TPWKY	This is Exactly Right.
Erin Allmann Updyke	"It just went completely white." This is how fisherman Akoyo Osumaka describes going blind in 2011 in the remote village of Babagulu in the Democratic Republic of Congo. It was a slow, creeping blindness that began a year earlier. It robbed him of his livelihood and threw his family life not disarray. Tragically, Akoyo had once fought against the disease that eventually robbed him of his sight by volunteering to distribute drugs that help prevent transmission of river blindness. The river Onane runs through Babagulu and is a perfect breeding ground for the black flies that swarm through the village, infecting people with filarial worms that cause river blindness.
	Akoyo is one of the many living in the village with the disease. Community leaders think that up to 3% of the community is blind. Okoyo felt the need to help so he volunteered to help distribute ivermectin. These programs rely solely on unpaid drug distributors to work with in their communities. He would travel to neighboring villages, often deep in the bush, to distribute the drugs. He was often bitten during his travels. One day his village had a stock out of the drug and he stopped taking it. "I was told to deliver all the drugs and then I would take it later once I started to have symptoms," he remembers. But then there were no more drugs to take. He then ended up missing distribution programs in his village because he was out fishing in forest streams.
	In 2010 Akoyo started to have difficulty seeing and in 2011 he went completely blind. His son Aito does not go to school and had to quit his job because of the stress of caring for his father. Aito has a number of nodules on his torso and forehead. The adult worms that cause river blindness live in these fibrous nodules. Taking care of his father is a full-time job. Ait also suffers from epileptic seizures about four times a month. Researchers have noted a potentially causal relationship between onchocerciasis infection and forms of epilepsy found in Africa. "I depend totally on my wife. She feeds and dresses me," says Akoyo. "Even my wife doesn't have a job. After I lost my sight, we couldn't send any of our children to school."
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	That's horrible.
Erin Allmann Updyke	Yeah, it's a tough and unfortunately not uncommon story.
Erin Welsh	Mm-hmm, yes. So that was adapted from an article titled 'Revealing the Neglect: River Blindness' from March 30th, 2018 on the website for Drugs for Neglected Diseases Initiative. And we will link to that story on our website and you should definitely check it out because not only is there more story to it but there's also a really cool video which is the story animated along with a traditional song recorded in Akoyo's region about river blindness. So definitely check that out. 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.
Erin Welsh	Welcome to another parasitic disease episode of our podcast.
Erin Allmann Updyke	I'm very excited about another parasitic disease, another vector-borne disease.

Erin Welsh	Yeah, me too. It's super complicated which gives us an opportunity to talk about all kinds of different aspects of this parasite, of this vector, of the human side of disease, of the history, it's complex is one word to describe it.
Erin Allmann Updyke	I think it's classic TPWKY, Erin.
Erin Welsh	Yeah. Actually it really is, it really is.
Erin Allmann Updyke	It is. Yeah.
Erin Welsh	So what are we even covering this week Erin?
Erin Allmann Updyke	We are covering onchocerciasis.
Erin Welsh	Aka river blindness.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	It is truly a very classic TPWKY episode in so many ways.
Erin Welsh	And speaking of classic TPWKY we have to start this episode with-
Erin Allmann Updyke	A quarantini!
Erin Welsh	A quarantini. What are we drinking this week?
Erin Allmann Updyke	We're drinking As The Worm Turns.
Erin Welsh	This is one of my favorite quarantini names.
Erin Allmann Updyke	We went back and forth for a long time but Erin won out, it is very good.
Erin Welsh	(laughs) And so I think that we were like, well we should save this because we're gonna do more wormy parasites in the future and this is a really good name should we do something else for this. But I found a quote from a researcher who was describing these that describes the worms as being undulating and turny and so it was just too good to pass up.
Erin Allmann Updyke	I mean they are very turny worms, like definitely. I agree.
Erin Welsh	They are. And also I really feel like now that we're getting into the whole 'worm' and 'world', swapping out those two words and idioms or whatever, we've got a whole host of opportunities for future quarantini names.
Erin Allmann Updyke	Exactly, this is not gonna be the end of the wormy world phrases.

Erin Welsh	Not at all. It's a small worm after all. I can't remember the other ones. Sitting on top of the worm. (laughs) Keep an ear out.
Erin Allmann Updyke	Oh goodness Erin, what is in As The Worm Turns?
Erin Welsh	Okay, yes. Let's do that. In As The Worm Turns is cognac, ginger simple syrup, lemon juice, and a splash of sparkling water and you garnish it with some candied ginger. It's actually really refreshing and good.
Erin Allmann Updyke	Yeah it sounds really good, it sounds both like warming and refreshing somehow at the same time.
Erin Welsh	Yeah. And we will post the full recipe for this quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com as well as on all of our social media channels, so make sure you follow us there.
Erin Allmann Updyke	Excellent. Any other business that we should attend to before we dive into this very interesting episode?
Erin Welsh	There's the usual stuff, go to our website, it contains links for merch, for bookshop.org affiliate account, for Goodreads reading list, for transcripts, for alcohol-free episodes, for anything. Any source you ever wanna find that we reference on this podcast, you can find it there.
Erin Allmann Updyke	Yeah. Definitely check out our website.
Erin Welsh	Okay. Is there anything else, Erin?
Erin Allmann Updyke	I think that you pretty much covered it quite well.
Erin Welsh	Wonderful, wonderful. Well in that case, should we dive into the episode?
Erin Allmann Updyke	Yeah, let's take a quick break and then we'll dive into the biology.
TPWKY	(transition theme)
Erin Allmann Updyke	So onchocerciasis is a disease that is caused by a nematode, a roundworm, named Onchocerca volvulus which is a type of worm known as a filarial worm which means it's a nematode transmitted by an arthropod vector. In this case onchocerciasis is also the second leading cause of infectious blindness worldwide after trichoma which is a bacterial disease caused by chlamydia trachomatis. So since this is an arthropod vectored worm, let's jump straight into talking about the transmission and life cycle of this parasite, shall we?
Erin Welsh	Let's do it.

