are infected with Chikungunya virus.

Erin Welsh

Whoa.

Erin Allmann Updyke

So it's a huge number. We don't know exactly what causes this chronic joint pain, this chronic arthritis, but so far it's not thought to be due to chronic infection.

Erin Welsh

Okay.

Erin Allmann Updyke

Because in general when we've tried to study it, people have not been able to isolate virus from the joint fluid of people with this chronic arthritis as a result of Chikungunya. So it's thought to likely be something that's immune mediated.

Erin Welsh

Right.

Erin Allmann Updyke

Which is something that we see with other arboviral, viral, and bacterial infections as well and one of those things that we still just don't really understand.

Erin Welsh

What causes the acute joint pain?

Erin Allmann Updyke

Ugh, great question, Erin. To say that we don't really understand the pathophysiology of Chikungunya virus I think is an understatement. And I always say that we don't understand things. In small animal studies we see that it's primarily musculoskeletal tissues that are infected by this virus, especially muscles surrounding joints as well as skin fibroblasts. Fibroblasts are this generic cell type that are involved in connective tissue formation. And so since this is a virus that has to infect our cells in order to replicate, these are the cell types, these fibroblasts and these muscle cells, that they tend to infect and replicate in. There is some evidence from these again animal studies that mice who lack T cells, especially certain subsets of T cells, have much less severe joint swelling and tissue damage as a result of this viral infection. So it's thought that perhaps it's at least in part a T cell mediated response that causes all of this joint pain and inflammation in those spaces because that's where the virus is actually infecting.

Erin Welsh

And that's the muscle? There's muscle involvement?

Erin Allmann Updyke

It can infect muscle cells, it doesn't mean that the inflammation will be in the muscles necessarily.

Erin Welsh

Okay.

Erin Allmann Updyke

But there's also often a lot of muscle pain with chikungunya as well.

Erin Welsh

Yeah. So only because we just covered gout, how does this joint pain differ from gout joint pain?

Erin Allmann Updyke

What a fun question. So gout tends to be a very one joint at a time or a few joints at a time.

Erin Welsh

Right.

Erin Allmann Updyke

This is every joint in your body. There's similarities in that in both of them a lot of the pain is going to be driven by the inflammation which is driven by our immune response to some kind of stressor.

Erin Welsh

Right.

Erin Allmann Updyke

In this case we think that it is the virus infecting particular cells, fibroblasts, muscle cells, other cells near and around our joints that then cause a lot of inflammation that then cause a lot of pain.

Erin Welsh

Okay.

Erin Allmann Updyke

The difference in gout of course is that we know exactly what those particular drivers are, see our gout episode for that.

Erin Welsh

Right, okay. Interesting.

Erin Allmann Updyke

But I do think it's important to talk about this pain and especially the chronicity that this pain can have, this can last for weeks to months to potentially years after this acute infection. And it can be debilitating. And Chikungunya virus is often portrayed as a much less virulent pathogen compared to other arboviruses like yellow fever or dengue. And in a lot of ways it is. In general the estimated case fatality rates for Chikungunya are less than 1%. It was thought especially historically to be very, very rare to die from Chikungunya, although with more recent outbreaks we have seen an increase in mortality especially in the very old, the very young, or the otherwise immunocompromised. So that less than 1% is probably an underestimate. But it's certainly historically has been much less virulent than dengue fever which if it causes dengue shock syndrome has a mortality rate of 20% or more, or yellow fever which has a case fatality rate between 10-50% or more.

Erin Welsh

Oh my gosh, yeah.

Erin Allmann Updyke

So when you compare those then yes, Chikungunya seems relatively benign. But months or years of debilitating joint pain can cause disability, it can cause inability to work which might mean inability to feed your family. So it does have really serious consequences. So I want to emphasize that it's not a benign illness by any means.

Erin Welsh

Yeah.

Erin Allmann Updyke

Chikungunya can also infect people during pregnancy of course, you can be infected at any point in your life. It doesn't seem to cross the placenta and cause fetal infection the way that something like Zika virus does but it can cause neonatal infections if someone is highly viremic, like has an acute infection at delivery and those can actually be very severe and have resulted in neonatal deaths.

Erin Welsh

Okay.

Erin Allmann Updyke

When it comes to whether or not you can have an asymptomatic infection which is something that we talk a lot about especially in viral diseases or mosquito-borne diseases, I don't know who to believe in terms of how many asymptomatic cases there are. A lot of papers that I read would say the majority estimate that it's actually very rare to have an asymptomatic infection which is quite different than something like dengue or Zika.

Erin Welsh

Yeah I think I saw a CDC cheat sheet that was like 3/4 Chikungunya cases are symptomatic and 1/4 dengue are symptomatic.

Erin Allmann Updyke

Yeah. It's estimated that anywhere from 5%-25% but most of the estimates I saw were about 15% of people will be asymptomatic which is pretty low.

Erin Welsh

Yeah, very low.

Erin Allmann Updyke

But then some of the papers were like lots of asymptomatic and I'm like I I don't know. But anyways I think it's low compared to dengue, compared to Zika as far as we can tell.

Erin Welsh

So joint pain is the hallmark symptom of Chikungunya. Are there any other organs that are involved?

Erin Allmann Updyke

Great question. There doesn't tend to be a ton of organ involvement that results in organ damage that we would then see on things like lab results or resulting in kidney failure, liver failure, which I think is why it's historically been considered a pretty mild disease. It can and has in more recent outbreaks caused neurologic effects but again tends to do that in a much lower rate than something like Zika.

