TPWKY	This is Exactly Right.
Reagan	My name is Reagan and I grew up in a very small town, I had exactly 17 people in my high school graduation. So I just wanted to set the stage of what I was dealing with in the medical community. When I was 16 my school was getting ready for homecoming and we were the last class that got to have a bonfire at ours, we really wanted to go all out for everyone, not just for us. And I really wasn't big on outdoors, I wasn't an outside fan, I didn't like wearing the long sleeves, the pants, the mosquito spray. But I worked hard for this and it was an amazing bonfire. It was actually only a few days later that I was with my grandmother and right after school I came down with a headache. And I wasn't interested in watching TV, I wasn't interested in eating dinner, I even went to bed before the sun set.
	And my grandmother was really increasingly worried over this behavior. She was checking on me every half hour, she wanted to take me to the ER but she knew, especially in a town like ours, that they were just gonna send me home with Tylenol. So then the fever hit and when it hit it came on hard and fast. And my grandmother called the hospital who said that all they would do was put me in an ice bath and send me home, that was their febrile protocol. So she called my mom who was a 5 hour drive away and all I remember her saying is, 'Something isn't right, I think you need to come home.' She'd been gone for school, she'd been with a friend, she didn't even have her own car but something in my grandmother's voice convinced her. So she rented something, she came home, and by the time that the fever got so bad that she was having to lay on me to keep the chills from shaking the bed, she decided she was done, we were going to the ER.
	I don't really remember much from then out, it gets really hazy. I remember being super uncomfortable, I remember begging my mom to go home, I just wanted my bed, I wanted to sleep. The doctors were asking me to do all these things that I couldn't do, I couldn't stand up, I couldn't stay conscious and they were asking me to like touch my chin to my chest and I couldn't do it, it hurt so bad and that's when things started to get scary. I didn't know until later that they told my family that I was gonna die and I was like in the room, laying on the bed. And my mother demanded that I be moved to the hospital that was in the bigger city, it was an hour away and they said that I wouldn't make it. And then there was one doctor who came into the room, said he was getting me an ambulance and that he would have a friend waiting for my arrival because he was very scared that this was something very serious.
	Everything after that kind of comes in flashes. I remember the night sky becoming the roof of an ambulance, I remember my mother's face as she stroked my hair, I remember being pulled away from her so they could do a spinal tap which was the scariest thing that has ever happened to me in my entire life. I remember too many hands on me while they moved me to a stretcher, I remember my father arriving which was like a big deal if my dad actually came to a hospital. And I remembered my pediatrician because I had been so healthy up into my teen years that I hadn't actually acquired a GP yet. I remember hazard suits because they didn't actually know if what I had was bacterial or viral. I was so dehydrated that they had blew my veins trying to give me IVs, I was so malnourished that I lost 15 pounds in the hospital, I was so weak that I had to relearn how to walk and I remember thinking that I was gonna die and I was okay with that. It was actually well before the results came in West Nile meningitis.

	I missed two weeks of school between treatment and recovery, it took even longer to return to normal and my classmates mad to help me carry things between classes because the walks were too long and my body was too exhausted. And I remember my teachers giving me gift baskets and extensions on my homework and my family made me homemade cinnamon rolls to gain my weight back. And it didn't occur to me until much later that everyone was doing this because I wasn't supposed to make it. Everyone had said that I was gonna die, preparations had been made at school for me to not come back. And because I did, nobody wanted to let me research what had almost killed me. They waited patiently for my obsession with it to disappear. And it did until I started listening to your podcast. And that's all. (laughs)
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Thank you so much Reagan for taking the time to tell your story. Wow. I mean what a story.
Erin Allmann Updyke	Yeah, wow. Thank you.
Erin Welsh	It's absolutely terrifying.
Erin Allmann Updyke	Yeah, seriously.
Erin Welsh	Yeah. Well 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 West Nile virus.
Erin Welsh	Welcome to West Nile virus and what is our second to last episode of this season.
Erin Allmann Updyke	I really, truly can't believe that we've made it this far, Erin. I'm gonna be completely honest.
Erin Welsh	I mean same.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah so after the end of this season, so not this episode but the one after will be the last of the season, we're gonna be taking a short break. Don't worry, we won't be gone forever.
Erin Allmann Updyke	We'll be back.
Erin Welsh	We'll be back. So make sure that you're subscribed to the podcast, to all of our social media so you know what we're doing in the break and also when we're coming out with a new episode.
Erin Allmann Updyke	Yeah or any other fun surprises that could happen, who knows? We don't know, anything could happen.
Erin Welsh	Anything could happen. (laughs) Bu yeah, West Nile. Erin this is our first mosquito-borne one of this season, is that right?

Erin Allmann Updyke	Is it? I guess it is. I'm gonna be totally honest, this season I don't even remember what things we've done. I know we did Chagas so I know that was a vector-borne disease.
Erin Welsh	I'm just also surprised that we hadn't done West Nile yet. This is a kind of a big deal.
Erin Allmann Updyke	Oh Erin. You could just play a broken record of us in our intro saying the exact same thing for every single episode.
Erin Welsh	It is true. Oh man, okay.
Erin Allmann Updyke	It's gonna be a good episode though.
Erin Welsh	It is for a number of number of reasons. So you just heard that incredible firsthand account and we have another fantastic guest lined up for this episode to help shed some light on the ecology of West Nile virus. And one of the most exciting things, you have to stay tuned for the very, very end of the episode and that's because there is a West Nile rap.
Erin Allmann Updyke	A West Nile rap.
Erin Welsh	It is called 'West Nile Story' and it is by friend of the podcast MC Bugg-Z who made it in collaboration with the Fairfax County Health Department working in the disease-carrying insects program. Fairfax County, Virginia. I had to look that up.
Erin Allmann Updyke	I am so excited for everyone to hear it.
Erin Welsh	Oh my gosh. So it is absolutely a fantastic song and not only that, this is not MC Bugg-Z's only song so make sure you go to YouTube, we'll provide a link, don't worry, and you can check out all of the raps. There's even one about COVID vaccines. It is incredible.
Erin Allmann Updyke	Ooh, awesome. Well and speaking of classic TPWKY it's about time for a quarantini.
Erin Welsh	It is. What are we drinking this week?
Erin Allmann Updyke	We're drinking For The Birds.
Erin Welsh	Which we want to make sure that you know it's for the opposite of the reason that people usually say 'for the birds'. We wanted to name it this to honor the birds.
Erin Allmann Updyke	The birds! It's for the birds.
Erin Welsh	It is for the birds, this is for the birds. How many times can we say it?
Erin Allmann Updyke	What is in For The Birds, Erin?
Erin Welsh	So For The Birds is actually based on an existing cocktail also named after a bird called the Yellow Bird cocktail.
Erin Allmann Updyke	Very apt, very apt.
Erin Welsh	And that is made with white rum, orange liqueur, Galliano, and lime juice.

Erin Allmann Updyke	Delish.
Erin Welsh	It is tart and delish.
Erin Allmann Updyke	We'll post the full recipe for that quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com and all of our social media channels.
Erin Welsh	Absolutely. Other business, website stuff.
Erin Allmann Updyke	Yeah.
Erin Welsh	Always.
Erin Allmann Updyke	Check out our website thispodcastwillkillyou.com.
Erin Welsh	Should we even go through what's on the website?
Erin Allmann Updyke	I mean everything is there, anything you could want is there.
Erin Welsh	Yeah, it is. Should we just get started on this episode?
Erin Allmann Updyke	Can we? Let's take a quick break and then dive straight in.
TPWKY	(transition theme)
Erin Allmann Updyke	West Nile virus is a Flavivirus which listeners of this show should be very familiar with by now because we've covered so many other Flaviviruses, right.
Erin Welsh	We have.
Erin Allmann Updyke	Dengue virus, yellow fever, hepatitis C even, so many viruses. We're running out of Flaviviruses to cover. Just kidding, there's always more. But anyways Flaviviruses, for anyone who hasn't listened to every one of our episodes, is a large family of RNA viruses, many of which are transmitted by arthropod vectors to animals and humans. West Nile virus causes a disease that is primarily what's called enzootic, that is it has a cycle that is completely independent of humans, it's essentially a vector-borne disease of wildlife. This cycle is maintained in nature specifically through an avian mosquito cycle, so birds and mosquitoes where mostly mosquitoes in the genus Culex feed on avian or bird hosts, they pick up the virus in their blood meal and then it passes through their gut, makes it to the salivary glands, they spit it back out and then transmit it to other birds. And that's the primary cycle.
Erin Welsh	Simple enough.
Erin Allmann Updyke	Yeah, simple enough especially compared to a lot of things that we cover. We'll make it more complicated, don't worry.
Erin Welsh	Oh yeah.