Erin Allmann Updyke	So the overall life cycle of this parasite is not very dissimilar from a number of vector-borne diseases that we've covered on this podcast but it is a different vector species than we've seen before. In this case it's a black fly in the genus Simulium. The black fly bites your skin, generally much like mosquitoes it's female black flies that bite a human, take a blood meal and in that blood meal ingest microfilariae which are the earliest teeny, teeny baby, newly hatched larval stages of Onchocerca volvulus. These microfilariae travel through the fly's gut - this is where it gets weird - they penetrate the gut walls, which we've seen other parasites do but in this case they migrate to the flight muscles of the fly. Like what?
Erin Welsh	Very weird.
Erin Allmann Updyke	Very weird. I just have to imagine there's a lot of like glucose happening because those are important, powerful muscles but I don't know. So in these flight muscles they live for a short time and in that time they mature into a second stage larva. And then from there they make their way down into the salivary glands near the proboscis, they mature one more time into a third stage larva and are now infectious. So that when the black fly takes its next bite of human flesh, they can spit out those third stage larva just under our skin. So that whole process in the black fly takes about a week give or take and now in the human these larvae that have been injected just under our skin will worm and twirl, as the worm twirls-
Erin Welsh	As the worm turns, mm-hmm.
Erin Allmann Updyke	(laughs) They'll worm their little way into our subcutaneous tissue and that is where they will live. They'll make a little home for themself in these little subcutaneous nodules that they kind of build and create and there they're pretty well protected from our immune system, which will become important later on. They feed off of our blood, both by actively feeding but also just by soaking up nutrients through their cuticle. And over a period of about 10-15 months or so, they mature into adult worms, they mate, and the begin releasing thousands of eggs which quickly hatch into microfilariae everyday. During the day these little microfilariae worm their way back up to the skin's surface where they can then be ingested by black flies which, coincidentally, bite during the day, thus completely their life cycle.
Erin Welsh	Question.
Erin Allmann Updyke	I know.
Erin Welsh	So you said that when the L3 larvae are injected into a person they form this little subcutaneous nodule in which they're fairly protected form the immune system. How? Like why are they fairly protected there? Because a lot of things could be injected into our skin and not be protected from our immune system.
Erin Allmann Updyke	Yeah. It's a very good question and it's a question that I don't have a good answer to. I will talk in a lot more detail about what causes an immune reaction to us but the question of why is it that living worms don't provoke much of an immune response in us is a very good one and not one that I have a good answer to.
Erin Welsh	And is that universally or are there people that do show immune responses and are like more protected from this parasite than others?

Erin Allmann Updyke	So people don't tend to show immune responses to the living worms aside form the formation of these nodules which you could think of as some kind of an immune response because it's kind of like making a little fibrous sheath around those worms and kind of walling them off from the body in some ways. But otherwise there's not much of an immune response that's provoked by the presence of the live worms themselves.
Erin Welsh	That's wild.
Erin Allmann Updyke	I know, it gets wilder!
Erin Welsh	So the immune system isn't even showing elevated antibodies or is it suppressed? Like are people who are infected with this worm, are they more susceptible to other infections? Sorry I'm kind of going like down the rabbit hole of questions here.
Erin Allmann Updyke	(laughs) You're going so many miles a minute. Let me keep going. And I'm not sure if I'm really gonna answer your questions or if I'm just gonna bring up even more questions, let's find out.
Erin Welsh	I'm along for the ride either way.
Erin Allmann Updyke	Excellent, good, I'm so glad. Okay so these adult worms that are living in these nodules, they can live for years. We're talking 10-15 years or more.
Erin Welsh	Oh yeah.
Erin Allmann Updyke	Okay? And this whole time they're producing thousands if not millions of microfilariae that whole time, not continuously, they kind of cycle like every 2-4 months or so they'll have a cycle but anyways. 10-15 years.
Erin Welsh	I have an estimate that I wrote down because I was so horrified. So the number of microfilariae released from one female adult worm during its life of 10-15 years is estimated to be greater than 10 million.
Erin Allmann Updyke	Yeah, that seems about right. Cause it's like 2-300,000 per cycle.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	That's a lot.
Erin Allmann Updyke	It really is. Okay. And so before we get into what the symptoms of this disease are, what I wanna tell you, you're gonna get mad at this, all of the symptoms that we see stem not from the worms themselves but from our immune response to the worms.
Erin Welsh	Oh, but hold on. You made a very strong point of saying the living worms, so I'm guessing these are dead worms.
Erin Allmann Updyke	I did. You are exactly right.
Erin Welsh	(laughs) But your right, I was like wait a second Erin. Then I remembered.

Erin Allmann Updyke	I know. So it turns out that they do not trigger these intense immune reactions until they die. So of course we have to answer the question why the heck and how the heck. So it's thought that the immune response that is triggered is in part due to proteins and other inflammatory markers that are released by the dying worms themselves. So proteins and things that are inside the worms but then not accessible to our immune system until that worm dies.
Erin Welsh	Okay.
Erin Allmann Updyke	But far more importantly and interestingly, it's also thought to be due largely to the release of the bacterial endosymbionts that they harbor. Say what!
Erin Welsh	It's so strange. Wolbachia has so many mysteries that surround it.
Erin Allmann Updyke	Wolbachia. So many mysteries. So we have talked about Wolbachia on this podcast before briefly in I think our dengue episode because they're important in the context of mosquitoes that transmit dengue and other arboviral diseases.
Erin Welsh	Yeah.
Erin Allmann Updyke	But basically as a recap, Wolbachia are a genera of bacteria that often inhabit the guts of insects and other invertebrates but it turns out that in filarial nematodes like Onchocerca volvulus but also Wuchereria bancrofti, which is the causative agent of lymphatic filariasis and other nematodes, these bacteria are essential endosymbionts. So without these bacteria the nematodes cannot survive or reproduce. We still don't know exactly what it is that they are doing necessarily but we do know that they are essential to the process of embryogenesis. So eggs can't develop into worms without the presence of these bacteria which are transmitted transovarially.
Erin Welsh	That is so interesting.
Erin Allmann Updyke	I know. And it seems that based on a lot of data the release of these bacteria from dead worms is thought to be a major part of the trigger for our immune response.
Erin Welsh	And so how does this trigger look different compared to other parasitic infection triggers? You know what I mean?
Erin Allmann Updyke	So that's what's so interesting is that what we see is still a lot of eosinophil response which is what you would expect with a parasitic disease. Not solely though, antibodies have a large role as well in the inflammation and the immune response to onchocerciasis as do neutrophils and other lymphocytes, and these are all different types of white blood cells. But you still do see a really large eosinophil response which is interesting. So maybe those are responding to the worm parts and it's the neutrophils and lymphocytes and antibodies that are responding to the bacteria, who knows. We don't fully know. But I'm also gonna put a pin in that and I just want for us to remember how important wolbachia are cause we'll talk more about them in the current events section. Okay?
Erin Welsh	Oh yeah. Yes.