Erin Welsh

Right, it's something that you would commonly see in huge outbreaks.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah, okay.

Erin Allmann Updyke

Yeah.

Erin Welsh

Okay so let's say that there's an outbreak of what is suspected to be Chikungunya and someone is sick with what is probably Chikungunya. What do they do? What happens?

Erin Allmann Updyke

Yeah, great question. So in terms of treatment it's mostly supportive care. We don't have any particular antivirals, we don't have any specific treatments targeted towards Chikungunya virus. Most of what you'll see online is Tylenol. That's it, Tylenol. What's interesting about that is that public health agencies do tend to specify Tylenol over any other things like NSAIDs like ibuprofen and the reason for that is because clinically during outbreaks both because the symptoms can be very nonspecific in the acute phase, they can overlap a lot and these two viruses tend to occur in the same areas, dengue and Chikungunya virus can be difficult to tell apart and NSAIDs can be very dangerous in dengue because it can lead to bleeding.

Erin Welsh

Right, okay.

Erin Allmann Updyke

Yeah. And so for that reason it's like if you're not sure, just Tylenol.

Erin Welsh

Yeah, okay.

Erin Allmann Updyke

And like many neglected tropical diseases, we don't have the best of diagnostics for Chikungunya either. But they exist. So that is Chikungunya and its biology or what I know about it. So Erin, tell me how where did this virus come from? Why does it infect us? Tell me about it.

Erin Welsh

Well I don't know if I can answer that second one but I'll certainly try for the first right after this break.

TPWKY

(transition theme)

Erin Welsh

The story of Chikungunya virus or at least part of the story of this virus will probably sound a bit familiar to you. Erin, it definitely will for you because we have recorded dengue and Zika episodes and you just talked about all the similarities but for our listeners too, not just the biology or the transmission or the epidemiology of these viruses will sound similar but also a bit of the history I think will sound a little bit echoes of each other.

Erin Allmann Updyke

Okay.

Erin Welsh

All mosquito-borne viruses, all on the rise, all recently attracting more attention and generating more headlines than historically they used to due to their recent geographic spread into new regions, especially regions like Europe and North America where the disease has changed from being an 'over there' disease to a 'wait it's here now' one. And with dengue and Chikungunya especially the similarities extend beyond epidemiology and disease ecology and down into the clinical side of things, since they can cause a lot of the same symptoms, as well as their histories which as I'll talk about have blended to together and are kind of in the process of being rewritten.

Erin Allmann Updyke

I love it.

Erin Welsh

Yeah. But with as many similarities as these diseases share, they are also distinct in many ways that play a huge role in their transmission, their evolution, and in the way that public health efforts are focused. And I'm not going to do a thorough compare and contrast between Chikungunya and dengue although I may call on you to help me Erin in some of these, we'll get to the section where I'm going to be like all right, let's take a closer look. But in researching for this, it struck me that these are viruses are often kind of lumped together and talked about as a single entity. And I feel like it's just as important to remember what differences among these infections can tell us as it is to ask what their similarities can say about these diseases.

Erin Allmann Updyke

Yeah.

Erin Welsh

And I think that throughout this episode we'll have the opportunity to do both. But first things first Erin, you asked as you always do where this virus came from and it's a great question that I'm only going to be able to answer in part.

Erin Allmann Updyke

Okay.

Erin Welsh

Most papers I read for this episode, if they mentioned the evolutionary origin of Chikungunya virus at all, it was just to say that it wasn't clear when or where this virus emerged.

Erin Allmann Updyke

Love it.

Erin Welsh

Right, of course. One paper gave a not super narrow estimate that the ancestor of Chikungunya virus emerged fairly recently, maybe as recently as 1850 or as far back as the year 650 CE. Which in the scheme of things is not a big range but it does seem like a big range.

Erin Allmann Updyke

That's still a big range.

Erin Welsh

It's a big range.

Erin Allmann Updyke

Yeah.

Erin Welsh

But there was a more recent paper that examined the different lineages of the Chikungunya virus and estimated that the virus emerged somewhere in Central or East Africa around 300-500 years ago.

Erin Allmann Updyke

Okay.

Erin Welsh

And the East Central South African lineage which I think is the predominant one in a lot of places, that appeared around 1903 and then gave rise to the West African and Asian genotypes or lineages in the decades after.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. So it's pretty recent and the most recent lineage, the Indian Ocean lineage, only emerged in the very early 2000s.

Erin Allmann Updyke

I know, I can't wait to talk about it.

Erin Welsh

It's so mind blowing. It really is. We'll get into it later. But long story short, this seems to be a relatively new virus whose ancestors infected mosquitoes and nonhuman primates and other vertebrates with occasional spillover into humans from this enzootic cycle. And then at some point this virus diverged into Chikungunya virus transmitted by Aedes mosquitoes and o'nyong'nyong virus. I don't know if that's how you pronounce it but that's transmitted by Anopheles mosquitoes. As humans began to settle in larger groups and especially began to store water, you didn't even have to store that much of it, that provided opportunities for the evolution of the more domestic Aedes aegypti aegypti mosquito subspecies which hung around these settlements and allowed for human to human transmission of Chikungunya. So it's maintained in just humans and mosquitoes. And that's in contrast of course to the spillover into humans from the enzootic cycle when a bridge vector species of mosquito, one that feeds on both humans and nonhuman primates or other vertebrate reservoirs, bites a human and transmits the virus.