Erin Allmann Updyke	It's thought that the virus is able to persist and perpetuate even in temperate regions of the world where adult mosquitoes aren't present all year round, both via adult mosquitoes that undergo diapause, so the virus persists in overwintering adults that are just not active. I have also seen that it's also possible that adults mosquitoes transmit it transovarially, I don't know how common that is. But it's also possible that migratory birds play a large role bringing in virus from areas of higher transmission or places where you have year round transmission or even just harboring low levels of virus and then during their migration cycles bringing that virus back to temperate areas. But in any case this avian mosquito cycle is the main enzootic cycle of West Nile virus and birds are the predominant reservoir host for West Nile virus.
	In North America alone hundreds of species of birds have been shown to be competent reservoir hosts, so harboring the virus whether or not they get sick and show symptoms. And the majority of bird species do seem to survive infection relatively unscathed. Don't worry, someone else is gonna talk a lot more about this virus in birds. I'm gonna focus on this virus in people. But other than birds and people, other animals can get infected as well, importantly horses also get infected relatively frequently. But humans and horses are what are called dead end hosts, that means that while we can become infected when a mosquito bites us and we can get sick, we can get clinical disease, humans and horses don't actually contribute to the cycle of infection. So mosquitoes that then feed on us don't tend to become infected from feeding on infected people.
Erin Welsh	Right.
Erin Allmann Updyke	And so I am going to focus on this disease as it manifests in humans but like we kinda said up front, it's also very important to understand the ecology and persistence of this disease is a lot more complex than just the human side of it.
Erin Welsh	Oh yeah.
Erin Allmann Updyke	So we'll get to that and I'm really excited to get to that later. All right. Just focusing then on humans. Let's talk about what it looks like when a person gets West Nile disease. First off it's unclear exactly how infectious West Nile virus is, that is how many people who get bitten by mosquitoes harboring West Nile virus actually go on to become infected, we don't really know.
Erin Welsh	Well and I would also imagine that the amount of virus varies mosquito to mosquito.
Erin Allmann Updyke	Definitely, absolutely. Yes. So we really don't know what the overall infectiousness of West Nile virus is. But we do know that of those people who get infected about 25%, some estimates say 20-40% but most that I've seen are around 20-25% of people will develop symptomatic disease, aka West Nile fever and about 1 in 150-250 or less than 1% of those people will develop what's called neuroinvasive disease or sometimes it's called WNND, West Nile neuroinvasive disease. And this include one of three possible neurologic manifestations that are common and then there's also honestly any range of neurologic complications that can happen. But the three big ones are West Nile encephalitis, West Nile meningitis, and West Nile acute flaccid paralysis. And because I know you're gonna ask me Erin, we don't fully know why exactly it is that some people get invasive disease and others don't. I know, I can see your downtrodden face.
Erin Welsh	(laughs) It's true.
Erin Allmann Updyke	We have some ideas, okay.
Erin Welsh	Okay.

Erin Allmann Updyke	It's likely a combination of that viral load like you already mentioned, so how much virus do you get injected with from this mosquito to begin with? And then a lot of other individual risk factors like older age, especially over age 65 or 70 is very strongly associated with increased risk of neuroinvasive disease and then other things like hypertension, kidney disease, things that affect your overall immune status. Also West Nile virus being a disease transmitted by mosquitoes into your bloodstream is a disease that can also then potentially be transmitted from things like organ transplants and people who have gotten West Nile infection from things like organ transplants are also far more likely to develop neuroinvasive disease compared to those that get infected from mosquitoes.
Erin Welsh	Interesting, okay.
Erin Allmann Updyke	But that is very rare, I'm just saying. So generally the incubation period for West Nile fever is anywhere from 2-14 days most of the time and symptoms can really range from a pretty mild, almost flu-like illness to like I mentioned, a very debilitating neuroinvasive disease. But in most people it often starts like this: a sudden onset of headache, very sudden onset of a pretty bad headache, generalized malaise, just feeling really crappy, a fever, muscle aches, and then fatigue. And very often as this fever starts to subside, a rash will develop usually along the torso and then extending out to the arms and legs. And this rash actually looks kind of like the rash from measles so it's like what we call maculopapular, it's little red, flat little pots with raised little bumps inside.
Erin Welsh	Yeah.
Erin Allmann Updyke	It's the kind of rash that really a lot of different viruses cause similar rashes. Unlike measles this doesn't tend to go head down.
Erin Welsh	Interesting.
Erin Allmann Updyke	This is just like a torso to extremities type rash.
Erin Welsh	Why?
Erin Allmann Updyke	Why?
Erin Welsh	Yeah.
Erin Allmann Updyke	Great question, I have not the slightest idea. (laughs) Honestly a lot of viruses cause similar rashes like this so whether it's a combination of the damage that that virus is doing to your cells vs just that kind of generalized immune response that's causing that rash, I don't know the answer.
Erin Welsh	Rashes.
Erin Allmann Updyke	Yeah. Rashes. Let's ask a dermatologist, I don't know.
Erin Welsh	I have a question about the complications, the neuroinvasive disease.
Erin Allmann Updyke	Oh don't worry, we're gonna get there Erin.
Erin Welsh	Okay but just the breakdown among them. So you mentioned the three different kinds.

Erin Allmann Updyke	Yeah!
Erin Welsh	What's the breakdown of those?
Erin Allmann Updyke	That's a good question, I actually don't have a good handle on the breakdown, everything just sort of said less than 1% will develop these complications.
Erin Welsh	Okay.
Erin Allmann Updyke	And part of it I think is probably because there's a bit of a spectrum. Like it doesn't mean that you maybe only have one of the three, you might have some acute flaccid paralysis with a little meningitis, you might have a meningoencephalitis. Yeah but that's a good question. Also I think because it is so rare we probably don't have really good numbers to be able to break it down when it's less than 1%.
Erin Welsh	Okay.
Erin Allmann Updyke	Okay but the rash, back to that. Those type of kind of mild symptoms can last anywhere from a handful of days to up to a few weeks, so this can be a pretty prolonged course of illness even if it's not severe. Now if it progresses to that neuroinvasive disease, the symptoms then just kind of look like whatever part of your nervous system is being invaded by this virus. So in the case of West Nile meningitis the symptoms look like meningitis which is a sudden onset of fever, a very, very massive headache, stiff neck, photophobia which is difficulty looking at light and it becomes very painful to look at light. If it progresses to encephalitis then you often have those same meningeal symptoms but then you also will have things like altered level of consciousness which means you can slip into a coma essentially or just personality changes because of swelling and inflammation in different areas of your actual brain. And West Nile encephalitis tends to be the most severe with the worst outcomes.
Erin Welsh	Okay and so this might be a very basic question but does it always progress meningitis and then encephalitis?
Erin Allmann Updyke	No, not necessarily. And we'll get to that in just a minute.
Erin Welsh	Okay.
Erin Allmann Updyke	Kind of, maybe. Well let me just keep going. So West Nile virus also then can cause acute flaccid paralysis. Erin do you remember what other disease we've covered that does this exact same thing?
Erin Welsh	Polio.
Erin Allmann Updyke	Ugh, you remembered so quickly!
Erin Welsh	Well okay but I have to confess I've watched a bunch of YouTube videos on West Nile virus and there was one where a physician came on and talked about it and was like, 'I haven't seen a polio case but this is apparently exactly like polio.'
Erin Allmann Updyke	Yeah, they actually call it poliomyelitis even though it's caused by a completely different virus which I think is really interesting.

Erin Welsh	That confused me, yeah.
Erin Allmann Updyke	It confused me too.
Erin Welsh	I was like but wait...
Erin Allmann Updyke	Yeah. But basically what can happen is that if West Nile virus specifically infected the anterior horn cells of the spinal cord, this is the part of our spinal cord where our motor neurons exit the spinal cord, that is the exact same area that poliovirus infects and causes swelling and then damage. And so this looks just like polio did. Your muscles and your limbs go weak. In the case of West Nile virus it's often asymmetric so it can look a lot like stroke.
Erin Welsh	Interesting.
Erin Allmann Updyke	It is interesting.
Erin Welsh	Why is it asymmetric?
Erin Allmann Updyke	I don't know. And it's not always, it's just that oftentimes it can be.
Erin Welsh	Okay.
Erin Allmann Updyke	Presumably it's just that this is where the virus ended up.
Erin Welsh	So if somebody goes to the hospital and presents with acute flaccid paralysis, are there other things or is West Nile sort of top of the list? I mean depending of course on geography and their history, etc.
Erin Allmann Updyke	Right. It would depend on all those things. And West Nile virus, of course polio can also cause it but that's not generally around most of the world these days. I don't know if there are other viruses, I imagine there are a handful of other viruses that can do that. One way that might differentiate this from stroke could be age range, especially if it's someone who has no other risk factors coming in. Importantly West Nile virus tends to not affect your cranial nerves and strokes often do. So if you think of stroke, they have those public information campaigns about looking for a drooping face, that's when your cranial nerves are affected which tends to not be affected with West Nile.
Erin Welsh	Okay.
Erin Allmann Updyke	In fact in many cases West Nile acute flaccid paralysis can mimic Guillain-Barré disease but Guillain-Barré usually has sensory symptoms as well and West Nile tends to not, although it can.
Erin Welsh	Okay.
Erin Allmann Updyke	I know, it's complicated.
Erin Welsh	It's complicated.

Erin Allmann Updyke

And with any of these neuroinvasive versions of West Nile virus, you may also have some other signs, things like nausea, vomiting, you might have a rash, you might have vision changes. So it's the constellation of all these symptoms, it tends to not just be one symptom isolated. And some people have the viral prodrome, so some kind of mild, viral-type symptoms, fever, chills, feeling cruddy, prior to the onset of these invasive symptoms. Others don't or at least don't remember having one. So the good news is that for most cases of West Nile virus, even the neuroinvasive cases, people tend to make a full recovery.

However the worst outcomes do tend to be in people who progress to encephalitis. And when we look at all of the neuroinvasive disease lumped together, so this is meningitis, encephalitis, AFP, but really the fatality tends to come from encephalitis or meningitis. In those neuroinvasive disease cases the case fatality rate can be as high as 10% overall or even higher for those that are older than 70. And for many, many people especially with these neurologic symptoms, the recovery process can be very, very slow, taking up to a year or more and in some cases especially with this acute flaccid paralysis or in some cases with encephalitis, people may lose function that they never are able to regain because nerves are damaged, things are damaged that just are not able to recover.

Erin Welsh

And the damage is caused by just inflammation by the virus being there.

Erin Allmann Updyke

Yeah so that's the question, right?

Erin Welsh

Right, right, yeah.

Erin Allmann Updyke

What is the pathophysiology of this disease? I haven't even started to talk about it. So here, let's try, shall we?

Erin Welsh

Let's do it.

Erin Allmann Updyke

Okay. So being a virus, we all know by now that viruses have to invade our cells in order to cause disease. It's thought that initially primarily when we get infected one of the major cells that West Nile virus tends to infect are our dendritic cells which are one of our immune cells that usually help to present antigens to our immune system like a flag so that we can make antibodies. So it's a pretty good cell for a virus to hide within and West Nile virus like many other Flaviviruses is very good at suppressing our overall immune response to infection. So as it invades these dendritic cells, those cells travel to our lymph nodes because that's where they like to go to present their antigens, but West Nile virus is then able to escape from those dendritic cells from our lymph nodes, enter our bloodstream, and travel wherever it wants. And as we've just gone over, one of the big hallmarks of West Nile virus is that it somehow can make it from our bloodstream into our central nervous system, our spinal cord, our meninges, or our actual brain.

So how is it actually able to do this? How can it be so neuroinvasive? We're supposed to have a blood-brain barrier that's supposed to literally stop this. And the answer is that we don't know exactly how it's able to do this. How is it so good at evading our immune response and making its way into our central nervous system? There are four at least different hypotheses. One is that it just releases or causes us to release a lot of cytokines. Probably a lot of people have heard of cytokines by now because of COVID and our influenza episode way back when. But these basically just increase the permeability of our vascular membranes, allowing more things to pass through, it's so that inflammation can get in there to do its job. But it also allows for viruses to make it across that blood-brain barrier. That's one hypothesis.

	The second is that is actually just can worm its way by entering through our endothelial cells, so cells that line the blood-brain barrier. It can invade those cells and then make it through. Another possible hypothesis is that it invades via macrophages, right. So macrophages are another one of our white blood cells that sometimes move across the blood-brain barrier for our protection but this virus can potentially be harbored within those macrophages. And finally my favorite hypothesis is maybe it does a little bit of rabies and it actually travels on our neurons and does retrograde axonal transport all the way to our central nervous system.
Erin Welsh	That is scary.
Erin Allmann Updyke	Yeah. And we don't know. We don't know which of those tends to be the biggest driver and why. Yeah. Its especially interesting because again, neuroinvasive disease can be very serious but it's very rare in West Nile and yet it's also one of the most common causes of viral, certainly of vector-borne viral encephalitis in North America.
Erin Welsh	Right. Interesting.
Erin Allmann Updyke	It's very interesting. So I don't have a good answer for you, Erin, in terms of how much of this damage is caused by viral damage directly vs our immune response and inflammation therein because we don't even fully understand how this virus makes it into our central nervous system to begin with.
Erin Welsh	So there are other Flaviviruses that invade the central nervous system.
Erin Allmann Updyke	Certainly.
Erin Welsh	And do we know the mechanisms for those?
Erin Allmann Updyke	I don't. I don't but I imagine that these hypotheses that have been proposed which I didn't come up with have been proposed based on both mouse models of West Nile virus infection as well as other similar Flaviviruses like Japanese encephalitis, etc.
Erin Welsh	Mm-hmm, that makes sense.
Erin Allmann Updyke	Yeah. So that's kind of the overall biology. It is I will say relatively easy to diagnose but also of course difficult to diagnose in other ways, mainly we tend to diagnose by looking for antibodies to the virus which tend to be apparent after about 8 days after the onset of symptoms. Most of the time you can find them after that amount of time but you have to be able to test between 8-21 days after symptoms start for that test to be accurate. You can test for the virus itself but then those tests are sometimes hard to come by depending on where you live, etc.
Erin Welsh	I've also read that it's not easily detectable because humans tend to circulate less virus in their blood.
Erin Allmann Updyke	Right, very low levels of virus. And then it also depends on are you testing blood or are you testing cerebral spinal fluid?
Erin Welsh	Right.

Erin Allmann Updyke	Is it for meningitis or is it just for like a general infection? In general at least as far as I could tell, we don't have any specific antiviral treatment for West Nile virus so treatment is just supportive the way that you would treat anybody with a meningitis or an encephalitis that's not bacterial, just sort of supportive care.
Erin Welsh	Okay.
Erin Allmann Updyke	And that is the biology of West Nile. Erin, I know you have a lot to tell me about where this little virus came from.
Erin Welsh	I do.
Erin Allmann Updyke	Okay, good. Shall we?
Erin Welsh	Yeah. I'll dive in as soon as we take a quick break.
TPWKY	(transition theme)
Erin Welsh	Well actually Erin, this history section is gonna be kind of like a total break from the last few episodes we've done.
Erin Allmann Updyke	Okay. In what way?
Erin Welsh	Well okay, diabetes, absolutely enormous history. Anthrax, huge.
Erin Allmann Updyke	Oh my gosh, so big.
Erin Welsh	Yeah. Chagas disease, super extensive history.
Erin Allmann Updyke	All of it.
Erin Welsh	But the history of West Nile, although it does date back probably further than you might think, it's fairly what I would say a bit straightforward.
Erin Allmann Updyke	Okay.
Erin Welsh	Which isn't to say, like that's not to say that it's uninteresting or that it can't tell us anything about big picture science or big picture society or big picture public health issues because it definitely can.
Erin Allmann Updyke	Oh I have no doubt, Erin.
Erin Welsh	But before we get to that we have to start back a bit, of course. Where did this virus come from and how did we get to where we are today with it?
Erin Allmann Updyke	And what did they say in the Ebers Papyrus?
Erin Welsh	Well sadly or not sadly, I don't know, it doesn't seem to be mentioned at least that I could gather.

Erin Allmann Updyke	Okay, well we tried.
Erin Welsh	So like you mentioned Erin, West Nile virus is a Flavivirus and it's related to other Flaviviruses like the ones you named, yellow fever virus which honestly it's been so long that I don't remember if I covered this in that episode but the name 'Flavivirus' actually comes from the Latin word 'flavus' for yellow. Which I also think then kind of adds a fun little layer to the base to the recipe for our drink.
Erin Allmann Updyke	Quarantini.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah, I agree. Also I can't remember if you said that in yellow fever either so I'm glad that you told us again.
Erin Welsh	Yeah. But yeah, dengue virus, Zika virus, Japanese encephalitis virus, St. Louis encephalitis virus, tick-borne encephalitis virus, and so on.
Erin Allmann Updyke	So many, so many.
Erin Welsh	So many. And of all of these Flaviviruses, West Nile virus is one of the earliest described and one of the most widely distributed.
Erin Allmann Updyke	Huh. Okay.
Erin Welsh	I know, it was a little surprising.
Erin Allmann Updyke	Yeah. I knew it was widely distributed, I didn't know it was one of the earliest ones. Get into it, I can't wait to hear.
Erin Welsh	Oh I am, I am. So we can use things like serological studies and genomic analyses to tell us how it came to have what is basically this global distribution. And what it looks like is that West Nile virus evolved in Africa, I don't have an exact or even a rough date estimate for that or an exact location or even a rough location. But that's where serological studies show that the virus is circulating continuously and has been that way for some time. And this year-round transmission is in contrast with the patterns in other places such as Europe where West Nile virus was introduced from Africa via migratory birds and where it tends to pop up in this more seasonal transient form. And West Nile virus was brought to India via trade probably around the early 1800s, 1820s or so, when there was extensive trade between Africa and India. And then to Australia or the Australasia region in the mid 1800s. And this last one, like how it got to Australia is a bit of a mystery because there are apparently no bird migrations that connect Australia and Africa although any bird friends, Nick, Fred, Cole, Maria, Nate-
Erin Allmann Updyke	We have a lot of bird friends.
Erin Welsh	We do have a lot of bird friends. Weigh in if you know something else. But yeah so because of that it's been suggested that West Nile virus was actually introduced to Australia from Africa in a similar way that yellow fever virus was brought to North America from infected mosquitoes on ships carrying enslaved people as Europeans traveled to Australia from Africa.
Erin Allmann Updyke	Oh, okay.

Erin Welsh	And it seems that really the only place where West Nile virus is not present besides the Arctic and Antarctica is in a lot of parts of Eastern Asia and the reasons for that are not quite clear, maybe it's a competition thing with other encephalitis viruses, I don't know, a mosquito compatibility, hosting compatibility, I don't know. And I'm not gonna get too much into the details of the different lineages and the clades that the virus can be broken down into cause there's a lot but just to say that they do exist and that they can help us in new outbreaks to see where the virus is coming from and identify possible ways that it got there. For instance was it a single introduction event or multiple? It's thought that West Nile virus was introduced to Europe and North America in several independent introduction events while it was brought to Australia in just one. And then how much has the virus evolved since arriving in a new area? Are there pathophysiological differences among the different clades that could have clinical implications or ecological differences that could change the way we control it, etc? So it's a useful area, it's just a lot of minute detail that's sort of open-ended questions in some ways.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. So I mentioned that West Nile virus was one of the earliest described viruses but the way that it happened was kind of a fluke.
Erin Allmann Updyke	Oh yeah?
Erin Welsh	Oh yeah. In 1937 researchers were conducting a wide scale epidemiological study on yellow fever in Uganda and a person from the West Nile district of Northern Uganda was brought into the study presenting with a fever. But when they tested this person's serum against yellow fever virus it didn't match. Instead it looked to be more similar to other Flaviviruses that cause encephalitis, St. Louis encephalitis and Japanese B encephalitis viruses. And even though the person only had a fever they noted that it seemed to have neurotropic tendencies. The researchers described this new virus in a paper in 1940 which is older than I expected for West Nile virus.
Erin Allmann Updyke	Yeah, it really is.
Erin Welsh	Yeah. Also I just have to complain here for a second because that paper published in 1940, so 81 years ago, is still behind a paywall.
Erin Allmann Updyke	Are you serious?
Erin Welsh	I am serious.
Erin Allmann Updyke	That's ridiculous.
Erin Welsh	Yeah. I mean can we just make everything open access? It would make the world a better place. Okay.
Erin Allmann Updyke	81 years old.
Erin Welsh	I know, I know.
Erin Allmann Updyke	Wow.

Erin Welsh	Frustrating.
Erin Allmann Updyke	Yeah.
Erin Welsh	Anyway so why did I call the discovery of West Nile virus a fluke? Well for one it was discovered kind of accidentally, like those researchers weren't out looking for the cause of an outbreak of unexplained febrile illness. And for two, over the next 60 years or so after its discovery West Nile virus was not really considered that much, it didn't rank that highly on the list of pathogens of public health importance.
Erin Allmann Updyke	Yeah.
Erin Welsh	There were a lot of other and there still ar a lot of other mosquito-borne viruses that cause a lot more widespread morbidity and mortality and so West Nile virus was kind of just like, 'Oh that's just another one of those Flaviviruses.'
Erin Allmann Updyke	Right.
Erin Welsh	And the third reason is that like we talked about in the biology, the virus isn't often easily isolated in infected humans like in blood, so the fact that they were able to isolate it at all I think is kind of interesting. So it wasn't until the 1950s that the first outbreaks of West Nile virus were observed, like the first time that people recognized that West Nile virus could be capable of causing widespread outbreaks.
Erin Allmann Updyke	Right, like an outbreak, not just an incidental disease here and there.
Erin Welsh	Exactly. And that started with the first recognized epidemic in Israel in 1951. 123 cases occurred in a small town the size of 303 people.
Erin Allmann Updyke	I'm sorry, you said 160 cases in a town of 300?
Erin Welsh	123 out of 300 people, yeah.
Erin Allmann Updyke	Oh my goodness, that's a pretty high attack rate.
Erin Welsh	I know! Really, really high. No fatalities occurred and in fact most of the people affected were children. But this was the first time really that the various disease symptoms that this virus could cause were recognized, things like you already mentioned, fever, headache, abdominal pain, vomiting, etc. And around the same time as this epidemic in Israel or not long after, a series of outbreaks of West Nile virus popped up in Egypt and during these outbreaks a lot more ground was covered in terms of understanding the disease ecology, clinical characteristics, and epidemiological patterns. For instance this is when researchers realized that a large proportion of people infected never showed any symptoms, that children in these areas tended to have more symptomatic illness but adolescents and adults tended to have higher seroprevalence, so suggesting that in these places where the virus was endemic and continuously circulating, people were likely exposed to the virus at a young age.
Erin Allmann Updyke	Interesting, interesting, interesting.
Erin Welsh	Yeah. And researchers also in these early outbreaks in the 1950s found the virus in many species of birds and also in some species of mammals and this is when they made the link between mosquitoes and the virus.

Erin Allmann Updyke	Okay, cool. Wow.
Erin Welsh	They have a lot of ground.
Erin Allmann Updyke	Yeah.
Erin Welsh	And finally some of the neurological complications of infection were observed during these early outbreaks in Israel and Egypt, things like these rare instances of meningitis or encephalitis. But overall these outbreaks really kind of served to reinforce the idea in many ways that West Nile virus was mostly asymptomatic or if anything generally like a mild mosquito-borne illness. And this prevailing perception can be seen in the experimental infection studies that took place in Egypt during this time where people with terminal cancer were intentionally infected with the virus to see if the resulting fever would help suppress the cancer's growth.
Erin Allmann Updyke	Oh gosh.
Erin Welsh	Well this was actually apparently like a fairly common or at least occasional type of experimental treatment during this time that people were exploring or looking into.
Erin Allmann Updyke	Interesting.
Erin Welsh	Yeah.
Erin Allmann Updyke	Was it effective?
Erin Welsh	So I don't know because again I don't have access to this old paper either from the 1950s which is kind of annoying.
Erin Allmann Updyke	Oh, okay. Great. Cool.
Erin Welsh	Which also means that I couldn't read between the lines to see whether this falls under actual experiment or medicalized torture.
Erin Allmann Updyke	Right.
Erin Welsh	Does "volunteer" have quotes around it, etc.
Erin Allmann Updyke	Yeah. Okay, yeah.
Erin Welsh	But these studies were terminated when several of the people who were infected developed encephalitis.
Erin Allmann Updyke	Makes sense, yeah.
Erin Welsh	Reasonably stopping point. But during these studies the researchers also did make some important observations in terms of things like viremia, like how much virus was circulating and when and how long it could be detected and how the amount of virus circulating correlated with the severity of disease.

Erin Allmann Updyke

Okay.

Erin Welsh

So following these outbreaks in Egypt and Israel, West Nile virus continued to make sporadic appearances across parts of Africa, the Mediterranean, and Europe, popping up in France, South Africa, Russia, Spain, and India, some other places. And in the course of these epidemics it became more apparent that this virus can absolutely cause neurological disease in some people which might have brought it more research attention at the time, so like in the 50s and 60s if not for the fact that large outbreaks of the virus all but stopped throughout the 1970s and 1980s. Like they just, I don't know whether it was observation plummeted or the ecology made it to just like really put it in a lull period, I don't know. But in 1996 a new era of West Nile virus began. First with the large epidemic in Southern Romania. And not only was this one of the biggest recognized outbreaks of West Nile virus with at least 393 hospitalizations and 17 deaths and who knows how many actual infections, but it also involved a lot of neurological cases and it was the first to happen in what was basically a mostly urban area whereas previous outbreaks had been more rural.

And over the next couple of years it became clear that this wasn't a one-off, West Nile virus seemed to be undergoing a change in its epidemiology. After the epidemic in Romania, the virus popped up in Morocco in 1996, in Tunisia in 1997, in Italy and Israel in 1998, and in Russia in 1999. And like the 1996 Romanian outbreak, these were also in urban areas, seemed to have higher rates of neurological involvement with a higher fatality rate, and had a tendency to impact mostly people in older age groups. So by the time August 1999 rolled around, the pattern had already been set. But West Nile virus still held one more big surprise for everyone and that was that it had made the leap across the ocean and into North America.

Erin Allmann Updyke

Big splash.

Erin Welsh

Big splash. So far West Nile virus I think has taught us a couple of really important lessons or at least like reemphasized them and since Erin, like we've talked about this many times and listeners, if you've tuned in before, these are gonna sound familiar but I'm gonna say them anyway.

Erin Allmann Updyke

Yeah.

Erin Welsh

The first is to not underestimate a virus.

Erin Allmann Updyke

Never underestimate a virus.

Erin Welsh

Yeah. Many viruses that appeared mild at first can go on to have serious complications or long term effects. Not all of course but the potential is there, like remember chickenpox for instance?

Erin Allmann Updyke

Remember it.

Erin Welsh

And the second lesson is that human movement and human modification of the environment can alter the dynamics of infection in a very major way.

Erin Allmann Updyke

Yeah.

Erin Welsh	This isn't new stuff but is definitely important stuff. And so these two lessons were also learned during what would be the first epidemic of West Nile virus in North America beginning in August 1999 but that outbreak also carried with it another hugely important warning. Human health is wildlife is domestic animal health is environmental health. It's all connected.
Erin Allmann Updyke	What's that? It's all connected? What's that? A one health approach?
Erin Welsh	A one health approach. So let's get into it. Do you remember the 1999 West Nile virus outbreak at all?
Erin Allmann Updyke	You know I remember when West Nile virus became a thing because my dad had a pond in the backyard and it was like oh no, we can't have a pond anymore cause West Nile virus made it to California. Yeah.
Erin Welsh	Yeah I don't remember specifically the 1999 one but I remember suddenly it was like West Nile, mosquitoes, put on that Off! whatever, all the time.
Erin Allmann Updyke	Right.
Erin Welsh	All I knew was that it appeared and then that was it.
Erin Allmann Updyke	Yeah.
Erin Welsh	So let me fill in some of the details.
Erin Allmann Updyke	Some of our gaps in memory?
Erin Welsh	Yeah. So beginning in the summer of 1999, all over New York City crows started dropping dead, like dropping out of the sky, just dead. Everywhere you went you could find the carcasses of dead crows. And maybe if you lived in New York City at the time you might have seen some of these dead crows and thought ugh, gross, these poor crows, probably rat poison, who knows? Bad pizza, I don't know. And then went on with your day.
Erin Allmann Updyke	Yeah.
Erin Welsh	But the sight of these crows brought a lot more alarm to one person in particular, Dr. Tracey McNamara who was the lead pathologist at the Bronx Zoo. If these crows were dying of some kind of infectious disease, the birds at the zoo, some of which were rare or endangered, were at serious risk. And that risk soon became a reality when some of the zoo birds began to die, starting with the snowy owl.
Erin Allmann Updyke	Oh no.
Erin Welsh	And this definitely pointed towards an infectious agent but what was it? Dr. McNamara examined some brain tissue from the dead birds under the scope to try to answer that question and what she saw in her own words took her breath away.
Erin Allmann Updyke	Wow.
Erin Welsh	Quote: "It was the worst encephalitis I'd seen in 18 years as a comparative pathologist."

Erin Allmann Updyke	Oh no.
Erin Welsh	Yeah, staggering.
Erin Allmann Updyke	Yeah.
Erin Welsh	Not far away at Flushing Hospital in Queens, an unusual number of encephalitis cases began coming in, some with paralysis and some leading to death but these were in humans rather than birds, just to clarify. And these encephalitis cases were clustered enough in time and space to make an infectious disease specialist at the hospital, Dr. Debbie Asnis, wonder whether there might be a link among them. So she brought in the Department of Health to ask the patients question after question about where they ate, what they ate, where they worked, where they lived, what train they rode, what shampoo they used and so on. The only commonality among them seemed to be that they enjoyed spending a lot of time outside especially in the evenings and household surveys of where they lived showed that there had been a lot of mosquito breeding habitats around. Could it be a mosquito-borne outbreak? It had been a long time since something like that had happened in New York.
Erin Allmann Updyke	Yeah.
Erin Welsh	Remember this was before Zika.
Erin Allmann Updyke	Right, way before.
Erin Welsh	Way before.
Erin Allmann Updyke	Before chikungunya, yeah.
Erin Welsh	But it was still a possibility, enough so that Dr. Asnis sent off samples to the CDC to have them test for any known infectious agents which side note, deserves some major props. Because there are plenty of doctors who would have chalked up the cases to coincidence, like there isn't always an answer in medicine and there are plenty of unexplained fevers or illnesses that resolve themselves without revealing what they really are. And so for Dr. Asnis to send out those samples is in many ways I think going above and beyond and likely helped enact control measures earlier than they would have otherwise. And so off those samples went to the CDC and before long they came back with a match, with an answer. St. Louis encephalitis virus. And this seemed like a reasonable explanation. St. Louis encephalitis virus is a rare mosquito-borne virus that can, as its name suggests, cause encephalitis. And it's a Flavivirus.
	But that answer which was now by this time reported in the news, like 'Outbreak of St. Louis Encephalitis' it didn't sit right with Dr. Tracey McNamara. After hearing about the human encephalitis cases she felt very strongly that there was a link between those cases and the sick and dying birds at the zoo. But if she was right and there was such a link, it couldn't be St. Louis encephalitis virus because birds can't get that virus. And so she reached out to the CDC with her concerns and urged them to test some of her samples to see if there was a match to the human samples. But the CDC turned her down.
Erin Allmann Updyke	Really?
Erin Welsh	Really. Okay, partly because it was a bureaucracy thing.
Erin Allmann Updyke	Yeah.

Erin Welsh	The testing of animal samples, all animal health stuff, that fell under the jurisdiction of the USDA I think.
Erin Allmann Updyke	Interesting.
Erin Welsh	And it was a totally different, like the CDC in some ways they were like, 'Well we don't have the capabilities to do this, we're not allowed to do this in the job description.'
Erin Allmann Updyke	Yeah. It's so interesting because as you were saying she reached out to the CDC I was like wow, how does one just reach out to the CDC?
Erin Welsh	That's a good question.
Erin Allmann Updyke	I mean yeah.
Erin Welsh	I guess if you're like the lead pathologist at a zoo you might have some...
Erin Allmann Updyke	I would think you'd have an in somehow.
Erin Welsh	Yeah.
Erin Allmann Updyke	But it's a bummer that she couldn't get around whatever bureaucracy existed.
Erin Welsh	It was bureaucracy but I think the other part was that she kind of ran into a lot of resistance wherever she faced and that's how she described it.
Erin Allmann Updyke	Yeah.
Erin Welsh	Because at that time there was this prevailing attitude that human health and wildlife health weren't necessarily connected and so the death of a few birds at a zoo, that doesn't have anything to do with the people sick with encephalitis at the hospital. Plus we already have an answer.
Erin Allmann Updyke	A lot of times, Erin, on this podcast we have stories like that from like the 1800s where you look back and you're like it was so obvious, how did you not see it? And this was 1999 so it feels painful.
Erin Welsh	It does, yeah. And it's also just kind of I think the aspect of the bureaucracy is frustrating.
Erin Allmann Updyke	Oh my gosh, yeah.
Erin Welsh	So yeah. But Dr. McNamara didn't let that stand in her way, her rejection by the CDC, so she sought out some colleagues in the army and asked them to test her samples.
Erin Allmann Updyke	Awesome.
Erin Welsh	And they did. And what they found was not St. Louis encephalitis virus but rather a virus that hadn't ever been detected in North America before.

Erin Allmann Updyke	Ooh.
Erin Welsh	Of course West Nile virus.
Erin Allmann Updyke	West Nile virus.
Erin Welsh	Suddenly the CDC became interested and stopped screening Dr. McNamara's calls. Just kidding. They reexamined the samples from Dr. Asnis' patients and sure enough, West Nile virus.
Erin Allmann Updyke	Yeah. It's not surprising that it cross-reacted.
Erin Welsh	Oh yeah, not at all. I think that's a very reasonable thing to happen I guess. And so I'm not 100% clear on the timeline but I did watch an interview with Dr. McNamara where she estimated that there was about a 2 or 2.5 month delay resulting from the CDC not testing her samples and so it's a couple of months where public health departments and wildlife health researchers could have gotten ahead of this virus to try to begin awareness campaigns and control efforts. And I think that one of the biggest lessons is that this 1999 West Nile virus outbreak revealed how siloed we were and in many ways still are in terms of monitoring the links between human, wildlife, and environmental health.
Erin Allmann Updyke	I feel like that's something we just touched upon in our anthrax episode.
Erin Welsh	It absolutely is. Like what good is a canary or crow in the coal mine if you ignore it when it signals danger? Or if you can't figure out what that danger is because you lack the diagnostic tools. This initial outbreak of West Nile virus in New York involved an estimated 8200 human infections, 80% of which were asymptomatic and the remaining 20% were mostly those with mild febrile illness and then less than 1% develop this neuroinvasive disease. But in terms of confirmed cases, those numbers were a lot lower.
Erin Allmann Updyke	Yeah.
Erin Welsh	62 cases I think and 7 deaths, something around there, like very low.
Erin Allmann Updyke	Wow, yeah.
Erin Welsh	The 1999 outbreak in New York City was not an isolated event, it continued onto New Jersey and then to Connecticut and it seemed likely that it was here to stay. The National Surveillance Program ArboNET was created by the CDC and state health departments to monitor bird and human disease to be on the lookout for potential outbreaks of arboviral disease like West Nile. And one good indicator of an upcoming outbreak is the die-off of birds preceding the emergence of West Nile virus in an area and that's exactly what happened in 2002 in the huge epidemic of West Nile in North America, reaching all the way to Montana and Texas and as far north as Quebec and Ontario. And this dwarfed the 1999 outbreak in New York with over 4100 confirmed cases of the disease and 284 deaths and I don't know how many estimated infections but with a lot of the cases of severe disease and just general illness happening in the Midwest US, so it had kind of shifted its distribution.
Erin Allmann Updyke	Right.
Erin Welsh	In the period of just a couple of years this virus had traveled incredible distances but we still don't know exactly how it got to the US.

Erin Allmann Updyke	Yeah.
Erin Welsh	It's possible that it was introduced from Israel but the mechanism is unclear and we may never know for sure. But in the time since these epidemics we have learned a lot about the virus and its ecology. We've learned that horses can become sick with the virus, we've learned that it can be transmitted through blood transfusions and organ transplantation, through the placenta and breast milk. Environmental conditions are hugely important, like warmer temperatures mean a shorter time from infection to infectiousness in the mosquito and they can also increase viral replication within those mosquitoes. So in cool weather the mosquito has to live a longer time in order to pass on the virus to humans so it has to live longer to become infectious after feeding on the infected bird.
	Average rainfall years seem to provide suitable conditions or the best conditions for mosquito proliferation. Warm winters mean more mosquitoes survive over winter. All of these bits of information are like pieces of the West Nile virus puzzle, the more we gather the more we can fit them together to get a better picture of why outbreaks happen, where and when they happen, the role that different bird species play in transmission, and how things like climate change and land use change may alter the landscape of disease risk for this virus. And we are so excited to bring on a special guest to help us with a huge chunk of this West Nile virus puzzle.
Erin Allmann Updyke	Yes, we told you it was coming.
Erin Welsh	And that is the bird part of the puzzle. We'll let her introduce herself right after this break and then after that Erin, I wanna hear more about West Nile virus in the world today.
Erin Allmann Updyke	And I wanna tell you about it.
TPWKY	(transition theme)
Sarah Wheeler	My name is Sarah Wheeler and I'm currently the biologist at Sacramento-Yolo Mosquito and Vector Control District. And at the district I am now focused on applied research into mosquito control but I started my journey on this path as an ornithologist and I spent a lot of time investigating the role of wild birds and the spread of West Nile virus, the spread, amplification, and maintenance of West Nile really. And so I'm happy to talk some more about that today.
Erin Welsh	Awesome! Thank you so much for taking the time to chat. I just kinda wanted to start off by talking about the effects of West Nile virus on birds. So in this episode so far we have talked about the range of effects that West Nile virus has had on humans, things like asymptomatic or mild disease all the way to these severe neurological complications or even death. So can you talk a bit about what infection looks like birds and is there a similar wide clinical range of symptoms?

Sarah Wheeler	Yeah, there's absolutely a wide range of symptoms and it can go from completely asymptomatic in some species or individuals to debilitating to the point where the animal can't survive on its own to completely fatal infections. And a lot of this can be somewhat generalized by the species, so we know that some species are more susceptible to West Nile virus, so generally we think of passerines or songbirds being more susceptible to West Nile virus but that is a huge range of bird species and even within the range of songbirds, some are more refractory than others. And so for a bird that is going to deal with an infection fine, you will never even know that they're infected, they fight have a couple of days of viremia or no viremia, that's virus circulating in the blood of the bird to the point where they could infect mosquitoes, they might not infect mosquitoes at all and not really become sick; to a bird that produces so much virus in its blood that it could infect any mosquito that feeds on it and it succumbs within 4 or 5 days. So yeah, it's a really wide range.
Erin Welsh	Okay. So in the ones that are severely impacted, what are some of the symptoms that they show?
Sarah Wheeler	Yeah so outward symptoms, if you see a bird with West Nile it might be kind of hunched and puffy-looking. So we're doing some work with house finches and West Nile virus and it turned out that they were sitting there just looking very puffed up and that's a common symptom in a bird that's sick. And those birds actually had really low body temperature so I think that it was having a hard time dealing with the infection and having trouble thermoregulating. Some birds develop acute neurological symptoms, so they get tremors or head tilts. So I think that sometimes birds that are in the transition period of just becoming very sick can actually just start acting weird. So we were studying the fatality events of crows in Davis, California and it turned out that many of the crows that died of trauma actually were infected with West Nile. So I mean a crow doesn't usually just get hit by a car but if it's not feeling well it might not get out of that gutter. Birds like raptors can actually develop ocular lesions which means that they can clear the infection but then they turn up at wildlife care centers in poor body condition because they can't hunt for themselves.
Erin Welsh	Right. So it's not necessarily that a lot of birds are dying outright or maybe some birds are dying outright from infection but others are dying as a consequence of infection simply because they can't, like you said, exist on their own or survive on their own anymore.
Sarah Wheeler	It has affected their fitness.
Erin Welsh	Wow, okay. Very interesting. And so as you mentioned there are some birds that seem to be more susceptible to West Nile virus infection than others. Do we know anything about the reasons for these differences in susceptibility?
Sarah Wheeler	You know what, I really wish I knew this. Cause it is a wide range and like I said before we think of it as being taxa-based, so crows, birds in the crow family, so crows, jays, magpies are for the most part exclusively sensitive to West Nile virus. They're very common in dead bird programs, they have higher mortality when exposed. They don't all die, we don't have a lot of evidence of crows surviving West Nile but we definitely have antibody-positive jays and magpies, this does happen. So they survive the infection, they produce antibodies, and that something we can detect in different sero surveys.

	But birds like pigeons, chickens - chickens are actually really common sentinel birds for West Nile virus surveillance, so we put them out in flocks and we bleed them every 2 weeks and see if they develop antibodies to West Nile virus. And this was a really classic way for doing arbovirus surveillance especially before you had PCR, you could put your chickens out and serology techniques have developed before PCR techniques so this is a really handy way of doing surveillance. And chickens show no sign of infection, they don't infect mosquitoes, it's a total dead-end host. So what is different between a chicken and a crow? I don't think we understand it but there's something different, whether or not it's some sort of pathogen effect where the virus is just not replicating as efficiently or it's that the bird is fighting it off more effectively, I don't think we know that.
Erin Welsh	Yeah, interesting. So a follow up question about susceptibility in birds with West Nile is about geography. So are there any patterns geographically in terms of susceptibility? Do there tend to be more resistant birds in places where the virus has been circulating for a really long time, like I'm talking on the scale of hundreds or thousands of years vs places where the virus has been introduced more recently such as in North America?
Sarah Wheeler	I think that that is plausible. I mean we don't see the mortality events where West Nile virus first evolved that we see in North America. So our birds in North America are living with West Nile currently, like multiple generations have now been living with West Nile and I don't know if we'll ever get to completely asymptomatic. But it's plausible to think that but what that might look like in North America is North America open question because it's not a static system, so how a bird deals with an infection, if it's able to fight that infection off and not develop as strong a viremia then that would push the virus to being more virulent. So there's always that post-pathogen interaction.
	And so West Nile compared to other arboviruses in North America has tended to be more virulent and we thought that this helped to drive it into more refractory mosquito species. So it took a higher viremia in order to get our native mosquitoes infected, so that's kind of helped drag the system. And in just over 20 years or West Nile virus I think that we've seen some species that felt like they getting more refractory and it might be happening but I don't know that we know that for sure. But West Nile virus transmission is not constant, it's not constant pressure. So a population that's under constant pressure might get a lot of West Nile exposure for multiple years and then we have 2 years of not a lot of West Nile pressure which allows that population to build back up, perhaps you have more open niches and more nesting success and so it allows populations to recover somewhat.
Erin Welsh	Yeah, that's really fascinating. You do have to consider all the different components of the system and the cycle that it's not just about the bird and the virus, it's also about the mosquito and the bird and the virus and all of these moving parts that are difficult to sometimes get a handle on.
Sarah Wheeler	Yeah I mean the mosquito is a huge part of this whole situation.
Erin Welsh	Yeah.

Sarah Wheeler

The mosquito is in a way like the driving force of the whole transmission cycle because the mosquitoes that transmit West Nile would almost like 9 times out of 10 prefer to feed on a bird. So Culex, they really like to feed on birds, they prefer birds. So if you look at blood meal ID studies where people collect blood-fed Culex and we look at the DNA in the blood meal and identify what they fed on. We'll generally see a bird species there even. Even though 9 times out of 10 that Culex mosquito is gonna feed on a bird, if a human is sitting out there barbecuing or making it easy for the mosquito, the mosquito might just take advantage of that. So that's why it's predominantly a bird-mosquito cycle cause the mosquitoes are predominantly feeding on the birds, the birds are the amplifying host, and that's kind of how it cycles with it occasionally spilling over into humans or horses. And I get the question a lot like, 'Well what about my dog or my cat?' And I think I'm sure that they're bitten by infected mosquitoes but we don't see any kind of reports of infection in dogs and cats, so probably just another dead-end host.

Erin Welsh

I'm now brimming with a bunch of questions about mosquitoes and mosquito ecology. And so is it really just sort of availability and opportunity of whatever hosts are there for the mosquitoes or do these tend to be more sylvatic species? Do they hang out mostly in wooded areas or are they also urban species? What are some of those differences among competent mosquito species?

Sarah Wheeler

So in our area the two main vectors of West Nile virus are Culex pipiens and Culex tarsalis. Culex tarsalis tends to breed more in rural areas, so in our area they breed really heavily in the rice fields that surround our urban centers. But Culex pipiens is totally an urban breeder, they love catch basins. So in your gutter there is that little grate and there's a little cement compartment down there that is supposed to catch the debris before it flows out to the creek or whatever. Well those almost always hold water and so Culex pipiens can really take advantage of that, a bucket of water in your backyard, or a green swimming pool, or any source that they can take advantage of and those happen quite regularly in urban areas. So you can definitely have both urban and rural transmission of West Nile virus so sometimes in urban areas you have a concentration of very competent amplifying hosts.

So in the city you see a lot of crows, you see a lot of jays, you see house finches, house sparrows and all these species are competent amplifying hosts. And then you also have the mosquitoes so you have a concentration of players that can contribute to an amplification cycle. When you get out into rural areas you also have competent amplifying hosts out there and great vectors, tarsalis is out, sometimes you can have pipiens and rural species but you might have an introduction of more species and sometimes the addition of greater species variety can have a diluting effect on effective transmission. So if you have a range of possible hosts and 50% of them are great amplifying hosts, that's gonna lead to a different transmission cycle than a scenario where 25% of them are great amplifying hosts. So that's why a lot of times we've seen West Nile be a little bit more urban in nature but I mean it does happen rurally absolutely.

Erin Welsh

Yeah. So before I shift to talk about sort of more of the role that birds play in the transmission cycle of West Nile virus, I wanna just ask an overall question about the impact that West Nile virus has had on bird populations in North America since it's been introduced. And I'm sure that it's not consistent across the board but have we seen substantial declines in some species and no impact on others?

Sarah Wheeler

Yeah. So especially when West Nile was tearing across the US and there was huge bird die-offs across the US, a lot of people were very concerned about different bird species like zoo collections were even getting hit and precious animals that might be sensitive or in decline, there was a lot of concern about what West Nile would do to those bird communities. And so myself and other researchers have spent some time trying to figure out what the impact of West Nile has been on these bird communities and the kind of data that you usually use for these kinds of analysis are some of these big bird census databases so the Christmas Bird Count or the Breeding Bird Survey can kind of help you understand impacts on bird communities because they've been in place for a long time before West Nile even got here. And so you can look at the impact on those bird communities after West Nile and see if there's been any kind of changes in their population dynamics.

It's not perfect, right, there other things that affect birds than West Nile and I would say especially within the first 5 years there are species that absolutely saw declines, there were declines. So a bird in our area, the yellow-billed magpie, it's a bird that's only found in the central valley of California, like a huge part of its population was under West Nile virus pressure, you could see clear declines in that bird. They're kind of noisy birds, they're a big black and white bird with yellow bill, you notice them, right. Anecdotally people were saying, 'Yeah, all of a sudden the magpies are just gone!' They by their own nature probably help preserve themselves a bit because not only can yellow-billed magpies themselves be somewhat nomadic in nature, like West Nile does not exert even pressure every year and I think that that was what really allowed them to kind of level out and get back on a better track with their population.

So when West Nile first came in we had multiple heavy years of pretty steady transmission and now from year to year it's like oh it's a big year for Sacramento and it's not a big year for San Joaquin, so it moves around, so it's not exerting that constant pressure on that bird population. Crows definitely have had some impact, like they're the most sensitive, they're just exquisitely sensitive. But the odd thing about crows and this is somewhat of a sidebar, they're always underrepresented in mosquito blood meal ID studies. So you're like, 'Well why do we have all these dead crows if mosquitoes aren't feeding on them?' So that may be a function of just how a crow lives its life or how those blood-fed mosquitoes are collected. But yeah, I think that West Nile has a huge impact on those species.

Erin Welsh

Yeah. I had heard that about crows but I think that's really curious about the lack of representation in the mosquito blood samples.

Sarah Wheeler

Yeah, that's a big story right there. So it's been a source of debate about why we don't see them represented in blood meal ID studies and it isn't that they're not really an important amplifying host despite the fact that they're exquisitely sensitive to West Nile virus and of the birds that have been investigated for their response to West Nile infection, their viremias are some of the highest, right. So they produce the most virus in their blood, makes them extremely competent amplifying hosts. So it's like are they not important amplifying hosts with all this virus and a crow especially, they'll sit there moribund for like 2 or 3 days before they actually succumb to infection so they could just infect any mosquito that comes by to feed on them. And so but when you do these blood meal ID studies you find a lot of pigeons, you find doves, you find robins, you find a lot of other species like house finches and you're like well that leads me to believe that they're more important because that's what mosquitoes are feeding on.

Erin Welsh

That is so interesting. Yeah. And so it's not as cut and dry as the birds that are the most susceptible and the most abundant in a community or in an area are the ones that are going to play the biggest role in transmission or risk of exposure to humans. So are there these other ecological characteristics or certain species that do play a larger role as these reservoir hosts?

Sarah Wheeler

So I feel like I used to see this more clearly than I see it now. So I think that before we had a lot more information, we had some good baseline data on what types of viremias different species of birds kind of produced. So basically the higher the viremia, the more likely that a greater number of mosquitoes will be infected to the point where they will then be able to transmit. So that is on itself a spectrum. So a mosquito needs to be able to take enough virus from the bird in order for it to become infected to the point where then it can transmit. So birds that produce higher viremias ultimately infect more mosquitoes that can then themselves transmit.

I used to think okay, like pigeons and doves, they're not great amplifying hosts, crows, jays, magpies, house finches, house sparrows, these tend to be pretty good amplifying hosts especially the corvids. But it's like once you get out of the box of looking at a figure on a paper of what's known about different viremia profiles for different birds, it is a whole assemblage, it's a community of birds. And you know that even though there are certain patterns that are followed for a given species, individual to individual are gonna vary. At this point I mean we never even used to test mourning doves as a part of our dead bird surveillance program because it was like well they're not great amplifiers so we don't even really need to look at them because chances are that they died of something else.

Well on a whim we decided well let's just test this and it turns out that no, this species that's pretty much refractory to West Nile virus infection can actually still die of West Nile or it can die with a high amount of virus in its blood and tissues which you would think then is that it actually succumbed to infection. Maybe it didn't but it had a high amount of virus in its tissues. So it's created less steady ground for assertions that I would have made in the past like they're not really playing a role, a bunch of doves, maybe that would not be a community that would produce as much virus as you would think if there were more crows and jays and things like that around. So when you look at an area, there could be 200 species in that area. Some of them will maybe never amplify West Nile. But once you take that scale of birds and run it all the way up to say a crow is the most susceptible in a community, it's going to be a spectrum, right. It's a spectrum.

And so as far as do certain assemblages of birds create a more risky West Nile virus scenario? I think that from a very high level view urban areas tend to create assemblages of birds that can lead to amplifying events. But it's not ever the bird that is dangerous to people, it's the mosquito, right. So people don't have to worry about protecting themselves from the birds, they have to protect themselves from the mosquito. And so that's why really when we think about risk, we think about mosquitoes. And so we think about well how many mosquitoes are in this area? What proportion of them are infected with West Nile virus? What can we do to interrupt that transmission cycle? Cause it's easier to deal with it and focus on the mosquito and it's the more direct link to exposure. Yes, bird community matters, it matters. But it's variable and it's hard to absolutely state what's the best amplifying community, you know?

Erin Welsh

Right. Ultimately it comes down to the mosquito and how many mosquitoes there are in a certain environment and how often humans are out and so on. Yeah, absolutely. So let's talk a bit about bird migration. So we know that bird migration has an impact on potentially the geographic spread of West Nile virus and potentially other bird-associated pathogens. But how do things like the stress of migration impact bird communities or the immune systems of birds in making them more susceptible potentially to West Nile virus?

Sarah Wheeler	Yeah. So migration has been definitely a thing we've spent a lot of time thinking about. So there is somewhat of a mystery with West Nile and that's where is it going in winter? So overwintering mechanisms for West Nile virus are not well understood. It was always a possibility that West Nile was overwintering down somewhere where it's warmer, where you have year-round transmission, and then reintroduction in events were kind of by migrating birds bringing it into new areas every year. And maybe that could attribute to why we see it flare up in different places from year to year. Looking at the genetics of the virus this is not really supported but we did spend a lot of time looking at migratory birds to kind of figure out if they were spreading the virus around.
	At some point I was down in the Coachella Valley along the Salton Sea and every year we would go down there and collect as many migratory birds as we possibly can and collect a small blood sample and test that blood sample for both antibodies and viral particles. Basically has this bird been exposed to West Nile and is it currently infected? So it's a long shot looking for a viremia especially in a migrating bird because migration is a very costly event for those birds. So for them to be able to be fit enough to migrate while acutely infected, I don't know if that's possible. It may be, I mean birds are amazing, they could do it especially for short hops, maybe from one stop to the next they might get infected and then be able to carry it to the next hop. And then if it's a species that's so refractory to West Nile that it's able to migrate in an infected state, how is that going to play a role in transmission events?
	So there have been other researchers that have found some kind of indication of birds migrating while infected. So I'm sure it happens but when we look at the data for the birds coming in and the birds that we here, it just really seemed like the majority of the infection was happening here. So when we did find migrants that were infected with West Nile virus, they were heading back down south, they weren't heading north, they had been here all summer and were heading back down to their Central American overwintering grounds and they had already been exposed. And so it really seemed like it wasn't migratory birds that were constantly reseeding infection just by what we're observing with West Nile virus activity in the birds. It seemed there was something, that it was overwintering locally and flaring up and then as migrants were coming through there was always potential that they could be exposed and then hop it to the next location.
Erin Welsh	That is very interesting. It kind of turns a bit on the narrative that is so like birds that move from one place to another and that makes it so easy for it to spread, it might not necessarily be why we see these events happening. And so on that note, about how long or is there any sort of window during which an infection there is circulating virus in the birds that are susceptible and do seem to have this viremia, is there a length of time during which you can collect virus?
Sarah Wheeler	Yeah. So if you're looking at a bird who's just been infected by about 2 days you can detect virus in the blood. And then by about 7 days if it's not cleared, it's most likely not gonna survive.
Erin Welsh	Okay. And then is there lasting immunity following or can a bird get reinfected?
Sarah Wheeler	It seems to be lasting immunity.
Erin Welsh	Okay. So as someone who works in the applied side of things and has this research background as well, what do you see as the biggest challenges to West Nile virus control?

Sarah Wheeler	Honestly for West Nile virus we have to be able to have good effective surveillance methods, we have to have effective mosquito control tools. And so thankfully we've gotten a very efficient system for how mosquito are trapped and how they're tested, these are kind of pretty well worked out. But at this point in mosquito control there are two active ingredients that are used for controlling mosquitoes. So you have pyrethrins and pyrethroids and you have organophosphates.
	So these are the insecticide classes and they're used in many, many other fields. So they're common in agriculture, they're common like if that pest control guy comes by your house and is like, 'Oh you know you have spiders all over, I could spray for that.' Well they're spraying what we're spraying and so insecticide resistance is a growing problem and so as we move forward we're gonna have to find creative solutions for how to break that transmission cycle through effective mosquito control. And this will continue to be a problem moving forward cause mosquito control is a small slice of the insecticide usage pie, especially public health mosquito control applications. So there aren't generally products designed especially for mosquito control because it's not the largest market, you know.
	There are innovations that are coming out. So for a species Aedes aegypti which is a terrible vector around the world, it spread dengue and Zika and chikungunya, it's been invasive in a lot of areas of California. So we're now dealing with aegypti in California and throughout California. And so there's a lot of talk now about well can we use sterile insect programs to control these mosquitoes and I think that that's being used more and more, like it's still an emerging option and it might not be like what we can use for Culex control. But it's an example of thinking of new solutions to old problems and I think that that's what we're gonna have to continue to do moving forward is think outside the box and push the envelope.
TPWKY	(transition theme)
Erin Allmann Updyke	Thank you so much, that was awesome. We knew that we were missing such a big part.
Erin Welsh	I mean I learned a lot.
Erin Allmann Updyke	So much.
Erin Welsh	So tell me more.
Erin Allmann Updyke	Let's hear even more. So we'll just now focus on West Nile virus mostly in humans and look at the big picture, shall we? Focusing first on North America since that's where we ended your section, Erin. Since West Nile virus made its debut in New York in 1999 the virus has resulted in over 48,000 reported cases in the US, 24,000 of those have been neuroinvasive and it has resulted in over 2300 deaths.
Erin Welsh	Wow.
Erin Allmann Updyke	Yeah, in about 20 years. Now it's estimated that the true number of infections is over 7 million human infections in the continental United States.
Erin Welsh	Wow, wow.
Erin Allmann Updyke	Yeah.
Erin Welsh	I just keep saying wow.

Erin Allmann Updyke	That's all we can say. It's by far one of the most important zoonotic diseases and one of the most important causes of viral especially vector-borne encephalitis in the US since its introduction. And like you said Erin, it has spread throughout the entire United States, it's present throughout all of North America, it's likely present in Central and South America as well. But we don't have great data on Central and South America whether that's because it's overshadowed by other infections that look similar like maybe dengue fever or whether it's there but at very low levels or it's just not being reported, we don't really know. But we don't have good data on it. But even within the US while over 50% of counties in the US have reported at least one case over the course of time, they're not evenly distributed, cases are not evenly distributed and outbreaks tend to happen in discrete areas that vary a lot year to year.
Erin Welsh	Right.
Erin Allmann Updyke	So overall the actual number of reported cases in the US since its introduction has been, it varies a lot year to year but it hasn't necessarily been steadily growing or anything like that but you do see a lot of year to year variation and a lot of geographic variation. Like one year you'll have a whole bunch in Montana and another year a whole bunch somewhere else, etc. And it's not just humans of course, West Nile virus is a substantial animal pathogen, in the US it's caused over 28,000 cases in horses and mortality that we know of in over 300 bird species, like we heard a lot about already. In Canada over 5000 human infections have been reported and across Europe outbreaks happen almost every year. But the biggest outbreak especially in Europe by far was in 2018 when there were over 1500 cases that we reported across Europe, that was over 7 times as many cases as had been reported in the previous 7 years.
Erin Welsh	Dang!
Erin Allmann Updyke	Right? In one single year. And so whenever we see outbreaks like this that happen, like really big outbreaks all of a sudden especially of a vector-borne disease, we have to think about what are the factors environmentally that are impacting this? And Erin, you kind of touched on this a little bit but we're gonna get into it a little bit more.
Erin Welsh	Ooh yay.
Erin Allmann Updyke	And then of course we're gonna talk about (trumpeting sound) climate change.
Erin Welsh	Climate change.
Erin Allmann Updyke	So like many if not all of the vector-borne diseases that we've covered on this show, it's not entirely clear how climate change either is going to affect or has already begun to affect West Nile virus incidence, prevalence, and also distribution. But we can gather at least a little bit of information based on especially that 2018 Europe outbreak as well as just what we know about the mosquito and the virus. So given that West Nile virus is mostly transmitted by mosquitoes in the genus Culex, their natural ecology is such that in an increasingly warm climate it's very likely that that type of climate will increase both the abundance of these mosquitoes as well as increase their overall distribution. And like you mentioned Erin, if they're better at harboring virus in warmer climates compared to colder climates where they're maybe not as good of vectors, that's important as well.
Erin Welsh	Oh yeah, that's not good.

Erin Allmann Updyke	No, it's really not. And that outbreak in Europe in 2018, it turns out that that year was not only one of the hottest years ever recorded, it was also a very, very wet spring that was followed by a summer drought which likely led to a very early expansion of the Culex mosquitoes which led to an increase in viral transmission. So what we saw that year was cases being reported earlier in the year than ever before and then an outbreak that was the largest ever recorded, more cases like I said in the previous 7 years. And over a larger geographic distribution than had been previously recorded. That year alone cases were reported in Austria, Bulgaria, Croatia, Cyprus, Czech Republic, France, Greece, Hungary, Italy, Portugal, Romania, Serbia, Slovenia, Spain, Turkey. Everywhere.
Erin Welsh	Yeah.
Erin Allmann Updyke	So despite its global prevalence, despite it being such a common cause of mosquito-borne infection in the US for over 20 years, we still don't have any specific treatments and we still don't have any licensed human vaccines.
Erin Welsh	And with every year I feel like becoming the hottest year on record.
Erin Allmann Updyke	Right? Yeah, every year. Yeah.
Erin Welsh	Every year it feels like. This one.
Erin Allmann Updyke	There are at least four different animal vaccines, I think primarily for horses and there have been phase 1 and 2 studies of human vaccines but there haven't been any phase 3 or the larger efficacy studies and it seems mostly because there's not a market for it financially which is so frustrating. And what's even more frustrating is that we have vaccines for a lot of other Flaviviruses like yellow fever virus we have a vaccine, Japanese encephalitis virus we have a vaccine, now we even have a vaccine for dengue virus. Apparently from a paper from 2019 there have been at least 6 different candidates of vaccines that have gone through these phase 1 and 2 trials. At least two of them seem to produce good immunity after a single dose which is what would be needed for it to be a cost effective vaccine. None of the animal or the horse vaccines are single dose, they all require multiple doses as well as annual boosters.
Erin Welsh	Okay.
Erin Allmann Updyke	But there is at least promise I think both in terms of the immunology of West Nile virus and of Flaviviruses in general and then the fact that at least we have vaccines in phase 1, phase 2 trials, it seems to be kind of a funding issue, etc. But in general because of this lack of vaccine, control efforts really rely on prevention of infected mosquitoes, so things like integrative pest management, mosquito infection like you mentioned Erin, sentinel bird surveillance, and all of that to try and reduce the prevalence of infected adult mosquitoes. And that my friends, that's West Nile virus.
Erin Welsh	That's West Nile virus.
Erin Allmann Updyke	That was a fun one Erin, I learned a lot.
Erin Welsh	Yeah. It was a really interesting one. I can't believe we hadn't done this yet.
Erin Allmann Updyke	Right? We did it now.
Erin Welsh	We did it now, yeah.

Erin Allmann Updyke	Sources?
Erin Welsh	Sources. I have a lot of papers, I'm gonna shout out just two. And one is by Sejvar from 2000 titled 'West Nile virus: an historical overview' and the other that I wanted to shout out for fun is by our PhD advisor Dr. Brian Allan.
Erin Allmann Updyke	Yay yay!
Erin Welsh	And that is Allan et al from 2009 titled 'Ecological correlates of risk and incidence of West Nile virus in the United States'. And I also watched as I mentioned several videos on West Nile virus and I will post links to these, there were a couple ones that were especially helpful, 'West Nile Virus: The First Decade' by Richard Oehler, one on PBS, West Nile Outbreak in New York City', and then also a great interview with Tracey McNamara in this video titled 'One Health and the Lessons Learned from the 1999 West Nile Outbreak' and that is by Microbe World.
Erin Allmann Updyke	I also had a good number of papers, a couple of my favorites for the general overview of West Nile virus were both titled 'West Nile Virus', one from The Lancet Neurology 2007 and one from The Lancet Infectious Disease in 2002, so kind of older papers but still really good. If you want more info on the development of vaccines there was a paper called '20 years of progress towards West Nile virus vaccine development' in Viruses from 2019. And we'll post all of our sources from this episode and every one of our episodes on our website thispodcastwillkillyou.com.
Erin Welsh	We will. Thanks again so much to the amazing guests for this episode, we so appreciate you coming on to chat with us.
Erin Allmann Updyke	Yeah, thank you. Thank you also to Bloodmobile who provides the music for this episode and all of our episodes.
Erin Welsh	And thank you to Exactly Right of whom we are a very proud member.
Erin Allmann Updyke	And thank you to you, listeners. We really love making this podcast so thanks for listening to it.
Erin Welsh	Yeah. And a special shout out also to our amazing, incredible supporters on Patreon, we love you. You're amazing. And everyone, you only have a few more seconds to wait until your ears get to be blessed with the joyous sounds of MC Bugg-Z and West Nile Story.
Erin Allmann Updyke	Blessed. West Nile Story. Bring us out, Erin.
Erin Welsh	Wash your hands.
Erin Allmann Updyke	You filthy animals!
TPWKY	(West Nile Story by MC Bugg-Z plays)