Erin Allmann Updyke	All right so then what does this disease actually look like? In its mildest form, it's possible that the only symptoms that you would have are these nodules that we've talked about. So these nodules are very kind of hard, deep, subcutaneous lumps I guess is the best word, often around the hip girdle but you can also have them really anywhere throughout your body. They tend to be most prominent where you have a bone, just because then you have less subcutaneous tissue between your bone and your skin. But in terms of symptoms that we see, the mildest symptoms present as a skin rash which is usually what we call maculopapular, that means a flat area of rash with a lot of little bumps on it that is incredibly itchy.
Erin Welsh	Right.
Erin Allmann Updyke	I think the word 'itchy' I feel like doesn't-
Erin Welsh	Doesn't quite do it justice.
Erin Allmann Updyke	Right, it's doesn't invoke I think the response that this really deserves.
Erin Welsh	No.
Erin Allmann Updyke	Yeah. So it's yeah, I wish I had a better word than just incredibly itchy. So this rash can resolve in some cases although the disease itself does not resolve, like we said, these worms can live for years. But more commonly this rash can become chronic and can actually generalize across the body instead of being present in just discrete patches. And this, as you can imagine, leads to even more severe itching. And then as our immune response ramps up, the way that our skin kind of heals results in very severe scarring. It's what's called lichenification, like a lichen that grows on a tree.
Erin Welsh	Yeah.
Erin Allmann Updyke	So it's like our skin becoming really thick and leathery. At this stage it can lead to hyperpigmentation of the skin, so it becomes very, very dark in patches. And like we talked about in our leishmaniasis episode, these types of skin manifestations can be associated with a lot of stigma and so they can be debilitating not only in the physical sense, like the amount of itching, I saw it described where some people couldn't even sleep except for on their knees and elbows because of the pain of the itching.
Erin Welsh	Yeah I saw some descriptions of people literally burning their skin because it was so horrifyingly itchy.
Erin Allmann Updyke	Itchy. But it can also be debilitating in the way that it is stigmatizing as well. And then over years of this infection, the changes can become even more chronic and the descriptors of these changes in the literature I think are also pretty stigmatizing, but basically what can happen is the skin can end up with its elasticity completely destroyed because of all of that damage to the kind of mid layers of the skin. So then the very top layers become really thinned out, they become atrophied, they're quite wrinkly and they can just sort of hang off of the body, you can lose pigment entirely in those areas because of all the atrophy. And so the skin manifestations can be severe. And this whole time, even as it becomes chronic, that itching persists.
Erin Welsh	Okay, question real quick again about the nodules. Where those nodules exist is where the black fly has bitten you?
Erin Allmann Updyke	Great question.

Erin Welsh	Or how much variation is there?
Erin Allmann Updyke	Yeah there's quite a lot of variation which is so interesting. So from what I read, black flies often like to bite on lower extremities, so they really bite a lot on legs. But these nodules tend to be present on the hips or even the forehead and on the head. So that would suggest that these adults worms can travel and decide where they're going to make their nodule home, but it also means that the microfilariae which are traveling to the skin's surface can also travel a really long way, they can go pretty much anywhere in our body.
Erin Welsh	Right.
Erin Allmann Updyke	Yeah.
Erin Welsh	And I also thought I read somewhere too about because, and I know you haven't gotten to this part yet but the Americas vs Africa in terms of the location and frequency of the skin nodules, black flies have different biting patterns, right? They bite more on the upper half of the body in the Americas compared to Africa where it's on the lower parts of the body.
Erin Allmann Updyke	I would believe that because I did read about more forehead nodules and things in the Americas compared to in Africa. Yeah.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	So that's kind of all of the skin manifestations which is one of the most important parts of this disease. The other is of course the ocular or the eye manifestations. That's where it gets the common name river blindness. So as these microfilariae travel out of nodules and towards the skin, some of them can travel to the eye. In the eye, the microfilariae that die also cause a localized inflammatory reaction and this results in a number of different manifestations. Kind of the most common one is called sclerosing keratitis which is where the cornea of your eye, which is the part that covers your iris and your pupil, that becomes inflamed and then will scar over. So this starts with a haziness around the edges of the cornea and then will eventually go in to encompass the entire thing causing complete blindness.
Erin Welsh	Ugh, yeah.
Erin Allmann Updyke	It's not only sclerosing keratitis because you can have these worms that end up in the posterior part of your eye which can cause inflammation of the retina and similar kinds of damage due to inflammation in all parts of the eye. And I think it's also important to point out that these microfilariae can travel kind of throughout the body and invade, for example, our lymphatic system and they've been found in a number of different organs. Like if you sample organs from someone who's died who was infected with onchocerciasis, you can find microfilariae in a number of different organs but we don't really have a good handle on what kind of disease might be caused by that. It's really the skin and the eye that are the two most common organs affected.
Erin Welsh	Right.
Erin Allmann Updyke	So yeah. I also want to mention because it's important but also because it was brought up in our firsthand account, there does seem to be increasing evidence that infection with onchocerciasis is also associated with an increased risk of epilepsy.

Erin Welsh	Is there any suggestion as to what the mechanism could be?
Erin Allmann Updyke	None at all.
Erin Welsh	Okay.
Erin Allmann Updyke	Which is the hardest part. So there's a lot of epidemiological evidence of association but there's not really any data on what could be the cause or the mechanism. So we don't really know if it is in fact onchocerciasis or something else.
Erin Welsh	Okay.
Erin Allmann Updyke	But there is epidemiological evidence for this association so I thought it was important to mention.
Erin Welsh	Yeah, definitely. Yeah.
Erin Allmann Updyke	Yeah. So yeah, that's kind of the basic overall picture. I think it's interesting that there does seem to be some strain differences. So in parts of West Africa it's long been noticed that in the savanna regions, the rates of blindness due to Onchocerca were much higher than in forested regions of West Africa. And in those savanna regions the rates of blindness really strongly correlate with the intensity of infection, so the more heavily infected somebody is, the higher their risk of ocular complications. But in other areas like in forested regions that doesn't seem to be the case. And so it turns out that there are different strains of Onchocerca volvulus but what I think is so interesting about this is that there's also some evidence that part of the differences in these strains is how much wolbachia they carry, Erin.
Erin Welsh	Mm-hmm. And it doesn't seem to be just that, as I'll get into. But yeah, that's definitely an interesting component for sure.
Erin Allmann Updyke	Yeah. Oh my gosh. So that's pretty much the whole biology aside from treatment. Do you have any questions Erin before I talk briefly about treatment?
Erin Welsh	Did you say already how long these worms are? How big they are?
Erin Allmann Updyke	No I was just about to!
Erin Welsh	Okay. (laughs)
Erin Allmann Updyke	These worms, the adult females get to be about 30-80 centimeters long which is over a foot or two.
Erin Welsh	That is very long and yeah, wow.
Erin Allmann Updyke	And then in each nodule you'll also have one or two males, but what is fascinating is that these males travel around nodule to nodule, they go like beep-boop-boop-boop, traveling along because the females have to be re-inseminated every time they have a reproductive cycle.
Erin Welsh	Interesting.

Erin Allmann Updyke	Isn't that cool? By the way, the microfilariae are so, so, so tiny, they're like 200-300 microns which is about the length of two sheets of paper is wide. If that makes sense.
Erin Welsh	That's very tiny, yes.
Erin Allmann Updyke	It's very small. And then they grow up to be quite large.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	Okay so what do we do about it?
Erin Welsh	Yeah.
Erin Allmann Updyke	We do have something that we can do which is phenomenal. Treatment though, like I said, we can't just kill all of the adult worms outright because that would trigger a huge immune response. So treatment is actually via a drug called ivermectin which is an antiparasitic that is very effective at reducing the load of microfilariae in the skin for several months at a time, which helps not only with symptoms but it also reduces the risk of complications like blindness. It doesn't though kill the adult worms at all, not even slowly. What's so fascinating is that ivermectin is a neurotoxin and it works on channels that we have as vertebrates, as mammals, but we have a blood-brain barrier so in us it doesn't have the same effects.
Erin Welsh	Oh.
Erin Allmann Updyke	Isn't that cool? So it's actually a very safe drug, which is awesome for humans, not for worms.
Erin Welsh	Yeah.
Erin Allmann Updyke	But while it causes a flaccid paralysis and eventual death in the microfilariae, in the adult worms what it does is just kind of block them from releasing eggs for a short period of time. So it's thought to kind of paralyze their reproductive tract but not much else.
Erin Welsh	Okay.
Erin Allmann Updyke	Which is so fascinating. I tried so hard to get the 'why'. Why can't this kill an adult worm? But I don't have the answer to that, I don't know.
Erin Welsh	Yeah that's very interesting.
Erin Allmann Updyke	It's so interesting.
Erin Welsh	Very strange.
Erin Allmann Updyke	Yeah. But that's the biology of onchocerciasis.
Erin Welsh	It's a big one.
Erin Allmann Updyke	It's a big one.
Erin Welsh	It's complicated.