Erin Allmann Updyke

Very much like dengue honestly.

Erin Welsh

It is very much like dengue and it's much like a lot of other mosquito-borne viruses or mosquito-borne infections.

Erin Allmann Updyke

Yeah.

Erin Welsh

There's this enzootic cycle that just happens all the time in the background and then it happens to spill over into humans and then depending on the circumstances that can cause this big outbreak.

Erin Allmann Updyke

Yep.

Erin Welsh

And so these big outbreaks would happen from time to time and it fed initially by the spill over and then it would just sweep through the population until most people became immune and then the virus would go quiet for a while. And this is essentially how the cycle would have continued for hundreds of years until its discovery in 1952. In July of that year, a seemingly new disease began popping up in the Makonde Plateaus region in Tanzania. Within two or three weeks of the first case appearing in a village, 60%-80% of the population became infected.

Erin Allmann Updyke

Whoa.

Erin Welsh

With some households reporting a 100% infection rate.

Erin Allmann Updyke

That is impressively fast and impressively infectious.

Erin Welsh

Yes. Honestly I just couldn't get over it.

Erin Allmann Updyke

Well and I think it so does lend credence to this idea that there's not a lot of asymptomatic infections.

Erin Welsh

Yes, totally. The disease seemed to come on suddenly with the rapid development of a high fever and these horrible joint pains. Quote: "The pain was frightening in its severity, completely immobilizing many patients and preventing sleep in the first few days of the illness. It was intensified by movement and localized in larger joints. In some cases there was also severe backache. Morphine was the only analgesic which was found to modify the pain."

Erin Allmann Updyke

Aye aye aye.

Erin Welsh

Yeah. No one in the region could remember a similar epidemic ever occurring there and so this disease was given a new name from the Makonde dialect, Chikungunya meaning 'that which bends up' or I've also seen it as the disease that bends up the joints. No one who had the disease got it a second time.

Erin Allmann Updyke

Wow.

Erin Welsh

And people said you either definitely had it or you definitely did not.

Erin Allmann Updyke

No inbetween.

Erin Welsh

There was just no inbetween, yeah. Researchers immediately suspected that it was mosquito-borne or at least transmitted by some blood sucking arthropod vector, both due to its pattern of transmission, its occurrence in the rainy season, and its similarity to dengue fever. In one of these papers reporting the initial outbreak, quote, "clinically indistinguishable from dengue if allowances made for the inherent variability of that disease." Because dengue is clinically quite diverse.

Erin Allmann Updyke

Super variable.

Erin Welsh

Yeah. Studies were carried out where researchers collected blood feeding arthropods from all around the villages where the outbreak occurred and sure enough, all signs pointed to *Aedes aegypti*. Because of the clinical similarity to dengue, people figured that when they found the virus it was just going to be like a new subtype or a new strain of the dengue virus. But analysis of serum samples collected showed that it seemed to be a new kind of virus, not a dengue virus. And so it got to keep the name that it got during this first outbreak, Chikungunya. And maybe it's because we've done so many episodes where the story goes something like 'the disease was first recognized in ancient times and people wrote about over hundreds of years but no one knew what caused it or how it was transmitted until recently'. But I just think it's so amazing that within a few years of its first appearance we had a name, we had a clinical picture, we had a vector, and a causative agent for this new disease.

Erin Allmann Updyke

Yeah.

Erin Welsh

I mean it shows how far we've come by the 1950s in terms of microbiology. If you cast your mind back to our dengue episode, you may remember that the first epidemics of dengue were described in the late 1700s and it took another 100 years and then some before it was linked to mosquitoes and decades after that before the virus was identified and classified. And here we are with Chikungunya, learning all that and more about this brand new disease in just a few years. It's amazing. Or is it? No, it is. But maybe things aren't as simple as I presented them.

Erin Allmann Updyke

Well Erin, I'm waiting for you to drop the other shoe because I know that our firsthand account was from the 1800s. So?

Erin Welsh

Yes. On that. Yeah. So maybe Chikungunya isn't as brand new as we thought it was, maybe 1952 was not the year of Chikungunya first being discovered, maybe some of those historical outbreaks of dengue weren't caused by the dengue virus after all but rather the Chikungunya virus. Of course that doesn't take away from how incredible it is to have built that knowledge about this seemingly new disease so quickly.

Erin Allmann Updyke

Yeah, totally.

Erin Welsh

But I did want to take some time to revisit the early history of dengue and see if maybe what people thought was dengue was actually Chikungunya. And this isn't something that I came up with on my own, there are lots of papers that have been looking into this possibility for decades and they've come up with some pretty convincing evidence. All right, so a 1971 paper by Donald Carey titled 'Chikungunya and dengue: a case of mistaken identity?' takes a closer look at many so-called dengue epidemics since the 18th century and uses clinical descriptions from eyewitnesses to see whether it seems more in line with dengue or Chikungunya. Because although the two diseases do bear many similarities and can be quite varied in terms of symptom presentation, there do seem to be some distinguishing features between the two. Like one of them is this lingering, long lingering joint pain in Chikungunya and also just the fact that dengue has a much higher mortality rate. And so these differences would be a lot more easily seen in outbreaks and epidemics when you can look at a whole bunch of people and see patterns emerge rather than looking at two people side by side that both have kind of a rash, both have headaches and joint pains.

Erin Allmann Updyke

Yeah, joint pain. Fever.

Erin Welsh

Fever, yeah.