Erin Allmann Updyke	It's so interesting.
Erin Welsh	It's so interesting, there's so many steps and there are so many different components and that's sort of the theme also that I will talk about in the history.
Erin Allmann Updyke	Would you please? Would you please? I'd love to hear it.
Erin Welsh	Let's take a quick break first and then I'll dive right in.
TPWKY	(transition theme)
Erin Welsh	I feel like I start off most of these histories or at least a lot of these histories, especially in episode about parasites, saying that this disease has been around forever, like millions of years forever. And then I go on to talk about how there was this fossilized poop found or evidence of infection in a mummy.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so I was surprised when I started researching for this episode that I wasn't finding any of that for onchocerciasis.
Erin Allmann Updyke	None of it?
Erin Welsh	Where were my Ancient Egyptian papyri? Where were my coprolites? None of it. Maybe they are out there, still waiting to be found either by me in the literature or by a budding paleo-epidemiologist or something like that. Let us know if you find anything. But most articles I read discuss the early history of onchocerciasis as starting either at the evolutionary roots of the parasite that causes the disease or they jumped ahead to the early scientific work classifying this parasite and detailing its transmission route and disease characteristics. And so we'll get to that part eventually but first I want to go back, of course, to the evolutionary ecology of this parasite.
Erin Allmann Updyke	Yes.
Erin Welsh	Where did it come from? How did it get to be distributed the way it currently is? And what role does the ecology of this complex parasitic infection play in it establishment and continued persistence?
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay here we go. This disease, onchocerciasis, exists in two main areas of the world, Africa where 99% of cases occur, and Central and South America where it's a lot more localized and less prevalent, partly because of control efforts that I'll go into later and partly because of the history and ecology of the parasite itself. And so based on this distribution, it's probably not that surprising that the parasite evolved in Africa and then was brought to the Americas at some point during the slave trade beginning in the early 16th century.
Erin Allmann Updyke	Makes sense.

Erin Welsh	But what may be surprising is that although the genus Onchocerca is likely millions of years old and also originated in Africa, the species that causes river blindness, Onchocerca volvulus, is a relatively recent parasite of humans.
Erin Allmann Updyke	Okay I saw that somewhere and I was like what!? And then I didn't read anymore cause I wanted you to tell me about it.
Erin Welsh	I know! Okay, okay. Well because genetic analyses that have compared many different species in the Onchocerca genus show that Onchocerca volvulus likely evolved from the ancestor of Onchocerca ochengi which is a parasite of African savanna bovids.
Erin Allmann Updyke	Okay but I'm so confused by that Erin because Onchocerca volvulus is pretty much a human-specific parasite.
Erin Welsh	Yes!
Erin Allmann Updyke	So that doesn't make sense.
Erin Welsh	This evolutionary pathway, this speciation is supposed to have occurred only within the last 10,000 years or so.
Erin Allmann Updyke	What?
Erin Welsh	Because it's supposed to correspond to the period when cattle were domesticated and that's when humans would have come into contact.
Erin Allmann Updyke	What are you telling me?
Erin Welsh	Well there's a side note too. Cattle were domesticated between like 10,000 and 37,600 years ago in parts of Asia but domestication is actually thought to take place later in Africa, like maybe between 4000 or 1500 years ago.
Erin Allmann Updyke	What?
Erin Welsh	And so it might be that this parasite evolved so rapidly.
Erin Allmann Updyke	Rapidly?
Erin Welsh	Yeah.
Erin Allmann Updyke	That's bananas!
Erin Welsh	I know and there's more on this too.
Erin Allmann Updyke	Oh my gosh.
Erin Welsh	So for much of that 10,000 year history, let's just call it 10,000 years.
Erin Allmann Updyke	Okay.

Erin Welsh	This parasite stayed in Africa, it drove human settlement patterns in such a way that perhaps people would settle near a river or a lake and then as more and more people developed this horrifically itchy skin condition or they lost their vision, they moved away to land that was further away from these sources of water, so the land was often less arable, it was more susceptible to erosion. And by the way, this is still happening today, like for example in parts of Ghana where people have moved away from these high onchocerciasis prevalence areas to more crowded, less arable areas that have led to an increase in nutritional deficiencies and food instability. But I'm getting ahead of myself. So yeah, so let's go back to this remarkably short evolutionary history.
Erin Allmann Updyke	Wow.
Erin Welsh	This is an obligately human parasite.
Erin Allmann Updyke	Yeah.
Erin Welsh	Like they have shown incidental infections in a gorilla I think I've seen or in some other animals but it is human specific.
Erin Allmann Updyke	Right, there's no animal reservoirs for Onchocerca volvulus, it's a human disease.
Erin Welsh	Right. And so within a relatively short time span, like let's say conservatively 10,000 years, this parasite went from a bovine host to just humans as hosts.
Erin Allmann Updyke	That's truly remarkable.
Erin Welsh	And so this definitely seems like there were some strong forces that drove speciation.
Erin Allmann Updyke	Yeah.
Erin Welsh	And there's also some evidence that suggest that there might be speciation happening currently within the parasite species Onchocerca volvulus.
Erin Allmann Updyke	Stop it.
Erin Welsh	Yes. And you touched on a little bit of this in talking about the strains.
Erin Allmann Updyke	Ooh, okay.
Erin Welsh	And I wanna talk a little bit more about that and about the ecology of this system overall.
Erin Allmann Updyke	Okay.
Erin Welsh	So as you mentioned, this parasite species is transmitted by multiple species of Simuliidae black flies and the distribution and habitat preferences of these black flies varies quite a bit. And warning, this is going to be oversimplified.
Erin Allmann Updyke	Okay.

Erin Welsh	But in Africa, for instance, you have some black fly species that are savanna dwelling and those that are forest dwelling. And you mentioned that there are savanna strains of the parasite and forest strains of the parasite. And these different black fly species transmit those corresponding strains of Onchocerca volvulus.
Erin Allmann Updyke	Yeah.
Erin Welsh	And what happens when researchers try to take a savanna strain of the parasite and put it in a forest dwelling black fly, they found that the parasite developed poorly or not at all. And the same thing happened with the forest strain of the parasite in the savanna dwelling black fly.
Erin Allmann Updyke	What Erin?
Erin Welsh	Yes.
Erin Allmann Updyke	And there's some regions that they can be co-infected, so is that maybe like... I'm getting too complicated, doesn't matter.
Erin Welsh	Well what it seems is that that's fairly uncommon. Like it's happening more today possibly because of control efforts and how that sort of changed the landscape of disease in this case, but at least like historically it really does seem that there has been some sort of barrier preventing the mixing of this savanna strain and this forest strain of the parasite.
Erin Allmann Updyke	What?
Erin Welsh	And so what some researchers think is that these different parasite strains may actually be diverging from one another.
Erin Allmann Updyke	So we're gonna end up with two species.
Erin Welsh	Mm-hmm. Possibly.
Erin Allmann Updyke	Oh my gosh.
Erin Welsh	And it also makes sense because these parasites rely so heavily on these flies for their transmission and development that they may become in a sense reproductively isolated quite easily. So basically how I was thinking of it was that the adaptations that these parasites have to survive and develop in one black fly species might not be the same ones that would allow them to do the same in others. And for what it's worth, these parasites don't seem to be harmless hitchhikers for these flies, at least for some of the species or vector parasite complexes and there have been some studies confirming that some black flies show innate and acquired resistance to filarial infection.
Erin Allmann Updyke	Oh I love that, I love when insect vectors have fight responses and fight back.
Erin Welsh	Fight back? (laughs) Yeah and so because there's such like, let's call it a tenuous relationship between the parasite and vector, it might be that putting all of your adaptive eggs in one black fly basket might be a favored strategy in terms of evolution.
Erin Allmann Updyke	Yeah you get really well adapted to that specific immune response.

Erin Welsh	Mm-hmm, mm-hmm. In any case, this diversity of black fly species and the complicated interactions between different strains of the parasite and different species of fly is just one example of the incredibly complex disease ecology of this parasitic infection. And I also think that this episode is a great opportunity to talk a bit about disease ecology in this context.
Erin Allmann Updyke	Yeah.
Erin Welsh	Because we get a lot of emails from people asking us the difference between epidemiology and disease ecology and I feel like even though I technically have a degree kind of in both, I still don't feel very qualified to go into those differences.
Erin Allmann Updyke	Same.
Erin Welsh	But I'm gonna try. (laughs) So there's a lot of overlap between these two fields and I think that this disease is a good way to show at least some examples in ways that the approaches or research questions could be different. And so overall, epidemiology is often defined very broadly as the study of patterns of disease and health in populations. And disease ecology is more concerned with the role that the environment and evolution play in the interactions between host and parasite. And so for example in the case of onchocerciasis, the transmission of the parasite depends on so many things that are influenced by the environment.
Erin Allmann Updyke	Right.
Erin Welsh	Which vector species is present? How abundant is that vector species? What are the things that determine its abundance? What season it is, what habitat it's in. And within a certain season or even a certain time of day, things like relative humidity, temperature, wind velocity, light intensity, rainfall, all of which could influence transmission in some way. And there's evidence to suggest that a lot of these factors do.
	And so a disease ecologist might ask something like how does the seasonal biting activity of different Simuliidae black fly species change across these different environments and how is that associated with the output of L3 larvae by those black flies? Like all of these things are sort of what role does the environment play in the transmission? And getting a better sense of the different factors at play can help to focus control efforts in a lot of ways to make them more impactful for more efficient. Like for instance, is there a distinct wet season, like a distinct wet and a distinct dry season? And should one of those seasons be targeted more for breeding sites for the flies? And should that time of year be targeted more for habitat removal or habitat spraying?
	And an epidemiologist conversely might ask about the geographical variation in infection prevalence and how these prevalences might be associated with past spraying or ivermectin campaigns. And a lot of these epidemiological questions, the way I look at it is that they help to get a sense of the extent of the disease, how human behavior or experience plays a role in the exposure, or to measure progress in control efforts. Erin, did I miss anything with disease ecology?
Erin Allmann Updyke	No that was really good, also how fun to get to talk about just broadly disease ecology and epidemiology.

Erin Welsh	Well it's really fun because as I was reading about the ecology of this system, and I didn't do a very comprehensive job of explaining it but I was struck by the number of questions that you could ask about how is the black fly feeding. Like at what time of day? What part of the body is it feeding on? What time of year? How does the current filarial load in the fly influence behavior? Like all of these things, I know, another PhD. PhD take two.
Erin Allmann Updyke	It's just so funny Erin because as you're talking about all that, I can hear how excited you are and I'm also getting so excited and so it's just so funny that of course this is a disease that would get us so excited to be asking these questions and that's why we did the degrees that we did. It all comes full circle.
Erin Welsh	Yep, yep. And I love too, like this is such a good example of the ways in which that barrier between epidemiology and disease ecology isn't really a barrier at all, it's very fluid.
Erin Allmann Updyke	Right. Eco-epidemiology, yo. You know what I'm saying? (laughs)
Erin Welsh	(laughs) There we go. And so it's really cool to see how the data derived from these two different fields in terms of research questions could be used synergistically or in the same applications. And I just love it.
Erin Allmann Updyke	Right. Well I'm also like can we get some immunologists to join this party too? Cause I still can't get over that this is a newly evolved human specific parasite that is so good at evading our immune response.
Erin Welsh	I know.
Erin Allmann Updyke	Like are you kidding me?
Erin Welsh	I know.
Erin Allmann Updyke	We should get back to onchocerciasis though.
Erin Welsh	Let's get back to onchocerciasis, yeah. We do need to do a careers episode one day.
Erin Allmann Updyke	Yeah, we do.
Erin Welsh	We wanna have other people define what an epidemiologist does and what a disease ecologist does. But yeah, I just wanted to kind of go through this because I think onchocerciasis with its three player cast of human parasite vector and its super close ties to environmental factors is a great way to think about how the environment ends up shaping transmission patterns leading to human disease.
Erin Allmann Updyke	Absolutely.
Erin Welsh	Okay. So I've talked for a very long time about evolutionary history and disease ecology in general but I haven't even started on the written history of onchocerciasis.
Erin Allmann Updyke	Let's get started.