Erin Allmann Updyke

And live in an area with *Aedes aegypti* and *Aedes albopictus*.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah. I'm really excited for this Erin because I do think it's really important. Many of the clinical papers written recently talk a lot about how difficult it is to distinguish Chikungunya and dengue say in the moment during a Chikungunya outbreak or a dengue outbreak when you don't know which one is at play or if both are happening simultaneously, which can absolutely happen.

Erin Welsh

Right, yeah.

Erin Allmann Updyke

So it is really interesting to be able to take a step back and look at things historically because there are patterns that emerge when you're able to look not at an individual person but at a population.

Erin Welsh

Yep. Ooh, that just actually made me wonder though, in places where both the viruses co occur, is there competition between them within mosquitoes?

Erin Allmann Updyke

Oh my gosh Erin, such a good question. There is some evidence in one of the papers that I read that especially, I think it's in *Aedes albopictus*, that some of the mutations that I know you'll talk about actually might facilitate co-infection with dengue and Chikungunya. It's terrifying.

Erin Welsh: What?

Erin Allmann Updyke: It's terrifying.

Erin Welsh: That is really terrifying.

Erin Allmann Updyke: Yeah. But anyways, sorry.

Erin Welsh: Anyways. No, no, that's fascinating. Okay. But the other thing about looking historically at dengue and Chikungunya is that *Aedes aegypti* achieved a global distribution since the 1600s or so.

Erin Allmann Updyke: Yeah, yeah.

Erin Welsh: And that greatly expanded the range of dengue and yellow fever. So it seems pretty plausible that Chikungunya, which has the same transmission cycle more or less, could have been another virus carried by these mosquitoes.

Erin Allmann Updyke: Yeah.

Erin Welsh: In 1779 there was an outbreak of something called knokkel korts or knuckle/joint fever in present day Jakarta and the description written by David Blyon who was witness at the time does suggest Chikungunya. Quote: "I noticed a gnawing pain in my right hand and in the joints of the hand and arm which gradually increased, extending to the shoulder and then over my whole body, so that at 9:00 that evening I was in bed with a high fever. I had a restless and sleepless night, suffering severe pains over the entire body, especially in the legs and arms and in the joints. This is a brief notice concerning a very well known disease which however in the memory of man here in Batavia, has never reached an epidemic and which has therefore seemed wondrous to the inhabitants."

Around this time an outbreak of a similar disease was happening in Cairo. This one known as quote "the knee trouble. It threw all the people into a fever. Its first attack lasted for three days after which the illness increased or diminished according to the disposition of the individual. It was accompanied by pain in the joints, knees, and extremities as well as inability to move and often with swelling of the fingers. The after pains lasted more than a month. The onset was sudden, the body being broken by it, and the head and knees taken hold of." So the descriptions of this disease painted this excruciatingly painful picture but not really a deadly one. And that was something that's in sharp contrast to what Benjamin Rush saw during a 1780 epidemic in Philadelphia of a disease that he nicknamed breakbone fever. This is often considered to be the first description of dengue fever. And I actually had this passage in my dengue notes and I don't think I read it in the episode. So I'm just going to read you a snippet of it here. And also this is a very full of quotation section.

Erin Allmann Updyke: I love it.

Erin Welsh: But I feel like it's important because we're going through historical outbreaks.

Erin Allmann Updyke: Yeah.

Erin Welsh

Okay. Quote: "The fever generally came on with rigor but seldom with a regular chilly fit. When the fever did not terminate on the 3rd or 4th day, it frequently ran onto the 11th, 14th, and even 20th days. In some cases the discharge of a few spoons full of blood from the nose accompanied a solution of the fever while in others a profuse hemorrhage from the nose mouth and bowels on the 10th and 11th days preceded a fatal issue of the disease. The pains which accompanied this fever were exquisitely severe in the head, back, and limbs. The disease was sometimes believed to be a rheumatism but it's more general name among all classes of people was the breakbone fever."

Rush's description which also mentions a rash and burning in the palms of the hands and soles of the feet, it does have some echoes of Chikungunya. There are lots of similarities between these descriptions that I've read so far. But it's also much deadlier, he's talking about hemorrhaging, he's talking about people dying and how often it happens. And that didn't seem to happen in the descriptions at least from the 1779 Jakarta epidemic as well as the series of outbreaks of a similar disease that occurred in India and the West Indies in the 1820s which like in Jakarta had a super high attack rate but a low mortality rate. In 1824-1825, an epidemic of Kidinga Pepo began in East Africa and spread to India where it caused huge outbreaks, with one contemporary observer estimating that 95% of the population of one region was affected.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. And although this has historically been chalked up to dengue, more recently it's been suggested to have been Chikungunya and that's in large part due to the emphasis on the sudden onset and extremely fast onset and lingering joint pain. Quote: "A protracted debility and long continued pains in the ankles and dull aching in the joints of the fingers and toes for many weeks after the cessation of the fever." The outbreak which also had high prevalence and low mortality that occurred in the West Indies a few years later, around 1827-1828, so that was a description from our firsthand account.

Erin Allmann Updyke

Okay.

Erin Welsh

And that's what led to the nickname dandy fever.

Erin Allmann Updyke

What?

Erin Welsh

Yeah.

Erin Allmann Updyke

I remember talking about that. Oh my gosh, how interesting.

Erin Welsh

Isn't that fascinating? So he even writes in that description this is not a deadly disease, this is not known to be deadly. And it's so funny because I definitely baited you by being like Erin, does that sound like Chikungunya? Is this a good firsthand account? Is this accurate?

Erin Allmann Updyke

I love it.

Erin Welsh

Yeah. So some researchers over the past few decades have started to think hey, well wait a second, was that actually dengue?

Erin Allmann Updyke

Right.

Erin Welsh

Or was that actually caused by dengue virus, I should say.

Erin Allmann Updyke

Yeah. Well it's interesting to to think about dengue potentially infecting a new population who has never been exposed vs endemic dengue.

Erin Welsh

Right.

Erin Allmann Updyke

Because if anyone remembers back to our dengue fever episode, initial infections tend to be much more mild. So if you have an entirely immune population, all of that is going to be primary infection and it's not until the second time that people are exposed that you have dengue shock, dengue hemorrhagic fever, and severe infections. So especially in an initial infection and in that acute phase, I do think that Chikungunya and dengue can be very hard to tell apart.

Erin Welsh

For sure.

Erin Allmann Updyke

Yeah.

Erin Welsh

But what I think is interesting is that people made a distinction. Doctors who wrote about these diseases during the 1800s made a distinction between dengue and Benjamin Rush's breakbone fever. So Stedman, who wrote the article where we drew the firsthand account from, he brings up this point in that article. Quote: "Some of the physicians here seem to consider this fever the same as that described by Dr. Rush under the name of the breakbone fever or the bilious remittent fever. I think that the diseases, though somewhat alike in a few symptoms, are essentially different. Four circumstances chiefly distinguish the fever that I have described. First, the suddenness and peculiarity in its mode of attack. Secondly, the well marked distinction between different stages. Thirdly, the peculiar eruption. Fourthly, the peculiar nature and duration of the after pains." So dengue and breakbone fever were not always used anonymously. And in fact for many doctors for a time they seemed to be written about as similar but distinct diseases with breakbone fever being this more deadly and debilitating disease and one that you could become reinfected with or you could be susceptible to multiple attacks is how it was talked about. And what they called dengue was milder except for the long period of lingering joint pain and it was a one time only disease.

Erin Allmann Updyke

That's very interesting, Erin.

Erin Welsh

Isn't it interesting?

Erin Allmann Updyke

Yeah and I don't remember it at all from our dengue episode.

Erin Welsh

No. I think I made a throwaway comment that was something like 'and some people think this could have been Chikungunya, who knows?'

Erin Allmann Updyke

Yeah.

Erin Welsh

But then with this it was like there's a lot more because I think...

Erin Allmann Updyke

That's so interesting that people made this distinction but in making that distinction, what were they calling dengue vs what were they calling something different? And what what was Chikungunya vs what was new introductions of dengue or first outbreaks of dengue?

Erin Welsh

Totally.

Erin Allmann Updyke

Ugh, how fun.

Erin Welsh

Isn't it? It's so interesting to think about.

Erin Allmann Updyke

Yeah.

Erin Welsh

And yeah, so throughout the rest of the 1800s, more and more outbreaks of what was called dengue or what was called breakbone fever, these were described across the tropics and subtropics. And some observant writers would note the clinical differences between the two but sometimes they would use the terms interchangeably. So how did the two become one? How did breakbone fever and dengue become absolutely the same thing?

Erin Allmann Updyke

Yeah.

Erin Welsh

How did we forget about these differences? And honestly it seems to me like it comes down to just a coincidence. So yeah, like I said a lot of physicians that wrote about these epidemics did distinguish between dengue and breakbone fever but by the 1800s, because they're such similar diseases, dengue became increasingly used to describe both. After *Aedes aegypti* was identified as the vector for yellow fever, researchers became interested in seeing whether dengue was also transmitted by mosquitoes. And I feel like I'm not doing a very good job of this but when I'm talking about dengue and these historic outbreaks, I really should be putting quotes around dengue. So what they were calling dengue, right.

Erin Allmann Updyke

Right, yeah.

Erin Welsh

And so when these researchers decided okay, let's see if we can link mosquitoes to this. There was an outbreak of quote "dengue" that was going on in Lebanon, in Australia, and in the Philippines. And these outbreaks provided the perfect opportunity to test this out, this mosquito hypothesis. Using human quote unquote "volunteers", researchers successfully demonstrated that the disease was caused by a virus and transmitted that virus from sick people to healthy people through the bite of an infected *Aedes aegypti*. But it just so happens that the virus that was endemic in these study sites, in this outbreak of quote "dengue" was not the Chikungunya virus but the dengue virus. And so it was assumed that this and all preceding historical epidemics that went under the name dengue were caused by this virus alone. And the reason I say coincidence, maybe that's not really the right word, just a matter of happenstance I guess-

Erin Allmann Updyke

Yeah.

Erin Welsh

Is because if these researchers had instead been working on an outbreak of quote "dengue" that was actually caused by Chikungunya virus, dengue would mean something different than it does today.

Erin Allmann Updyke

Right.

Erin Welsh

It would mean that Chikungunya virus or what we call the Chikungunya virus and the virus that we call dengue today would probably have a different name.

Erin Allmann Updyke

How fascinating, Erin.

Erin Welsh

Isn't that neat?

Erin Allmann Updyke

So at the end of it we still can't actually distinguish a lot of those early descriptions of quote "dengue" and Chikungunya.

Erin Welsh

Of course not. I mean we can try but no, that's definitely something that I think is a key takeaway.

Erin Allmann Updyke

Yeah.