Erin Welsh	But don't worry, it's a pretty straightforward story so it's much more straightforward than its ecology, I'll say that. Before I begin, I also want to acknowledge that before the quote unquote "discoveries" of western scientists regarding this disease, the people who lived in Africa among this disease for thousands of years were already well aware of several aspects of onchocerciasis including the association with rivers or bodies of water, the role of the black fly in transmission, and both the skin and blindness manifestations of disease. But you know, this long standing knowledge is rarely if ever noted in the official histories of scientific achievements, not just in terms of onchocerciasis but in terms of many, many diseases that we have covered or will cover.
Erin Allmann Updyke	Right.
Erin Welsh	So taking that into consideration, where do these official histories begin? In 1874 there was a British naval surgeon by the name of John O'Neill who was assigned to the HMS Decoy off the coast of what is now Ghana. He noticed several people living along the western coasts of Africa had an itchy and irritating skin disease with nodules and pustules. Locally it was called craw-craw and he thought at first could this be scabies? And so he examined some of these nodules under a microscope and quote: "Succeeded at length in discovering a filaria which I believe to be the immediate cause of complaint. Thread-like in form, at one time undulating and now twisted as if into an inexplicable knot. Then having rapidly untwined itself, it curls up into many loops." It's a very poetic description of a filaria, yeah.
Erin Allmann Updyke	It is.
Erin Welsh	O'Neill's observations of this parasite were followed pretty closely by Rudolf Leuckart who in 1890 received a nodule of worms the size of a pigeon's egg that an unnamed German surgeon had removed from someone also in the Gold Coast that is now Ghana.
Erin Allmann Updyke	Actually, how big is a pigeon's egg?
Erin Welsh	Actually that's a great question. I'm gonna look it up. A pigeon egg is smaller than a chicken egg. Looks like to me it's like 1/2 the size to 2/3 the size.
Erin Allmann Updyke	Yeah, I would say that.
Erin Welsh	So he received this nodule the size of this pigeon's egg from this guy who had sent it to him asking for identification. And Leuckart looked into it and he didn't make any announcement of his own regarding the description of the adult form of this worm but he did tell the famous parasitologist Sir Patrick Manson who published a note in which he gave Leuckart credit for both the discovery as well as the naming of the worm, which eventually because Onchocerca volvulus. 'Onchocerca' from the Greek words meaning barber tail and 'volvulus' from the Latin for to roll or turn. As the worm turns.
Erin Allmann Updyke	(laughs)
Erin Welsh	(laughs) By this time several other helminth species had been discovered in Africa and elsewhere and Onchocerca volvulus didn't really seem to attract any particular interest which I find interesting.
Erin Allmann Updyke	Yeah.

Erin Welsh	I mean they simply noted it as 'it's probably this old disease' and also they seemed to think that it was more of a rare curiosity rather than a common occurrence, but that belief would later be turned on its head. So despite the much higher prevalence of river blindness in Africa compared to Central and South America, a good chunk of the big leaps forward in terms of understanding this disease were made by Rodolfo Robles in Guatemala. In 1917, he published a report linking the parasite to blindness as well as the dermatitis that had previously been observed. And the link between blindness and the parasite wouldn't be discovered in Africa for another decade or longer by researchers working there, which I find very interesting.
Erin Allmann Updyke	Yeah.
Erin Welsh	And I wonder if one of the reasons for that is because of the biting preferences of the black flies in Central and South America compared to Africa.
Erin Allmann Updyke	Like that they were more kind of visible?
Erin Welsh	More visible, more... No I mean in terms of the blindness, that there happened to be more nodules on the face and head compared to Africa. I don't know. But Robles also suggested that Simuliidae black flies might be responsible for transmission of the filariae and that removal of the nodules might provide relief in symptoms. And speaking of nodules, in his quest to see whether these parasitic worms were the same species as Onchocerca volvulus or if they were a New World species, spoiler alert: they're the same species, he was wrong. He had a hard time getting the worms out of the nodule intact and so he used, quote, "the novel technique of removing the fibrous tissue by active digestion in the stomach of a living dog."
Erin Allmann Updyke	(laughs) What?
Erin Welsh	Yeah, that's all the explanation that I found for that one.
Erin Allmann Updyke	So he fed the nodules to a dog.
Erin Welsh	He fed a dog this nodule. Mm-hmm. Who then presumably pooped out worms.
Erin Allmann Updyke	Pooped out worms or did he like induce vomiting or something?
Erin Welsh	Oh that's another possibility. I don't know.
Erin Allmann Updyke	I don't know either.
Erin Welsh	Yep.
Erin Allmann Updyke	It's weird that it was effective, honestly.
Erin Welsh	It's weird that he thought of it.
Erin Allmann Updyke	(laughs) There's a lot that's weird.

Erin Welsh	There's a lot that's weird. And the next big jump in onchocerciasis research was when Donald Blacklock made the link that black flies were responsible for transmitting the parasites through observations of the guts of Simulium black flies. Robles had just suggested it but Blacklock actually did the experiments. Although again, this link I wanna say was well known among people who had been living there.
Erin Allmann Updyke	Right.
Erin Welsh	By the 1930s, interest in onchocerciasis had picked up and scientists had started to realize that it was much more widespread than previously thought. But they were still missing one big piece of the puzzle, the piece that Robles had found nearly 20 years before, the link between the parasite and blindness. In 1931 or 1932, I can't remember, a researcher named Gene Hissette published a report that showed that in a part of the Democratic Republic of Congo, 20% of the people with onchocerciasis were blind and 50% of that population suffered from eye troubles. Unlike in many other places in Africa, the nodules and cysts were concentrated on the head rather than lower down the body which was also kind of the pattern in the Americas. And although Hissette's work seemed to show a clear connection including he found microfilariae throughout the eye, the link wouldn't be widely accepted until the mid 1940s at the earliest.
Erin Allmann Updyke	Wow.
Erin Welsh	Which also coincided with this period of increased European troop presence in onchocerciasis prevalent areas.
Erin Allmann Updyke	Not unsurprising.
Erin Welsh	Not unsurprising. As researchers got a better handle on the scope of the disease and the devastating effects that it could have, campaigns to control or eliminate the disease were started. The earliest campaigns targeted the vectors of the parasite, relying on the use of DDT which was developed in 1941 and found to be extremely effective as an insect killer and also as Rachel Carson has made us all aware, as a killer of many other things. Some of these early control programs seem to actually be quite effective. So for instance in the Kodera region of Kenya which had been nicknamed the valley of the blind due to a prevalence of onchocerciasis of 70%-
Erin Allmann Updyke	Oh my gracious.
Erin Welsh	DDT applications over a 6-7 month period led to eradication of the black fly vector in that area.
Erin Allmann Updyke	Wow.
Erin Welsh	Mm-hmm. I know. It feels weird to be like wow, DDT worked really well.
Erin Allmann Updyke	Wow.
Erin Welsh	But it did until it didn't and then until it killed a lot of other things.
Erin Allmann Updyke	It did until it didn't. Yeah.