Erin Welsh

Right? This was a very long winded way of me saying that Chikungunya has probably been around longer than since the 1950s and that it probably caused some historical outbreaks attributed to dengue. But I wanted to kind of dig a little bit deeper because I think it's a fascinating example of how the history of the disease is constantly evolving, whether through the discovery of old texts that put it in a new place or bring it back even farther or through molecular tools tracing the actual evolution of a pathogen or a vector or because modern events add to the story. The history of Chikungunya that somebody tells in 10 years probably isn't going to sound the same as this one, the one that we're telling now. And the second reason is that I think this highlights both the benefits of using historical descriptions of disease because they allow you to retrace the steps of its spread and how our understanding grew. But it also highlights the drawbacks.

It certainly seems likely that Chikungunya has been more widely distributed for longer than we initially thought, given some of these historical descriptions being pretty on the money about Chikungunya and also the fact that it's vector, *Aedes aegypti* or one of its vectors, was present in a lot of these places which would have made transmission feasible, possible. But we can't know for sure. We can't know whether the author of an account was highlighting an unusual case or a typical one, whether they were interested in a certain set of symptoms so they played those up while ignoring others, whether there was some reason that they were invested in making a difference between dengue and breakbone fever and really like highlighting those differences. These are also similar viruses with a substantial overlap in disease symptoms and geographic range. And it's possible that one outbreak of dengue was actually caused by dengue virus, while another was caused by Chikungunya virus. Maybe another was caused by o'nyong'nyong virus or a different virus entirely.

But in any case, these historical accounts aren't just useful for historians but like you talked about Erin, also for modern day researchers looking for clues into a disease's ecology and epidemiology. What do we see on a big scale? What are the things that stand out historically and why? But speaking of modern day researchers, let's head back to the 20th century to see what happened with Chikungunya once it was formally identified in the 1950s. So as you might expect, having a name, a vector, and a virus made it easier for people to recognize subsequent outbreaks which occurred throughout the 1960s and beyond in Sub-Saharan Africa. Chikungunya was first detected outside of Africa in 1958 in Thailand and over the next few years the virus continued its spread throughout Asia into Cambodia and India. Although it was probably not its first rodeo there.

Erin Allmann Updyke

Yeah.

Erin Welsh

Because antibodies against Chikungunya were found in serum collected from people in India in the early 1950s. And you've already heard this whole spiel that I just gave about mistaken identity between Chikungunya and dengue. But what was happening in the 1950s, the 1960s, into the 1970s is that the scale of these epidemics seemed to be growing with one epidemic in Chennai, India in 1964 causing over 400,000 cases. But Chikungunya didn't maintain this huge growth because after the 1970s things seemed to cool down a bit, possibly thanks to a high rate of immunity from previous epidemics. It seems unclear but researchers have pointed to a possible cyclical nature of Chikungunya outbreaks which I think is interesting. But then in 2004 everything changed.

Erin Allmann Updyke

Yep.

Erin Welsh

Or rather an amino acid in the virus changed. So it's been hypothesized and I think pretty well supported from experimental research that this change of this amino acid resulted in this viral lineage of the Chikungunya virus being able to be more easily transmitted by *Aedes albopictus*, a mosquito species that previous to this had not really been implicated as a major vector. It was like *Aedes aegypti* for the urban human to human cycle and then other *Aedes* species for the enzootic cycle. But now suddenly there's this new *albopictus* species in play and the result of that was that Chikungunya exploded in 2004 from Eastern Kenya into islands in the Indian Ocean, involving hundreds of thousands of people and attack rates as high as 35% or even 63% I saw on one island.

Over the next years Chikungunya grew to be a major public health problem, causing massive outbreaks in South and Southeast Asia involving millions of people where for the first time these neurological and other complications of the infection were observed. And with *Aedes albopictus* now as this major vector, its potential for global spread grew tremendously because *albopictus* also extends further than *Aedes aegypti* into temperate regions. It's a great urban mosquito that overwinters really well, like you talked about Erin, loves feeding on humans, has these desiccation-resistant eggs. We're up against quite a lot in terms of Chikungunya control. And I do have a little asterisk there in terms of genotype by genotype interactions between *albopictus* and the virus, so some combos don't do as well as others. It's complicated but still.

Erin Allmann Updyke

Yep.

Erin Welsh

And it gets even more complicated when you add urbanization and climate change to the mix as you have to do when you talk about disease or vector-borne diseases. But yeah, this is kind of a rapid wrap up but I think what I took away from this is that we have a lot to learn about the future of Chikungunya and it seems quite daunting. But I think looking at the past and even the very recent past, Chikungunya can serve as yet another lesson along with dengue, along with Zika, along with other arboviruses on just how easily mosquito-borne viruses or other pathogens can reach global distributions. But also it's an important reminder that we have to consider their individual ecologies and pathologies in predicting future risk, like for instance dengue's multiple circulating serotypes or Chikungunya's increased transmission via *albopictus*. It's all very messy and it's all very complicated but it's so important. With that Erin, can you tell me what's going on with Chikungunya today?

Erin Allmann Updyke

I can't wait to right after this break.

TPWKY

(transition theme)

Erin Allmann Updyke

Unsurprisingly, Erin.

Erin Welsh

Let me guess, we don't have good numbers?

Erin Allmann Updyke

We don't. Yeah, it's hard to get a sense of global numbers. But what's interesting and different about the reason why for Chikungunya than anything else that we've covered is that Chikungunya really only tends to be reported in outbreaks. Everything about Chikungunya is there was an outbreak this year, there was an outbreak in this area, and an outbreak, an outbreak, an outbreak. It's like when do we just start saying it's everywhere and these are just the cases that are happening?

Erin Welsh

Well that's a question though.

Erin Allmann Updyke

I know, it's a real question I don't have an answer to. It's like a genuine... It sounded like a sarcastic question, it's a genuine question.

Erin Welsh

No, yeah, I'm very curious. Because it does seem like Chikungunya could have more of a propensity to pop up in outbreaks.

Erin Allmann Updyke

Right. Because it does, spoiler, provide pretty long lasting immunity. And so as it races through a population, causes a huge outbreak, then everyone has been exposed and now there's no more susceptible people in that particular population and you have to wait for new people to be born or to move in or for that virus to move to the town next door. So let's talk a little bit about the numbers that we do have and that we have seen and what Chikungunya has been doing globally, shall we? Like you mentioned Erin, starting in 2004 an outbreak in Kenya spread throughout the Indian Ocean and persisted for several years, this kind of one big outbreak. It spread to La Réunion island where more than a third of the entire population became infected. It spread to India where cases reached more than 1.5 million people by 2006. By 2007 it continued its spread and autochthonous, one of my favorite words.

Erin Welsh

Me too.

Erin Allmann Updyke

Basically local transmission was reported in Europe for the first time possibly ever with several hundred cases reported in 2007.

Erin Welsh

Thank you albopictus.

Erin Allmann Updyke

Yeah, that's what I was just going to say is that much of those outbreaks in the early 2000s were due to spread by albopictus. And so the strain that we saw of this virus was this strain that had these particular mutations that made it more able to be transmitted by Aedes albopictus which is the predominant vector in a lot of these parts of the globe. So that's fascinating and it was terrifying, right. This was millions of people being infected in the early 2000s. By 2013, if we jump ahead, 2013 is when we see Chikungunya spread to the Americas for the first time. In 2013 it was across Caribbean islands where cases reached tens of thousands in a matter of months and then rapidly spread to the South American, Central American, North American continent with 2014 having over one million suspected cases reported to the Pan American Health Organization. Now these cases, these strains do not have that albopictus gene and are spread primarily by Aedes aegypti. So we've got both all over the world.

Erin Welsh

Well and how difficult would it be for the one that doesn't have the Aedes albopictus ability to gain it?

Erin Allmann Updyke

To gain it, exactly. I mean it's already done it once.

Erin Welsh

Right. Or the one that does have it to continue its spread.

Erin Allmann Updyke

1000% Erin, yes. And that's kind of the concern. At this point in a lot of parts of South America, Chikungunya is now considered endemic and yet still we mostly see reports of outbreaks. I tried to get a sense of scale globally, just like averages and I did find one paper that was looking at both Chikungunya and Zika virus but trying to estimate the disability adjusted life years which we've talked about on this podcast. These are imperfect measures but they are one way to get a sense of the impact and burden of disease and I think in the case of Chikungunya a really good way to do it because we're not necessarily going to see a lot of death or mortality from Chikungunya but we are going to see a lot of years of healthy life lost as a result of this disease and that's what the disability adjusted life years are measuring. So in the case of Chikungunya, these researchers estimated a global annual burden looking at data from 2010-2019 of 106,000 disability adjusted life years.

Erin Welsh

Wow.

Erin Allmann Updyke

Which is a lot.

Erin Welsh

Yeah. It's a lot.

Erin Allmann Updyke

And these estimates were based on case estimates, so combined total global case estimates of anywhere from 50,000-350,000 cases per year.

Erin Welsh

Okay.

Erin Allmann Updyke

And we know that again that varies because some years it might be more than a million and some years it might be less. So it's pretty major and again up to 40% of people infected are going to have chronic or in some cases permanent joint pain and potential disability as a result of this disease.

Erin Welsh

That's such a high proportion.

Erin Allmann Updyke

I know. It's really terrifying. One theme that I think we end up touching on a lot in this podcast and you mentioned it, Erin, especially in our vector-borne disease episodes are the potential effects of things like land use change, climate change, urbanization and its effects on disease incidence and disease prevalence. And especially in the case of a vector-borne disease that is spread by urban human-loving mosquitoes like Chikungunya, this is a particularly important thing to be worried about. Both of these mosquito species are very well suited for urban environments so there are a lot of papers that have looked specifically at the effects of rapid urbanization on mosquito density and distribution and the long and short of it is that it's terrifying news in terms of mosquito-borne disease, not just Chikungunya but including Chikungunya.

Because these papers tend to conclude that urbanization across the globe, not localized to one particular part of the world, correlates with a higher risk and abundance of these Aedes mosquitoes. You have an increase in favorable breeding grounds, you have higher larval development rates in urban areas compared to natural areas, you have potential for greater adult survival time, and all of these things mean that you have a potential for greater vector competence, that these vectors are living longer and therefore transmitting or at least having the potential to transmit disease more readily.

Erin Welsh

It's not good news.

Erin Allmann Updyke

It's not good news. And then of course there's also going to be the effects of climate change. Warming temperatures might mean shifts in vector distribution and vector habitat. That also will mean shifts in rainfall patterns and prevalence as well as an increase in the strength or severity of natural disasters. And all of these have the potential to at a minimum shift, thereby moving into new populations if not also increase mosquito prevalence disease burden across the globe. I guess I didn't mean for this to be such a bummer of an ending but I feel like that's an important part. Arboviral diseases like Chikungunya have been popping up throughout human history always, they have been here with us, and I think that many of us probably remember when Chikungunya was making a ton of headlines in 2013 and 2014 because we had cases in Texas and in Florida and then it went away and we forgot about it. Except that it didn't go away.