Erin Welsh	Yeah. Leading into the 70s, which was when probably the largest campaign began, the WHO Onchocerciasis Control Program, OCP, still the strategy for control focused on interrupting transmission by vector elimination.
Erin Allmann Updyke	Yeah.
Erin Welsh	In this program which targeted initially 7 countries around the Volta Basin of West Africa with additional areas or countries added later on, insecticide was applied either on the ground or aerially. And the plan was to continue these types of vector control activities for 20 years, the length of a female worm's life, like the maximum length.
Erin Allmann Updyke	Yeah, yeah. That makes sense.
Erin Welsh	But there were several challenges that emerged that either interrupted or slowed down progress. And one was that several areas were re-invaded by adult flies from outside the target areas. Studies showed that some flies in the Simulium damnosum species complex could migrate up to 500km.
Erin Allmann Updyke	Yeah, I forgot that part.
Erin Welsh	310 miles. Yeah.
Erin Allmann Updyke	They're really far fliers which makes it so much more complicated.
Erin Welsh	So much more difficult. And another issue was insecticide resistance. So the OCP adapted to overcome these challenges by rotating different insecticides to reduce the likelihood of resistance and there was another development that actually helped to overcome these challenges as well and that was the discovery of ivermectin which was developed in 1975 and provided for free by Merck starting in 1988.
Erin Allmann Updyke	Yeah.
Erin Welsh	And its developers were actually awarded a Nobel Prize in 2015.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. That really changed the landscape of control. This one two punch of insecticide and treatment allowed the OCP to make incredible strides in onchocerciasis control. So by 2002 it was estimated that the OCP had rid 250,000 square km of farmable land of onchocerciasis with 40 million people having been protected and 600,000 cases of blindness prevented in at least 7 countries. And the incredible amount of work done by this program not only greatly reduced the burden of disease in some areas but also led to a huge amount of knowledge being gained about the ecology and the epidemiology of this disease which could then be integrated into future control efforts. And I just wanna make a little note, another bright moment during the OCP era happened in 1981 with the release of the J. Geils Band song 'River Blindness'. I'm gonna read you the first two verses.
Erin Allmann Updyke	Okay. You're not gonna sing 'em?
Erin Welsh	I'm not gonna sing them, I actually haven't listened to the song yet which is so bad but I found it like right before we started to record.

Erin Allmann Updyke	Okay.
Erin Welsh	Okay. "Human kindness, river blindness. Black flies rise as the water flows. Human kindness, river blindness. Angels cry as the fever grows. Indications, demographics, control of the basics is all you see. Correlations, disintegrations, cessation of life expectancy."
Erin Allmann Updyke	We need to ask if we can get permission to play that song on the pod because please.
Erin Welsh	(laughs) I know, I know. I had no idea. It was on like a '10 thing you probably didn't know about river blindness' and I was like, you're right! I did not know about this.
Erin Allmann Updyke	I did not. (laughs)
Erin Welsh	The J. Geils band song. The only other song that I know by The J. Geils Band is 'Centerfold'. Like, (singing) "My angel is a centerfold."
Erin Allmann Updyke	Wait, I know that song!
Erin Welsh	Yeah. So I think it's very funny in their repertoire of songs, one is 'Centerfold' and the other is 'River Blindness'.
Erin Allmann Updyke	Wow. Fascinating.
Erin Welsh	Yeah, there we go. Okay. Anyway after the OCP ended, onchocerciasis control was headed up individually by many of the countries involved in the OCP and since the mid 90s there have been many other control programs started in countries that had not been involved in OCP. And on the other side of the Atlantic, other elimination campaigns had started up in the Americas and these were slightly different than those in Africa due to the ecology of the disease. So whereas in Africa large parts of 31 countries are affected by onchocerciasis, in the Americas the distribution is much more limited or focused and has been. And so in those areas, mass drug administration with ivermectin seemed to be the ticket. And in 1993 the onchocerciasis elimination program for the Americas began and there have been many success stories there. For instance, and I hope I'm not stepping on your toes Erin but rather setting you up to wrap up this story-
Erin Allmann Updyke	I love it.
Erin Welsh	Onchocerciasis was declared eliminated in Colombia in 2013, in Ecuador in 2014, in Mexico in 2015, Guatemala in 2016, and parts of Venezuela in 2017. And from what I can tell, the areas where most of the transmission still happens is the southern parts of Venezuela and the northern part of Brazil where they border one another in sort of like the Amazon area. So Erin, it seems like there's been a great deal of progress in the control of this disease but it still seems like we have a long way to go based on some prevalence numbers I saw.
Erin Allmann Updyke	Yeah.
Erin Welsh	So take me through where we stand and what we have left to do with this neglected tropical disease.
Erin Allmann Updyke	I would love to. We'll take a quick break and then get into it.

TPWKY	(transition theme)
Erin Allmann Updyke	So World Health Organization estimates based on data from 2017, which is the most recent data that they have listed, estimates that worldwide almost 21 million people are currently infected and living with Onchocerca volvulus.
Erin Welsh	It's so many people.
Erin Allmann Updyke	It's still a very, very large number.
Erin Welsh	Yes.
Erin Allmann Updyke	It's estimated that of those 21 million people, about 14.6 million of them have active skin manifestations.
Erin Welsh	Wow.
Erin Allmann Updyke	So they have active disease. And about 1.15 million have some degree of vision loss if not complete blindness.
Erin Welsh	Will everyone who is infected with this parasite develop blindness? Is it just an inevitability?
Erin Allmann Updyke	Great question. No, definitely not. And not everyone would even necessarily have all of the skin manifestations.
Erin Welsh	Okay.
Erin Allmann Updyke	But I could not find a solid number on what that percentage or proportion is.
Erin Welsh	Okay.
Erin Allmann Updyke	I think it largely has to do with disease burden. So the higher the intensity of burden, the more likely you are to have severe disease including vision loss.
Erin Welsh	Right, okay.
Erin Allmann Updyke	Yeah. Like you said Erin already, it is still the case that over 99% of those who are currently living with onchocerciasis live in 31 countries across Africa, the other 1% are located in foci in Latin America as well as Yemen. And the thing is that onchocerciasis doesn't kill people outright but it is no less debilitating and it does reduce life expectancy even though it doesn't kill people directly. So like you mentioned Erin, before control efforts ramped up, in some endemic areas up to 35% or 46% of people would become blind eventually.
Erin Welsh	That is just...yeah.
Erin Allmann Updyke	Yeah. And in many areas where onchocerciasis was endemic, up to 10% of the adult population would become blind.
Erin Welsh	Wow.