Erin Welsh

No.

Erin Allmann Updyke

And these viruses, these diseases are not going away. And it takes a huge effort of multidisciplinary public health work to be able to understand these risks and potentially reduce them.

Erin Welsh

And it seems like an incredible challenge to do that. You're working against so many things.

Erin Allmann Updyke

I know.

Erin Welsh

I have two questions.

Erin Allmann Updyke

Okay.

Erin Welsh

They're unrelated.

Erin Allmann Updyke

Okay.

Erin Welsh

The first one is about the impact of infection with Chikungunya virus in mosquitoes. Does it have any sort of negative impact?

Erin Allmann Updyke

Great question. I didn't see anything on it, so not as far as I know and I would guess if it's so easily vertically transmitted then it's not as likely I would think to have detrimental effects on the mosquitoes themselves.

Erin Welsh

Follow up related question before I get into my second question, Wolbachia?

Erin Allmann Updyke

Yeah. So Wolbachia for anyone who doesn't remember, I think I talked about it in our dengue episode.

Erin Welsh

Sure.

Erin Allmann Updyke

Question mark. I think it was dengue. Wolbachia is a symbiotic bacteria that live in a lot of insect species including mosquitoes and there is a lot of really interesting research on Wolbachia and other microbiome bugs that live inside of these mosquitoes and their potential effects on either increasing or decreasing the ability of these mosquitoes to spread disease. I don't have a final answer because I just didn't have time to dig into it but there does seem to be at least some evidence that some Wolbachia if introduced to Aedes mosquitoes might decrease the transmission of Chikungunya. So maybe.

Erin Welsh: Okay, interesting.

Erin Allmann Updyke: Asterisk, there's more there, I just didn't read it.

Erin Welsh: There's potential, got it. Okay so now my second nonrelated question is a vaccine.

Erin Allmann Updyke: Yeah.

Erin Welsh: Because Chikungunya induces a long immunity.

Erin Allmann Updyke: It does. So there's a lot of theoretical potential for a vaccine. There's also a lot of various groups and people that have been working on vaccine development. So there are at least 10, possibly more candidate vaccines that are all at various stages in clinical trials. There's probably one or two in almost every phase 1, 2, and 3. Most of them are in pretty early clinical trials but there is a vaccine of almost every flavor. There are mRNA vaccine candidates, there's live attenuated vaccine candidates, there are measles vector vaccine candidates and viral particle vaccine candidates. But we don't have any that I could tell were particularly close to licensure at this point.

Erin Welsh: Okay.

Erin Allmann Updyke: Womp-womp.

Erin Welsh: Womp-womp.

Erin Allmann Updyke: Yeah. But the potential exists and there's people working on it. I have a feeling it's largely down to funding.

Erin Welsh: Yeah. As per usual.

Erin Allmann Updyke: As per usual. So that's Chikungunya, Erin.

Erin Welsh: Okay.

Erin Allmann Updyke: I don't know, is that enough?

Erin Welsh: I think so. I mean there was a lot there. I mean it's very clear that there are limitations in knowledge about Chikungunya.

Erin Allmann Updyke: Yeah, I can't wait to see what we learn in the coming decades, Erin.

Erin Welsh: Hopefully it'll be a lot. Well...

Erin Allmann Updyke: Sources?

Erin Welsh Sources. Speaking of learning a lot. I have a ton of sources for this episode. I will post them all but I want to shout out two in particular. So one by Weaver and Forrester from 2015 was really great about sort of the evolutionary history and the history of its spread since 1952. And then for the discussion of dengue vs Chikungunya and all of that there's that paper by Donald Carey from 1971 called 'Chikungunya and dengue: a case of mistaken identity?'

Erin Allmann Updyke That one sounds fun. I also had a lot of papers for this episode. One of my favorites for the biology was a Nature Reviews Microbiology paper from 2010, so a little old, that was called 'Biology and pathogenesis of Chikungunya virus'. And one of my favorites because I love this topic was from PLOS Neglected Tropical Diseases in 2021 that was 'The role of urbanization in the spread of Aedes mosquitoes and the diseases they transmit: a systemic review'.

Erin Welsh I think I had that one too.

Erin Allmann Updyke It's a good one.

Erin Welsh Yeah.

Erin Allmann Updyke We'll post our sources from this episode and every single one of our episodes on our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com) under the EPISODES tab.

Erin Welsh We certainly will. Thank you so much to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Allmann Updyke Thank you to Exactly Right network.

Erin Welsh And thank you to you, listeners. I hope that you enjoyed this first foray into a mosquito-borne virus this season. Sounds like a very specific topic now that I say it but it's not.

Erin Allmann Updyke I feel like we have done our mosquito-borne diseases in very interesting orders.

Erin Welsh Totally.

Erin Allmann Updyke But yeah, thank you listeners. Hopefully you enjoyed this. A special shout out to our patrons, thank you so much for your support.

Erin Welsh Absolutely, we can't thank you enough.

Erin Allmann Updyke And this is our second to last episode as a reminder.

Erin Welsh As a reminder.

Erin Allmann Updyke So make sure you are subscribed to our social media and to our podcast wherever you're listening so that you don't miss it when next season drops.

Erin Welsh Very well done, Erin.

Erin Allmann Updyke Thanks.

Erin Welsh And until our season finale, wash your hands.

Erin Allmann Updyke

You filthy animals!