Erin Allmann Updyke	Just depending on the overall worm burden in the area. And even without considering permanent disability like blindness, these skin lesions, I really can't underestimate how debilitating the itchiness can be. People can't sleep, they can't work. So if we look at the disability adjusted life years, which is an imperfect measure but still a measure of overall disease burden, onchocerciasis is estimated to account for between 1 million and 1.5 million disability adjusted life years annually, depending on which paper you look at. And the itching and skin manifestations account for over 60% of these, so it's not just the blindness. I think that with a common name like river blindness it can be overlooked how impactful the skin disease really is as well.
Erin Welsh	Right, I think that's definitely the case.
Erin Allmann Updyke	Yeah and also the skin manifestations can result in open wounds and just as well... Erin you asked really early on whether people become immunosuppressed in some ways. When you have a very, very high worm burden, it does cause your immune system to be more likely to have other infections on top of having potentially open wounds on your skin that can be an area where you can become infected.
Erin Welsh	Okay. Right.
Erin Allmann Updyke	So overall it's estimated that onchocerciasis, though it doesn't kill people, it does reduce overall life expectancy by 13 years.
Erin Welsh	That's not insubstantial at all.
Erin Allmann Updyke	Right, not in the slightest. But the good news is that control efforts have been ongoing for decades now. Early on Erin, like you talked about, they relied on a lot of integrative approaches using both vector control pest management as well as ivermectin. Most of the programs that are out there today really just rely on community directed treatment with ivermectin annually. This has worked very, very well in some areas like in the Americas, it has not worked as well in very, very highly endemic areas in Africa largely because it doesn't kill these adult worms and you administer ivermectin annually but it really only reduces symptoms and slows the transmission for a few months. So ivermectin alone is unlikely to completely control or eradicate onchocerciasis.
Erin Welsh	And in terms of how it's only given once a year, is administering it more frequently bad for you?
Erin Allmann Updyke	Yeah, it's a great question. It's a possibility and there's some data that suggests that maybe in these hyperendemic areas that could be a good option to administer it biannually instead of annually, but the data doesn't suggest that that would actually result in that big of a decrease.
Erin Welsh	Okay.
Erin Allmann Updyke	Because annually does make a really big difference, it's just that in places where this is hyperendemic it's just not quite enough, essentially.
Erin Welsh	Well and I think it's also interesting too going a little bit back to the ecology is that I saw a few line graphs looking at the biting frequency and how it does peak at certain times of year. And so if you reduce the microfilaria presence during those times and time the drug administration then, then...

Erin Allmann Updyke	Exactly. Precisely, exactly, yeah. So kind of targeted administration as well. But overall in 2017 145 million people, which is about 70% of the estimated population at risk were treated with ivermectin through these various control programs, which is phenomenal. It's not quite where we need to be because in every region you would need at least 80%-85% treatment to really help reduce and interrupt transmission but it's good progress. But the big question is can we do better? We've been doing this now for decades. Can we do better especially as it relates to actually curing disease rather than just treating symptoms or halting progression which requires treatment for 10-15 years or more? Right.
Erin Welsh	Right.
Erin Allmann Updyke	Enter wolbachia.
Erin Welsh	Oh yeah, I'm excited for this.
Erin Allmann Updyke	I told you we'd come back to them. So like I said in the biology section, the more that we know about the disease pathophysiology of onchocerciasis, the more it becomes clear that wolbachia play a very important role. But we already know that we can't just kill the adult worms outright because the the wolbachia that are in them would make us really sick, right? So some researchers have wondered what if we just kill the wolbachia bacteria inside of these worms instead?
Erin Welsh	How do we do that?
Erin Allmann Updyke	Great question, Erin! We can do it.
Erin Welsh	Okay.
Erin Allmann Updyke	Treatment with doxycycline, which is an antibiotic, it's a relatively common one that we use for a lot of diseases including tick-borne diseases like rickettsias, which wolbachia are closely related to rickettsias.
Erin Welsh	They are indeed.
Erin Allmann Updyke	So treatment with doxycycline can interrupt embryogenesis, stop adult worms from being able to reproduce for at least a year if not two years which is far longer than the few months that ivermectin can do.
Erin Welsh	That's incredible.
Erin Allmann Updyke	So it's unclear whether treatment with doxycycline can fully just kill the adult worms very slowly, I think in some studies it suggests that these adult worms will then die. But certainly it stops their reproduction, it stops the production of microfilariae for years.
Erin Welsh	That's wonderful news.
Erin Allmann Updyke	So why aren't we mass administering this?
Erin Welsh	Yeah.

Erin Allmann Updyke	Yeah. It's a little tough. So ivermectin is a one single dose treatment. One dose once a year and you have effect. Doxycycline on the other hand requires 100-200 milligrams per day every day for 4-6 weeks at a time.
Erin Welsh	Yeah.
Erin Allmann Updyke	There's also a pretty large range of people including pregnant people, breastfeeding people, children under 9 who can't take doxycycline for various reasons. So there are groups that are doing research to try and find other compounds and drugs that might have the same effect but be administered in a more practical way, so not needing people to take drugs for six weeks at a time, but also to a wider range of people who are at risk of infection or who are living with infection. But what's really cool is I saw some papers that were suggesting that this could be something that's particularly beneficial in those areas that are hyper endemic where we've been treating with ivermectin but it doesn't seem to be having the effect. Or also in areas where you have a high burden of disease but you also have loa loa which is another filarial parasite that if people are coinfected with onchocerca and loa loa, you cannot treat them with ivermectin because the loa loa worms will also die but they are larger and they can block blood vessels and cause brain damage and death.
Erin Welsh	Yeah.
Erin Allmann Updyke	So that's bad.
Erin Welsh	Yeah.
Erin Allmann Updyke	But loa loa don't have wolbachia.
Erin Welsh	Interesting.
Erin Allmann Updyke	So doxycycline and drugs that work like it don't affect them. So that's a pretty promising area of research for that reason as well because areas where both onchocerca and loa loa are present have been very difficult to do control strategies.
Erin Welsh	We need to keep a list of like...
Erin Allmann Updyke	Things we need to follow up on?
Erin Welsh	At the end of these episodes where like oh, all these future directions, let's keep an eye on how these things are progressing.
Erin Allmann Updyke	I know, there's a lot I feel like. There was a lot in the dengue episode where it was like this is happening now!
Erin Welsh	Right, right.
Erin Allmann Updyke	But it's pretty awesome, I think there's some good research that's going on, I think that overall things are not great in terms of onchocerciasis but they're a lot better than I expected quite honestly.
Erin Welsh	They're a lot better than I expected and I think that the past 50 years or so of control efforts have really shown that a lot of progress can be made.

Erin Allmann Updyke	Exactly, yeah. Like we've made massive progress, it's just that because the life cycle of these parasites is so long, you still have really high prevalence of disease.
Erin Welsh	Right, right.
Erin Allmann Updyke	But yeah, we've come a really long way, so we can end on kind of a positive note for once.
Erin Welsh	Yay! I like when that happens.
Erin Allmann Updyke	Me too. So sources?
Erin Welsh	Sources. So i have a thousand different articles, not that many but I have a lot of different articles, I'll shout out a couple. One resource that was great is a book called 'A History of Human Helminthology' by David Grove. And in terms of papers I wanna shout out a few. One by Basáñez et al, 2009; another by Crump et al, 2012; Krueger et al, 2007; and Lefoulon et al, 2016. Those were all really great papers. I will post these papers as well as all the other ones I didn't mention on our website.
Erin Allmann Updyke	Same, I have a very long list of recommended reading, everything from the specific biology and pathophysiology to a lot more details on the role of wolbachia and ivermectin, it's a really fascinating drug. If you wanna learn more about it you can find all our sources for this episode and every one of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab.
Erin Welsh	Absolutely. Well thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	Thank you to the Exactly Right network of whom we are very proud to be members.
Erin Welsh	And thank you to you, listeners, for allowing us to make this podcast and for listening even if we talk about really scary subjects or really weird subjects.
Erin Allmann Updyke	Yeah.
Erin Welsh	We're glad to have you along for the ride.
Erin Allmann Updyke	Yeah, this is really fun, we hope you enjoyed this episode.
Erin Welsh	Yeah. Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals!