

Erin Allmann Updyke

"Rahab Joshua runs a small business in Plateau state, Nigeria selling rice and ground maize at the local market. She has a great smile, six bright children, a supportive husband, and she has lymphatic filariasis. 'I used to have fever attacks and for weeks, I could not do anything. Not even take care of my family.' Rahab noticed the symptoms of lymphatic filariasis or LF when she had her fourth child and the progressive swelling of her legs sent her on a desperate search for treatment. The journey for relief brought none and depleted her family's finances. 'One man used a razor blade, he made cuts in my leg, then used the suction device. He told me he had removed something. But if he took something out, why was the leg getting bigger and bigger?' As Rahab's deformity grew, her circle of friends shriveled. 'Someone gave me new clothes to pass on to another woman but she refused to collect them because they came through me. During that time I cried a lot. You can't imagine how happy I am that my children and grandchildren will never have to go through this.'"

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh

Oh wow. Yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

It's awful. It's unbelievable.

Erin Allmann Updyke

And it's still so prevalent.

Erin Welsh

It is. And fortunately there are a lot of great organizations doing work on this such as the Carter Center. So Rahab's story was featured in a video produced by the Carter Center titled 'Living With Complications From Lymphatic Filariasis'. And we will post the link to this video as well as to the Carter Center's website on all the incredible work that they are doing to eliminate or at least reduce the burden of lymphatic filariasis in many countries around the world.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah. 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

And today we're talking about lymphatic filariasis.

Erin Welsh

This has been on our list for a very long time. It's kind of amazing that we haven't covered it sooner. It's one of the most prevalent and debilitating neglected tropical diseases. And I thought I knew a good amount about this disease from like public health classes and what not. But I was wrong.

Erin Allmann Updyke

Same, same.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah. But before we get into all of the things that we now know about lymphatic filariasis, is it-

Erin Allmann Updyke: Quarantini time?

Erin Welsh: It is.

Erin Allmann Updyke: It is.

Erin Welsh: What are we drinking this week?

Erin Allmann Updyke: We're drinking It's A Small Worm After All.

Erin Welsh: Continuing with the worm world puns for our quarantini titles. It's really like, it's a deep well.

Erin Allmann Updyke: It is.

Erin Welsh: So it's good. And what is in It's A Small Worm After All?

Erin Allmann Updyke: It's a lovely little hard cider bev with hard cider and some ginger beer and lemon juice and some Applejack in there as well.

Erin Welsh: Yeah.

Erin Allmann Updyke: And we'll post the full recipe for that quarantini and the non alcoholic and equally delicious placeborita on our website thispodcastwillkillyou.com and our social media.

Erin Welsh: On our website thispodcastwillkillyou.com, you can find all sorts of things. I have actually the website open in front of me.

Erin Allmann Updyke: I love it. I love it when you do.

Erin Welsh: We have got links to bookshop.org affiliate account, our Goodreads list, merch, and we've got some new merch coming for you this winter which is pretty exciting, so keep an eye out. We've got links to Patreon. We've got a form for your firsthand account, if you want to submit a firsthand account. We've got transcripts and we've got the sources to each and every one of our episodes. Plus some more hidden Easter eggs that you might find on the website.

Erin Allmann Updyke: Ooh, Easter eggs, Erin.

Erin Welsh: Yeah.

Erin Allmann Updyke: All right. Well shall we get into the biology of lymphatic filariasis?

Erin Welsh: We shall. We'll take a quick break and then dive in.

TPWKY: (transition theme)

Erin Allmann Updyke

So lymphatic filariasis is the disease that is caused by three different but closely related nematode worms. Specifically a type of worms called filarial worms, which are like a whole super family of these little round worms, small worms that are entirely parasitic. So almost all of these filarial worms infect mammals and some infect birds or reptiles. Apparently they do not infect fish.

Erin Welsh

That we know of.

Erin Allmann Updyke

That we know of. Good one, Erin. And generally they have a pretty complex life cycle with an arthropod intermediate host. So at minimum, we're talking about a two host life cycle. Pretty classic for parasites. And the worms that we'll talk about today are all in the family Onchocercidae, which we've already talked about one other time in our river blindness episode. Onchocercidae volvulus. But today we're talking about three others. We're talking about Wuchereria bancrofti, Brugia malayi, and Brugia timori.

Erin Welsh

Just side note here, we both did a lot of digging to try to find the correct pronunciation for these worms.

Erin Allmann Updyke

Could not come to a solid conclusion.

Erin Welsh

There is no consensus, it appears. Any YouTube video, you're bound to find a million different pronunciations. So this is what we're going with.

Erin Allmann Updyke

We tried really hard.

Erin Welsh

We did.

Erin Allmann Updyke

So it's these three worms. And even more specifically, 90% of lymphatic filariasis infections are caused by bancroftian filariasis which is caused by Wuchereria bancrofti. I think that, I suspect that most listeners of TPWKY are relatively familiar with the life cycle of arthropod-borne parasites by this point. But we'll go over it because that's what we do here. And in this case, we'll start with the L3 larvae, so the third stage larvae are what mosquitoes will spit under the skin as they bite us in order to infect a human.

Erin Welsh

Is spit the technical term for this?

Erin Allmann Updyke

Yeah, that's the official scientific term for a mosquito bite. They will inject from their salivary glands the L3 larvae during a bite.

Erin Welsh

That sounds like spit to me, so yeah.

Erin Allmann Updyke

Exactly. And by the way, you may ask, Erin, what species of mosquito are we talking about?

Erin Welsh

Is it lots of them?

Erin Allmann Updyke

It is all of them almost, it seems.

Erin Welsh

That's really amazing.

Erin Allmann Updyke

Yeah. So this is a parasite or these are parasites rather that are found across the globe, especially in the tropics, throughout the tropics. And so in different parts of the world, unsurprisingly we have different vectors that are predominant. In Africa, across most of Africa, the most common vector are Anopheles mosquitoes of a few different species. In the Americas it tends to be Culex quinquefasciatus. But Aedes mosquitoes and Mansonia mosquitoes can also transmit the infection, especially in the Pacific, in Asia and the Pacific. And these are predominantly Brugia species. These are also entire genera of mosquito, it's not just like one or two species that we're talking about here.

Erin Welsh

Yeah. Okay, so tell me what's going on inside of these mosquitoes that these parasites are somehow able to do everything to all of them.

Erin Allmann Updyke

Such a good question, Erin. I don't know. So these are parasites, and we'll talk about this in how they affect humans especially, but they are very well adapted to their hosts. They do a lot to modulate our immune system in a way that creates tolerance so that they can persist for their lifetime. So I imagine, though I don't know the details of how they do this in all of these various mosquito species as well. It is impressive that a single parasite can do so in so many different species of mosquito.

Erin Welsh

Yeah. I feel like that's sort of the opposite. And maybe it's not, maybe that's just like human bias or human infection bias. But that we've seen with a lot of vector-borne diseases where the parasite or pathogen is super loyal to their vector species but not necessarily to their hosts. Like they can infect a wide range. Just seems like gambling. Like which basket do you put your eggs in?

Erin Allmann Updyke

Yeah. And this really is the opposite because especially Wuchereria bancrofti, it's a really human specific disease.

Erin Welsh

Yeah.

Erin Allmann Updyke

It can infect other animals but in general, it's not found in other animal species. And so it's almost like the opposite where this parasite has specialized on its primary host and is a generalist when it comes to the vector that transmits it.

Erin Welsh

Question.

Erin Allmann Updyke

Okay. I love that we haven't even started.

Erin Welsh

I know.

Erin Allmann Updyke

I'm like you've got a larvae under your skin, that's as far as we've gotten.

Erin Welsh

This is an important part of the process.

Erin Allmann Updyke

I love it.

Erin Welsh

Do we know whether or not these parasites have detrimental effects on their mosquito hosts?

Erin Allmann Updyke

Such a good question. I don't.

Erin Welsh

Okay.

Erin Allmann Updyke

I don't know. I didn't specifically look for that information, so I don't know if that information is known. A lot of other pathogens we know do have detrimental or at least some negative effect on the mosquitoes or arthropods that transmit them. I don't know in the case of the parasites that cause lymphatic filariasis.

Erin Welsh

Okay.

Erin Allmann Updyke

I can tell you that when it comes to the development within a mosquito, these worms have to molt twice within the mosquito host. And it's a process that takes between 10-12 days, or maybe even up to two weeks per some papers, before they are then able to be transmitted to another host. So there is certainly time in there to exert kind of a selective pressure on that mosquito. And a mosquito has to survive for at least those 10-12 days in order to be able to transmit the infection.

Erin Welsh

Okay, yeah. That makes sense.

Erin Allmann Updyke

Yeah. Okay, so back to these L3 larvae, they developed twice in the mosquito and now they are spit into our skin. These tiny little larvae enter our lymphatics and swim their way towards our lymph nodes. And that is where they live. They molt into L4 larvae and then into adults in a process that takes 6-12 months, long standing infection.

Erin Welsh

It's so long.

Erin Allmann Updyke

Oh just wait, it gets longer. The adult female will then mate and then start releasing live young. And these young are called microfilariae. And they release them into the lymphatics, they can swim out of the lymphatics and into our bloodstream. Now Erin, you may ask how many microfilaria are we talking about that this adult female worm is releasing?

Erin Welsh

That's definitely a question I would ask.

Erin Allmann Updyke

Well let me tell you. These adult worms live inside of us for up to 7-8 years after they become adult worms. And different papers have slightly different estimates like 4-6 or 5-8. In any case, a number of years. And they are releasing 10,000 microfilariae, wait for it, per day.

Erin Welsh

What?

Erin Allmann Updyke

That is millions upon millions of microfilariae over their lifetime.

Erin Welsh

That is shocking.

Erin Allmann Updyke

And then it gets more shocking. The adult worms are living inside of our lymphatic system. And we'll talk in a lot more detail about our lymphatic system, don't worry. But these microfilariae predominantly travel to our blood vessels and during the daytime preferentially hang out in our larger blood vessels. And then at night, when mosquitoes are most active, they travel to surface blood vessels so that mosquitoes can more efficiently pick them up in their blood meals and then go on to transmit them eventually.

Erin Welsh

I mean we've come across parasites that do this like malaria but still, every single time is horrifying and fascinating.

Erin Allmann Updyke

And it's even more fascinating to me in the context of how many different species of mosquito can carry this parasite because we do actually see different circadian cycles in these species of filarial worm depending on the part of the world that you're looking at and the mosquito species that is most commonly transmitting it in that region. So for example, in the Pacific Islands where they're transmitted by mosquitoes that are more diurnal, you see the microfilariae out in the surface blood vessels more during the day than at night. Like they're just so well adapted. It's incredible.

Erin Welsh

That is really interesting. And I wonder how we could trace sort of spread or like how quickly that diurnal pattern evolves to match the local mosquito host. Because like what happens if a new mosquito host comes in and is now suddenly the predominant mosquito host and can also transmit filariasis? And yeah.

Erin Allmann Updyke

Yeah. Oh I know, it's so much. So that is the transmission cycle of this parasite, of these parasites. So what does this disease, lymphatic filariasis, actually look like? It turns out that thankfully most people who are infected are asymptomatic. It's about 1/3 of people who are infected who end up having clinical disease, actual symptoms of this disease. But even when people are asymptomatic, they generally still have some degree of damage to the lymphatic system. And this damage is progressive. And so the predominant symptom of lymphatic filariasis is lymphoedema, swelling in a limb or in a body part due to disruption of the lymph system. And this swelling, this lymphoedema lends itself to secondary infections. Really, really easy to get a secondary infection when you have so much stasis of fluid.

Erin Welsh

So why does that... Like how does that happen? And maybe my question is just like how does the lymph system work? What does it do?

Erin Allmann Updyke

Yeah. Let me get into that and then I can talk a little bit more about like what those symptoms end up looking like. Okay?

Erin Welsh

Yeah.

Erin Allmann Updyke

So the primary cause of disease is the blockage of our lymphatic drainage. So we've only talked in very brief about our lymph system on this podcast. But what our lymphatic system is is a system of tubes, vessels, and clusters of nodes, lymph nodes. So it's very similar to our blood vessels in that what our lymph system is doing is carrying fluid from place to place in our body. Our blood vessels are carrying blood and our lymphatic vessels are carrying lymphatic fluid. What is lymphatic fluid? It's basically just all the fluid in our body that isn't blood. So this means anything that either extravasates, comes out of our blood vessels and into the extracellular space, any cells that kind of burst open and release all of their lovely liquidy juices, that's going to become fluid in the extracellular space. So it's fluid and large molecules like proteins, etc, hanging out in all of the space between our cells.

This fluid eventually is absorbed into the lymphatic system and carried through these tubes, through these lymphatic vessels into our lymph nodes. It kind of drains into our lymph nodes. Our lymph nodes are these areas where a whole horde of our immune cells, especially our white blood cells, hang out. Because the fluid that's traveling through our lymph, it has antigens in it, it has pathogens in it, it has just a bunch of junk. And so what our lymph nodes are doing are essentially cleaning it all up, filtering out all of the junk in this fluid, and then eventually running that fluid from our lymph nodes through our spleen which is not really a giant lymph node but kind of like a giant lymph node in a way. And then sending that fluid eventually back into our vascular system. So putting that fluid, once it's all cleaned up, back into our blood vessels. Does that make sense, what our lymph system is and does?

Erin Welsh

Yeah. Like extra plumbing. Non blood plumbing.

Erin Allmann Updyke

Yeah, extra plumbing. That's a really good way of looking at it. Okay, so then lymphatic filariasis, how do we get here? In lymphatic filariasis, the adult worms are living inside of our lymph system, inside of these vessels and near our lymph nodes. And they're not just passively hanging out there, they are, like I said, making millions, tens of thousands of eggs per day for years. The adult worms live in these little nests, they make these little nests. And because they need to exist in a space that is... Like our lymph nodes' job is to clear out pathogens, right?

Erin Welsh

Yeah.

Erin Allmann Updyke

That's our immune system's literal only job is to prevent things like worms from living inside of us. So these worms are actively secreting compounds to modulate our immune system's response to them existing inside of us.

Erin Welsh

Like what better place to do that? It's just hiding in plain sight.

Erin Allmann Updyke

Exactly, exactly. So it just so happens that these worms secrete all of these compounds that end up favoring an anti-inflammatory immune response. So what they do is suppress the T cells that are pro-inflammatory and they upregulate our anti-inflammatory response. So this overall suppression of inflammation is what allows these worms to persist inside us for so long, they create this condition of immuno tolerance. And that is why that many people living with this infection for many years might have no clinical signs or symptoms.

However that doesn't mean that there's not some degree of inflammation happening within these lymphatics because of this infection, because of these worms. Because they are producing these microfilaria that are bursting out of our lymphatics, running rampant and getting into our blood vessels. And so what we see is that even in people who have subclinical disease, that is they don't have any symptoms of lymphatic filariasis, if you look inside of their lymphatics, they do still have some degree of inflammation in the lymph system. And over time, eventually people are at increased risk for overt disease. So the question that you asked is what triggers this, right? And while we don't fully know as usual, it's thought that it's related to the frequency and intensity of our eventual immune response to these worms, specifically the response to these worms as they die.

Erin Welsh

Okay. And these are the adult worms or the microfilaria?

Erin Allmann Updyke

Yes, the adult worms. Yes.

Erin Welsh

Okay.

Erin Allmann Updyke

As these adult worms die, it causes an increase in inflammation. If you think about it, if they're actively secreting stuff to reduce inflammation and then they die, now they're not secreting those anti-inflammatory compounds.

Erin Welsh

Right.

Erin Allmann Updyke

So now you have an increase in inflammation. That increase in inflammation causes lymphangitis, which just means like swelling, inflammation in your lymph system; lymphadenitis which is inflammation specifically in the lymph nodes themselves.

Erin Welsh

Okay.

Erin Allmann Updyke

And then that is going to cause activation of our immune response. And we've talked a lot on this podcast about that inflammatory cascade where once you have inflammation, you're going to have more swelling, you're going to have this positive feedback loop that continues to upregulate these inflammatory pathways, which leads to more swelling and more swelling and more inflammation and importantly more pain. This is a very painful process. And the frequency and severity of these attacks can then lead to chronic changes over time. Another factor that's involved in the development of this symptomatic disease is a particular bacterial endosymbiont and longtime friend of the pod, Wolbachia.

Erin Welsh

Friend might be a generous term but yes.

Erin Allmann Updyke

But I heard you say that on our last episode and I loved it so much. It was about Koch but I really wanted to say it again because I got a kick out of it.

Erin Welsh

I love it.

Erin Allmann Updyke

So these particular little endosymbiotic bacteria live inside of these tiny worms. And while the worms themselves are secreting anti-inflammatory compounds, Wolbachia happens to induce our innate immune system enormously and stimulate inflammatory pathways. They're like all inflammation.

Erin Welsh

And this is again once the adult worm has died? Or is this while the adult worm is living, these Wolbachia are secreting these?

Erin Allmann Updyke

Potentially both.

Erin Welsh

Okay.

Erin Allmann Updyke

But I think the thought is that a lot of it might be on death or like release of these Wolbachia. So exposure to these likely also plays a role in the development of this lymphangitis, this inflammatory lymph system and eventual lymphoedema.

Erin Welsh

So we talked about this with onchocerciasis, the Wolbachia did the same thing then I think, right?

Erin Allmann Updyke

Yeah, yeah. Wolbachia, man.

Erin Welsh

Yeah.

Erin Allmann Updyke

Now the other and possibly most important component of the progression of this disease is how open it leaves people to secondary infections. Both because of the suppressive effects of this immune modulation, right, suppressing our immune system so that we tolerate these worms makes people more susceptible to other pathogens like malaria or tuberculosis. But also because the damage that's happening to the lymph system and the eventual development of swelling, of this lymphoedema, this fluid stasis leads to secondary bacterial infections. And that process where you have fluid stasis, things not draining and then secondary infections, is literally how so many infections in our bodies happen.

Like kidney stones lead to kidney infection, gallstones lead to infection of the gallbladder, milk duct blockage leads to mastitis. Like that is a very common phenomenon and that is what's happening here, where you have blockage of your lymph system from this inflammation leading to fluid getting backed up in a limb, etc. And then that's a nidus for bacterial infection. And that bacterial infection is going to cause a lot of inflammation, further damage, and exacerbation of all the damage that's already been caused. And so secondary infections are a huge contributor to the overall disability that we see with lymphatic filariasis.

Erin Welsh

Question about the swelling and sort of the timeline of symptoms. So I know that you said that you can see markers of infection even in people who are asymptomatic or without these more pronounced severe symptoms. But for those pronounced severe symptoms, is that usually like 7-8 years after infection because that's sort of the end of the adult worm's life?

Erin Allmann Updyke

It's a good question. I don't have a number like that.

Erin Welsh

Okay.

Erin Allmann Updyke

It used to be thought that children didn't get infected with lymphatic filariasis. That is not true, unsurprising.

Erin Welsh

Right.

Erin Allmann Updyke

But what we know now is that this is a chronic disease. So even though any individual worm might only be living for seven years, only seven is a long time, it's the accumulation over time, right, of multiple infections. Because generally people are not infected with a single or even a couple of adult worms. And so it's a process that takes a long time but I don't have an exact number on it. But you can think of it as very much a chronic disease if it is untreated.

Erin Welsh

Okay. So that actually kind of brings up another question that I had, which is infectious dose. Like how many times do people have to be bitten by an infected mosquito? Or is it just sort of like we don't know?

Erin Allmann Updyke

Yeah, yeah. Great question. We don't.

Erin Welsh

Okay.

Erin Allmann Updyke

In general it is thought that this is something where people do have to be exposed and therefore infected multiple times. Because again, it's not like a single worm is going to cause the major symptoms of lymphatic filariasis.

Erin Welsh

Okay.

Erin Allmann Updyke

But yeah, the how many worms do you have to have? No idea.

Erin Welsh

Okay. Another question. Sorry, I have so many and I have two more written down for later too. What is the average worm burden?

Erin Allmann Updyke

Oh I have no idea.

Erin Welsh

Okay, okay.

Erin Allmann Updyke

Yeah. So that's like the pathogenesis, right, that's like what's happening in our lymph system. But what does this end up looking like? Like what are people living with, right?

Erin Welsh

Right.

Erin Allmann Updyke

Lymphoedema is not a very specific thing.

Erin Welsh

Yeah.

Erin Allmann Updyke

So lymphoedema is just the swelling from this disruption of the lymphatic drainage. The secondary infections and these inflammatory states drive this process with a very fancy term called dermatolymphangioadenitis.

Erin Welsh

Wow.

Erin Allmann Updyke

And that are these attacks of fever, pain, swelling. These are the times at which this lymphoedema and this lymph system dysfunction is being exacerbated. And so each one of these attacks, eventually it just causes further damage to the lymph system that over time will lead to a finding called elephantiasis, which is something a lot of people may have heard of. And this is what happens when the lymph system has become so damaged that the body part that is being affected is significantly enlarged, it's very swollen, and the skin over time becomes very thick, very dry, and discolored. So it either darkens or it can become kind of like a grayish tone. And then you can see these very large protuberances on the skin that are caused by dilated loops of these lymph vessels, essentially like redundancy trying to be able to drain all of this fluid but not being able to. And then because there's so much swelling, this leads to these redundant skin folds, that kind of fold over on themselves and create yet another environment that is just ripe for secondary skin infections.

Erin Welsh

Right.

Erin Allmann Updyke

Now the two most common places that we see this type of damage, this lymphoedema, is in the legs, the lower limbs, and in the testes in people with testes. Hydrocele, which is fluid accumulating in the scrotal sac, is actually the most common complication especially in people with testes. And again, it leads to all of these same issues, it's just this lymph dysfunction that ends up accumulating fluid in the scrotum rather than a limb. But in addition to leading to eventual elephantiasis in the scrotum, this can also lead to other urologic complications like infections in the inguinal lymph nodes, it can potentially cause issues even leading up towards the bladder. It can be pretty severe.

And while predominantly this is a disease that's affecting the limbs and causing this swelling and lymph stasis and disease in the limbs, it's not limited to the limbs. Our lymph system is everywhere and it's draining all of the fluid in our body. And so lymphatic filariasis can also affect the kidneys. Filarial antigens that are released and traveling are eventually filtered by the kidneys and these can cause kidney damage. You can also have fistulas that form between the lymph system and the kidney, which essentially means the lymph system starts draining directly into the drainage system of the kidney, which means that you lose essential protein and fat because your kidneys aren't even filtering that lymph anymore, it's just being drained directly into your bladder.

Erin Welsh

Right.

Erin Allmann Updyke: And if the microfilariae as they're traveling through our blood vessels, right, the babies are traveling through our blood vessels rather than our lymph system, they can get trapped in our lungs and then release antigens that can cause inflammation in our lungs and can result in a cough and wheezing, especially at night when the microfilariae are more active.

Erin Welsh: That's horrible.

Erin Allmann Updyke: Yeah.

Erin Welsh: It all is. It's all horrible.

Erin Allmann Updyke: It's all horrible. And so it's maybe unsurprising hearing how horrible this disease is and how chronic this infection is to know that lymphatic filariasis is, based on many reports, the second largest cause of permanent and long term disability worldwide. Because in many cases, it can cause the loss of function of a limb or both limbs or just these very, very enlarged scrotal sacks that are just really difficult to be able to live with and kind of function with.

Erin Welsh: Yeah.

Erin Allmann Updyke: So that's the main biology of lymphatic filariasis.

Erin Welsh: Before we move on to treatment, which I'm assuming is the next chapter.

Erin Allmann Updyke: It sure is.

Erin Welsh: I have two questions. The first one is can there be co-infection with multiple species of these parasites?

Erin Allmann Updyke: Yeah, great question. I didn't see anything in the literature about it but they certainly can overlap in distribution. So I don't see why not.

Erin Welsh: Okay. And then the second question is about differences in symptoms among these different parasite species.

Erin Allmann Updyke: Yeah, it's a good question. I don't have a lot of data on that. Because *Wuchereria bancrofti* is 90% of all infections, all of the literature really tends to focus on bancrofti filariasis or filariasis caused by *Wuchereria bancrofti*.

Erin Welsh: Okay.

Erin Allmann Updyke: So I don't really have a lot of data on the other species.

Erin Welsh: Okay.

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

Erin Welsh: Okay, that's it for now.

Erin Allmann Updyke

Well then, let's move on to the good news, goodish news is that we do have treatment. There are a few different drugs that are effective at eliminating this parasite from the body. And so the mainstay of treatment and I'll talk in a lot more detail in the epidemiology section about this idea but the mainstay of treatment across the globe is something called mass drug administration. And this means not even checking anyone for infection but giving whole populations anywhere that is at risk drugs once or twice a year, depending on the drug, to target and kill these parasites. And what this does is it reduces the density of microfilariae in the blood which then reduces the transmission to mosquitoes which then reduces the spread to the population. The problem is that there's a few problems. One is that you need really high coverage like 65%-80% coverage of a population to effectively interrupt transmission. And because these aren't necessarily killing the adult worms and these worms are living in us for so long, you have to then keep this up for 5-6 years in a row at least.

Erin Welsh

Right.

Erin Allmann Updyke

Because filarial disease also often co-occurs with other parasitic diseases, you also have to be very cautious about which drugs you use in which regions so as not to exacerbate, for example, onchocerciasis or loiasis which is another worm that infects the eyes. But it is possible to do this kind of mass drug administration and that is the mainstay of treatment. However the other big problem, besides how difficult it is logistically, is that mass drug administration and really like using the drugs that we use for mass drug administration doesn't do much at all to treat the people who already have clinically overt disease, especially those who have already progressed to severe lymphoedema or elephantiasis. For those cases, it's all about prevention and treatment of secondary bacterial infections, right. So trying to prevent as best we can further exacerbation.

Erin Welsh

Are there surgeries or anything like that that can help with some of that swelling?

Erin Allmann Updyke

in the case of hydrocele, yes. So in case of scrotal infections, surgery can be done to help correct it. But I didn't see a lot on if that is also true for lymphoedema. And in general, lymphoedema is really difficult to treat. And lymphoedema is something that can happen from a lot of different causes, it's not just lymphatic filariasis. And it is really difficult because once you have those lymph tracts say going down your leg damaged, there's not really a lot of ways to fix that. Whereas with a hydrocele, you can kind of close off the area that's allowing fluid into the scrotum and then potentially drain that scrotum and then prevent further fluid damage because it's not like directly the lymphatic system that's draining into the scrotum.

Erin Welsh

Right, right.

Erin Allmann Updyke

But for like the legs which is the most common place, it's not really surgically correctable as far as I can tell.

Erin Welsh

Okay.

Erin Allmann Updyke

So that's lymphatic filariasis. I mean it's a really awful disease. It's really horrible.

Erin Welsh

Yeah, it is a really horrible, horrible disease.

Erin Allmann Updyke

Yeah. So Erin.

Erin Welsh

Yes, Erin.

Erin Allmann Updyke Where did this pathogen come from, please? How did we get to here? How?

Erin Welsh Yeah. Well I've got some answers to some of those questions that I'll get to right after this break.

TPWKY (transition theme)

Erin Welsh Throughout its long, long history, lymphatic filariasis has inspired dozens of names, caused a whole lot of confusion in the medical field, it's been represented in art and myths, it's led to tremendous stigma and suffering, and gave rise more or less to the field of medical entomology. Yeah.

Erin Allmann Updyke What?

Erin Welsh I know.

Erin Allmann Updyke Okay.

Erin Welsh I'll tell you about it, I'll tell you about it.

Erin Allmann Updyke Yeah, please.

Erin Welsh Like so many of the other neglected diseases we've covered on the podcast, the history of lymphatic filariasis is deep and rich and the mystery of its biology was mostly completely unraveled long ago. And yet, and yet.

Erin Allmann Updyke And yet.

Erin Welsh This quote unquote "old friend" of humanity remains today, infecting tens of millions of people around the globe, with nearly a billion people around the world at risk of infection, as well as the tremendous health, economic, and social burden that often accompanies these parasites. That's what puts the neglected in neglected tropical disease.

Erin Allmann Updyke Yeah.

Erin Welsh So what I want to do today is to take us through that vast history of lymphatic filariasis up through the period when medicine began to figure things out. And then rather than asking why we haven't completely eradicated or at least eliminated this disease today, because the answer to that is multifaceted but also mostly comes down to there's no profit in curing this disease or preventing this disease, which is disappointing and depressing and not surprising. But instead of doing that, I want to do a mini exploration of a potential target for treatment and what exactly is so cool about this target. In other words, what the heck is this old friend of the pod, Wolbachia? And why is it so important to ferial parasites and how can we use that to our advantage?

Erin Allmann Updyke Yeah.

Erin Welsh All right, let's get started.

Erin Allmann Updyke Okay.

Erin Welsh

All three of the filarial species that infect humans are ancient, ancient little worms that likely evolved in Southeast Asia. When that happened is as per usual a slightly trickier question to answer. I read one paper that estimated that the most recent common ancestor of *Wuchereria bancrofti* and *Brugia malayi*, which are the two species responsible for most lymphatic filariasis in humans, emerged around 4-6 million years ago, which the authors pointed out was around the time that the common ancestor of humans and chimpanzees began to diverge. But I'm also not sure how well that matches with the hypothesized geographic origin of these parasites. But it's still question mark here.

Erin Allmann Updyke

Okay.

Erin Welsh

But in the third more localized species, *Brugia timori* is also thought to be ancient, parasitizing nonhuman primates until humans ventured into their realm. And it still parasitizes nonhuman primates. The two genera, *Wuchereria* and *Brugia*, are thought to have split from each other more recently, around 675,000 years ago. But the larger group that includes these filarial parasites has ancient roots, probably diversifying around the time that mammals did and getting well acquainted with their numerous mosquito vectors. I feel like I just used a whole bunch of words to say these parasites are old. But you know I like to put a little precision in there, just be precise about what we don't know and how much we do know about it which is not very much.

Erin Allmann Updyke

I love it.

Erin Welsh

But even in the earliest medical writings about lymphatic filariasis, it seems to be assumed that the disease was ancient and oh are there writings and stories and alleged sculptures and illustrations. Have you ever heard of skiapodes?

Erin Allmann Updyke

No.

Erin Welsh

Okay. They are mythical beings dating back at least to Ancient Greece that are represented as having one big leg which they use as shade protection by lying on their backs and sticking their legs straight up on a sunny day. So like their foot protects them from the shade.

Erin Allmann Updyke

Okay.

Erin Welsh

They were said to be from Ethiopia or India or other places as well. The word skiopode comes from the Greek for 'shadow foot'. And some researchers think that the skiopode myth has its origins in cases of lymphatic filariasis and others tend to dismiss that idea and they're like what evidence do you have? There's a lot of different reasons that this could have originated.

Erin Allmann Updyke

Okay.

Erin Welsh

Another alleged ancient representation of this infection is from one of the earliest sculptures, the queen of Punt stela, AKA like stone slab, which depicts a woman ruler visiting Egypt from the land of Punt. This stela was found in the funerary temple of the ancient Egyptian queen Hatshepsut from around 1500 BCE. And since its rediscovery, many researchers, particularly in the mid to late 20th century, they've had many things to say about this stela and the queen represented. So the queen of Punt, whose name was Ati, is depicted with a body, arms, legs, hips, that's larger relative to those of the other people on the stela. For decades researchers decided that she must have a physical ailment in order to be portrayed in this way. And they would pathologize her appearance to a kind of ridiculous extent, like it wasn't conceivable to these authors that she just had thick thighs and wide hips, she must have had lymphatic filariasis.

Erin Allmann Updyke

Wow.

Erin Welsh

All based on one image, no skeletal remains, no writings, just this image. And I think it's interesting because I came across the queen of Punt described as like definitely a representation of lymphatic filariasis. And then I found other papers where it was like yeah, this is kind of controversial. And then I found another paper that was like hey, can we stop pathologizing women in ancient representations when we have no reason to believe that it was representing a disease? Like was it part of a medical text or was it just a stone slab representing a visit from a queen from a different land? But I think that this queen of Punt stela and the discussion around it serves as a good reminder to just keep in mind how limited we are in making retrospective diagnoses of any kind. And to ask whether we're pathologizing something because of our own biases or lack of context. Speaking of which, there's also the quote unquote "curse of Saint Thomas" which was a belief held by Christian inhabitants of some regions of India that the swollen leg characteristic of lymphatic filariasis happened to those who martyred him.

But anyway, aside from these more questionable ancient references to lymphatic filariasis, we have plenty of unquestionable ones. Medical writings from Ancient Persia, China, India, Greece, and elsewhere clearly described the condition. Although whether it was filarial or non filarial elephantiasis is harder to discern in these ancient texts. But in general it was seen as a shameful condition, often a punishment. Although in at least the Ancient Indian text, the Sushruta Samhita, it was observed that high prevalence of the disease happened in areas with lots of stagnant water. Kind of interesting observation considering what we know about mosquitoes now. So far in the episode we've primarily been using the name 'lymphatic filariasis' but that's far from the only name that has been used historically to describe this infection, which like I found challenging when trying to find papers about its history.

Erin Allmann Updyke

Oh I bet.

Erin Welsh

So I would just have to search like lymphatic filariasis and then like all of the variations that it has been called throughout the decades and centuries.

Erin Allmann Updyke

Right.

Erin Welsh

So the other common one that you mentioned, Erin, is elephantiasis. And so we use that now to describe like the particular symptom or manifestation. And so historically that was used as just sort of a cover all for swollen limbs. And it's not entirely clear when and where elephants began to be associated with the disease because that is where it comes from. But it may have been in that Indian text I mentioned, the Sushruta Samhita from around 70 CE. The author, Sushruta, uses the term 'slipada', 'sli' for elephant and 'pada' for leg, to describe the condition. And about 1000 years later, Ancient Persian physicians were also using terms like 'dal-fil' or 'dal-fil', elephantine disease, in reference to lymphatic filariasis. As to the why of this, like why elephants, some people have suggested it's to describe the changing texture or the changing color of skin in affected areas or the fact that certain limbs would grow to a certain size. And I should note that elephantiasis was not used exclusively to describe lymphatic filariasis but also other swelling or thickening of the skin caused by other conditions such as leprosy which was written about in Ancient Greece.

The first use of the word elephantiasis in English was I believe sometime in the mid 1500s. But even into the 20th century, elephantiasis was and still is often used split into filarial and non filarial elephantiasis. But aside from elephantiasis, there was also a whole host of other local names for the condition. Barbados leg, yam leg, yava leg, malabar leg, St. Thomas leg, bucnemia tropica, sarcoma mucosum, and so on. And the listeners of the podcast can probably guess what I'm about to say next, which is that the wide variety of names for the disease I think serves as an indication of just how prevalent and widespread it was in the ancient world. And with global travel and trade ramping up in the 16th century and beyond, these filarial parasites were about to travel to strange new worlds where they would find ample hosts and suitable mosquito vectors to continue their life cycle mostly unchecked.

The transatlantic slave trade beginning in the 16th century led to *Wuchereria bancrofti* becoming endemic in some Caribbean islands as well as on the North and South American mainland. Lymphatic filariasis was actually endemic in Charleston, South Carolina until the early 20th century. As its distribution grew, so did the medical community's interest in this infection. Over the preceding centuries, medical writers had of course paid lots of attention to lymphatic filariasis but they were mostly at a loss to do anything more than just describe it and try out some mostly unsuccessful treatments. For real medical progress on understanding what exactly was going on with this disease under the surface, a key piece of technology had to be invented and refined.

Erin Allmann Updyke

A microscope?

Erin Welsh

The microscope. This tool is what French physician Jean-Nicolas Demarquay would use in 1863 to inspect the milky fluid that he extracted from the swollen scrotal sack of an 18 year old with elephantiasis.

Erin Allmann Updyke

Ugh, young.

Erin Welsh

I know, awful. In the first major breakthrough on the infection in centuries, Demarquay reported quote: "Attention was drawn above all to a little elongated and cylindrical creature that had extremely rapid movements of coiling and uncoiling." Endquote. He wasn't sure what exactly he was looking at besides worms, nor could he explain why they were absent once the scrotal fluid had cooled down. The answers to those questions would have to wait for other physicians. Four years after Demarquay's report, Otto Edward Heinrich Wucherer was in Brazil inspecting a urinary blood clot from someone experiencing bloody urine and found similar worms. Wucherer was curious whether these worms were the same as those that Theodor Bilharz had found 15 years earlier to be the cause of hematuria, AKA the causative agent of schistosomiasis, Bilharzia. One look under the microscope told him that he had some very different worms on his hands but he wasn't sure exactly what they were. He published his finding quote "as an incentive for some of my colleagues better qualified and more fortunate than I to attempt to shed light on a disease, the etiology of which is still enigmatic today" Endquote.

Erin Allmann Updyke

I love that. That's a really cute quote somehow.

Erin Welsh

It is. It's also sort of like, I don't know but someone else can do this.

Erin Allmann Updyke

Yeah. Hey, here you guys go. Figure it out.

Erin Welsh

Someone more intelligent and gifted than I.

Erin Allmann Updyke

Yeah.

Erin Welsh

The next step in understanding lymphatic filariasis was taken by a physician named Timothy Richards Lewis who found worms, which he called filariae, in the blood and milky urine of a couple of his patients, also noting that the filariae were not present in the blood at all times. He named the parasite *Filaria sanguinis hominis*, which I found it interesting. I know that names change and they don't stick around but like literally none of those names remained for very long to describe that parasite.

Erin Allmann Updyke

Right.

Erin Welsh

At this point in the 1870s, what we've got are some enticing pieces of information about a parasitic worm and the infection that it causes, but no comprehensive picture of how this parasite caused disease and how it was spread. Enter Patrick Manson. I feel like I must have mentioned Patrick Manson, I'm sure that I have and at least a couple other episodes on parasites.

Erin Allmann Updyke

Probably schistosomiasis.

Erin Welsh

Schistosomiasis, dracunculiasis, more, I don't know. But he's a pretty famous dude in the history of parasitology and medical entomology especially and he owes a big part of that fame to lymphatic filariasis. In the late 1860s and into the 1870s, Manson worked as a medical officer in the Chinese Imperial Maritime Customs Service. And as a result, he treated many people with the infection, seeing the full range of manifestations from what he called quote unquote "scrotal tumor" to classic elephantiasis and tropical chyluria, like lymph in your urine. He realized that these conditions, which had been treated as distinct diseases for the most part, were actually all caused by the filarial worm that had been described by Lewis. Manson then went even further, suggesting that mosquitoes played a necessary role in the transmission of these filaria. His first hypothesis was wrong though, which is that humans got infected when they drank water contaminated by the filaria which had escaped from their dead mosquito hosts. He later revised this with some colleagues and got it right. He also suggested that the diurnal activity of the worms in the bloodstream was directly tied to the periods when mosquitoes were most active.

Erin Allmann Updyke

That's incredible. This was in what year did you say?

Erin Welsh

The 1870s.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah.

Erin Allmann Updyke

That is really fascinating.

Erin Welsh

And this was the first time that an infection of humans was directly linked to mosquitoes, like shown to be linked to mosquitoes, that mosquitoes played a necessary role in the development and transmission of this parasite. So this was the birth of medical entomology as a field essentially.

Erin Allmann Updyke

What?

Erin Welsh

Yeah. Manson's final major contribution to lymphatic filariasis was finding out exactly where those filaria go when they disappear from the peripheral blood, the microfilariae. Turns out it's larger blood vessels like of the lungs and other places. Really the only thing that he didn't do when it came to understanding the life cycle of lymphatic filariasis was demonstrate the presence of adult worms in patients with the infection. That honor would go to Joseph Bancroft, earning him the Bancroft in *Wuchereria bancrofti*. Sidenote, *Wuchereria* wasn't originally the genus name but *Wuchereria*'s colleague wrote in after the name was announced saying my friend also deserves credit for discovering this parasite.

Erin Allmann Updyke

My friend, I love that.

Erin Welsh

Yeah. I mean I don't know if it was my friend or it was like my colleague will not stop talking about this and complaining in the break room and I really need you to make this change so that we can move on with our lives. I don't know. It could have done that too.

Erin Allmann Updyke

Either one, either or.

Erin Welsh

It works. The 20th century saw more advances in lymphatic filariasis research, treatment, and control, including the discovery of additional species of filarial parasites as well as patterns in disease manifestations associated with different species. Effective antiparasitic treatments were only developed really in the 1970s and they leave something to be desired considering the sometimes serious side effects associated with their use as well as the fact that while many of them are great at killing the tiny larval worms, the microfilariae, they aren't super effective for the adult parasites. This is what you mentioned, Erin.

Erin Allmann Updyke

Yeah.

Erin Welsh

So treatment has to continue for many years, like you said 5-6, before there's a chance of stopping the transmission cycle. And there is some suggestion that resistance to these drugs might be on the rise, which is terrible, terrifying. Given all of this, we better start looking for alternatives, right?

Erin Allmann Updyke

Right?

Erin Welsh

That's where *Wolbachia* comes in. What the heck is *Wolbachia*? It may sound familiar to you listeners out there because we've mentioned it here and there on the podcast before. A quick search of our transcripts shows that we've mentioned *Wolbachia* in our dengue, chikungunya, Rocky Mountain spotted fever, and of course our onchocerciasis episodes. *Wolbachia* is a genus of intracellular bacteria, so they have to live inside cells, that infects arthropods like mosquitoes and filarial nematode parasites like *Wuchereria bancrofti* and *Brugia malayi*. I feel like I haven't said those species names the same way twice throughout this entire episode so far. Anyway, *Wolbachia* are extremely widespread, with an estimated 65% of all insect species infected with *Wolbachia pipientis* and nearly half of filarial species in Onchocercidae are infected, including nearly all of those that infect humans and those that cause heartworm in dogs and cats, which we should do an episode on.

Erin Allmann Updyke

Ooh, it's on our list.

Erin Welsh

It is. Yeah, you're right. How do these *Wolbachia* get into their arthropod and filarial hosts in the first place?

Erin Allmann Updyke

Well I don't know.

Erin Welsh: For arthropods, it's a combination of vertical transmission, like female to offspring, along with horizontal transmission which is unusual considering that these are intracellular bacteria, like they have to live within a cell.

Erin Allmann Updyke: Yeah.

Erin Welsh: But it seems that at least some research suggests that they can live outside of host cells for brief periods of time and go across cell membranes.

Erin Allmann Updyke: So what, are mosquitoes pooping them out and infecting other mosquitoes? How does that work?

Erin Welsh: I don't know.

Erin Allmann Updyke: Or is it like in arthropods that consume other arthropods? So food-borne kind of?

Erin Welsh: Yeah actually, I feel like it could be that for sure.

Erin Allmann Updyke: Interesting.

Erin Welsh: And I think that it's so fascinating because these patterns of transmission help to explain the genetic relationships among Wolbachia and their insect hosts. There's not necessarily a super close match.

Erin Allmann Updyke: Interesting.

Erin Welsh: Yeah. On the other hand, the bond between Wolbachia and filarial hosts is extremely tight. You can trace the evolutionary relationships among different species of filarial parasites by looking at the Wolbachia they harbor because there doesn't seem to be exchange or much exchange of different Wolbachia strains among the parasites.

Erin Allmann Updyke: Interesting.

Erin Welsh: In these species, Wolbachia is transmitted exclusively vertically from female to offspring. What does Wolbachia do inside their arthropod and filarial hosts? I feel like we've talked about this a little bit.

Erin Allmann Updyke: A little bit.

Erin Welsh: And I'm just going to talk about it, probably repeat a little bit again. No great detail. In arthropods, they often act as reproductive parasites, affecting things like sex determination, sexual differentiation, sperm-egg incompatibility, and even the cell cycle. While in filarial parasites, Wolbachia are more in a teammate, mutualistic role necessary for reproduction. And that's generally how I found they're talked about. So for arthropod hosts, it's like Wolbachia can be detrimental or at least like change things in a way that's not necessarily beneficial to the arthropod host. Whereas in filarial parasites, they're necessary and it's like a mutualistic relationship.

Erin Allmann Updyke: How weird.

Erin Welsh: Isn't that bizarre?

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah. Without Wolbachia, many species of filarial parasites can't reproduce and without their filarial hosts, those Wolbachia also can't replicate. And it's this key feature of the filarial-infecting Wolbachia that has gotten researchers so excited over the past couple of decades. Because if there was some way to kill the Wolbachia inside the adult parasites, say through the use of antibiotics, it may not kill the parasites themselves but it will prevent them from reproducing. And an antibiotic in combination with these existing antifilarial drugs could be the ultimate solution. So you're getting rid of the microfilariae throughout the bloodstream while also preventing the production of more microfilariae.

Erin Allmann Updyke

Yeah.

Erin Welsh

And Erin, you talked about this treatment strategy in our onchocerciasis episode and you also mentioned... I totally forgot too, your face is crazy.

Erin Allmann Updyke

I have no memory of that whatsoever.

Erin Welsh

So I didn't either because I looked up Wolbachia being like okay, when did we talk about this? And you went through this whole thing, it was great. We cover a lot of stuff.

Erin Allmann Updyke

We do. I almost forgot that we had covered that until I was researching this. And I was like oh, we did that already.

Erin Welsh

We did that. Yeah. Gosh. I know. Anyway.

Erin Allmann Updyke

But that's awesome.

Erin Welsh

Yeah, yeah. And you also... So in your wonderful explanation of how this could work, it really was great, you also mentioned a couple of drawbacks. One of which is that while most antifilarial drugs can be administered once or twice a year, which is great in terms of like logistics, the recommended course for antibiotics, primarily Doxycycline which is what would be used to treat the Wolbachia, that course is 4-6 weeks long, which as you can imagine is super logistically difficult. And taking doxy for that long is not recommended for children under the age of 9 and people who are pregnant or breastfeeding. Those are some pretty major hurdles. Fortunately, there has been some promising research done on alternative antibiotics that have shorter treatment regimens or more specifically target Wolbachia and leave the other parts of the human microbiome alone, right. Like you don't want to just continually wipe out your gut microbiome for 4-6 weeks.

Erin Allmann Updyke

Yeah.

Erin Welsh

And then there's phage therapy. So possibly using bacteriophages, viruses that infect bacteria, to kill the Wolbachia. And anyone who's interested in learning more about phage therapy should listen to our antibiotics part two episode for more of that story in general.

Erin Allmann Updyke

Yeah.

Erin Welsh

But to me, the moral of the Wolbachia and lymphatic filariasis story is not a very surprising one at all. It's just that the more that we invest in learning about Wolbachia, in identifying species differences among these filarial parasites, in disentangling the relationship between the mosquito vectors and these parasites, in developing treatment programs that take into consideration logistical ease and long term efficacy, and in understanding the tremendous social and economic impacts resulting from infection, the more we do all of these things, the more we can reduce the burden that these ancient parasites continue to have on the tens of millions of people around the globe living with this infection. So Erin, tell me where are we with lymphatic filariasis today? You have any good news for me?

Erin Allmann Updyke

I have news.

Erin Welsh

Okay. I guess I'll settle for that.

Erin Allmann Updyke

We'll get to it right after this break.

TPWKY

(transition theme)

Erin Allmann Updyke

So our numbers are unsurprisingly imperfect but we have more than I feel like we've had lately. So let's get into it. So first of all, an important piece of context when it comes to lymphatic filariasis is that in 1997 the World Health Organization classified this disease as eradicable or potentially eradicable. Which I think we've talked in previous episodes about what makes a disease a good candidate or a good target for eradication. But it's a lot to do with how it's transmitted, whether it can infect nonhuman animals, etc. So in any case, the World Health Organization said yeah, this is one, we could do this. And in 2000 they created the global program to eliminate lymphatic filariasis. And they passed a resolution with a goal to eliminate the parasitic infection of lymphatic filariasis by the year 2020.

Erin Welsh

Ugh.

Erin Allmann Updyke

This isn't that story. It's not eliminated, spoilers. But let's talk about where we were and where we are. So where did things stand in the year 2000 and where do things stand now in the year 2023, 3 years after this elimination target? In 2000, before this program, it was estimated depending on which paper you read that somewhere between 125-200 million people were living with lymphatic filariasis. Most papers were around the 120 million people estimate but at least one was 200,000.

Erin Welsh

It's so many people. It's so many people.

Erin Allmann Updyke

It's so many people. And within that, that's an estimated 40-45 million of whom had actual clinical overt symptomatic disease. And in addition, between 1.1-1.2 billion people, that's 18% of the global population, was living in an area at risk.

Erin Welsh

Oh my gosh.

Erin Allmann Updyke

At this time in the year 2000, it was also estimated that lymphatic filariasis caused almost 5 million disability adjusted life years annually.

Erin Welsh

Oh wow.

Erin Allmann Updyke

Which is the highest of any tropical disease after malaria. It cost over a billion dollars just in lost productivity every year. And the total cost of the burden of lymphatic filariasis was estimated at 5.25 billion dollars every year. And again is still to this day a leading cause of disfigurement which leads to so much stigmatization and ostracization and the second leading cause of permanent disability worldwide. So that's 2000. Then there's this initiative, mass drug administration all over the place, let's eliminate it. By 2018, it was estimated that the number of people living with lymphatic filariasis had dropped to just over 50 million people.

Erin Welsh

That's amazing progress.

Erin Allmann Updyke

It's amazing progress. It is nowhere near eliminated.

Erin Welsh

No.

Erin Allmann Updyke

But it is incredible progress. And this is where I really want to get into some public health information. Because what I think is really interesting to look at in these numbers is to try and understand not just how have we decreased the global burden of disease but how much disease have we potentially prevented?

Erin Welsh

Yeah.

Erin Allmann Updyke

Because when you think about it, especially in the case of lymphatic filariasis, the mainstay of these programs was and remains mass drug administration of these antiparasitic drugs that sure can prevent the progression of disease, but primarily are designed to interrupt transmission. And what interrupting transmission does is prevent people from getting infected or from getting more infected than they already are. These campaigns were not and are not curing disease for those who already have damage done. It's not fixing the damage causing lymphoedema, causing eventual elephantiasis.

Erin Welsh

Right.

Erin Allmann Updyke

And so in public health, one of the things that can be really difficult is quantifying that impact because if you're doing a good job in public health and we've talked about this before, you're preventing things from happening. And if you're doing that, you're not making money which is what agencies care about. You're saving money and saving lives and preventing disability. But it's really difficult to measure that because you're measuring things that don't happen rather than things that do happen.

Erin Welsh

Right.

Erin Allmann Updyke

So to try and quantify this, I found a really great paper from 2022 that I really enjoyed that used modeling, math modeling to try and estimate based on how many treatments have been provided, based on places where risk still exists, and what the numbers were like in terms of infections prior to the start of these campaigns compared to what they are now, to try and mathematically estimate how much of an impact these mass drug administration programs have had on the global burden of lymphatic filariasis. Specifically at three different cohorts of people. First is people who are protected from ever getting infected in the first place. Secondly is the cohort of people who had disease but are being protected from progression to symptomatic disease which is like secondary prevention. And then thirdly is that those you are preventing from having even worse morbidity from this disease. So based on this paper, the estimates are that between 2000-2020 this program has benefited a total of 58.5 million individuals. 26 million of whom, that's 44%, are primary prevention. That's 26 million people who never got infected as a result of this program.

Erin Welsh

That's amazing.

Erin Allmann Updyke

14.8 million people were in that second cohort, that is people who had the disease but are prevented from symptomatic disease by administration of these drugs at large. And 17.7 million in that third cohort, people who already have clinical disease but at least are prevented from getting worse and worse and worse. So what that overall looks like is the prevention of an estimated 44 million cases of symptomatic lymphatic filariasis, symptomatic hydrocele or lymphoedema. And if you project that over the lifetime, it's estimated that these programs have averted 244 million disability adjusted life years. So you're not seeing that progression of disease. Does that make sense?

Erin Welsh

Yeah. And it's incredible. And I feel like it's a really important thing that we look at oh the elimination goal was 2020 and there were still 50 million cases? But like okay, what aren't we seeing?

Erin Allmann Updyke

Right.

Erin Welsh

Like what else has been done?

Erin Allmann Updyke

Yeah.

Erin Welsh

And it is a long process but I like hearing about these things that are more difficult to measure but that are estimated secondary impacts of this program, of this initiative.

Erin Allmann Updyke

Right. Because it's also again a chronic disease that people who at the start of this program who already had clinical and symptomatic disease, these mass drug administration programs are not treating them. They are, as we see in this math model, potentially preventing further morbidity. But the point of these mass drug administration campaigns is really in the prevention of disease, primary and secondary prevention, which is really incredible. Now what's important is that these are models and like all models, they're only as good as the data that is input into them.

And inevitably, the data that existed prior to the start of these campaigns was limited in terms of what the true prevalence was prior to any of these controls and the baseline disease burden. And of course we are still talking about tens of millions of people who already have clinical disease and these campaigns are not ever going to be enough to treat their conditions. So there is a huge need for accessible and adequate treatment and management even after the interruption of transmission for this chronic disease. Because despite how much progress we've made, there are also still like you mentioned, Erin, nearly a billion people who live in areas that are still at risk. So where do we go from here?

Erin Welsh

Yeah.

Erin Allmann Updyke

Like you mentioned Erin, in addition to the mass drug administration campaigns, there is a promise of potentially targeting this bacterial endosymbiont, Wolbachia, and I find it hilarious that I talked so much about this in the onchocerciasis episode because I don't remember that. And because nothing that I saw talked specifically about using antibiotics per se to target it. But there have been an effort to produce vaccines that specifically target Wolbachia rather than vaccines that target the filarial worm itself. However there's also a theoretical promise for the development of vaccines to target *Wuchereria bancrofti* specifically, although most of the vaccines under development use *Brugia* as their model because it's easier to grow in other animal species, so it's easier to use in the lab.

Erin Welsh

Like one great thing about *Wuchereria bancrofti*, the only great thing is that it is potentially eradicable because it only infects humans. But that does make it harder to study in lab settings.

Erin Allmann Updyke

Right. So we have this other species that we use primarily to grow and do these vaccine studies and things like that, but it's imperfect.

Erin Welsh

Yeah.

Erin Allmann Updyke

But there's a theoretical promise based on this possibility that you can in fact develop immunity against these parasites. But it's really tricky because mostly our immune system develops this tolerance, which isn't necessarily going to be enough to have a vaccine that actually prevents infection. So far, the studies that have been done have at least suggested that any vaccine that is developed would have to be a multi antigen vaccine because anything that they've tried so far that targets just a single parasitic antigen definitely hasn't worked. Which makes sense when you think about how complex and interrelated the relationship between this parasite and our immune system is at baseline. So all that is to say that there is a lot of work being done to try and develop novel therapies and novel vaccines to try and reduce the burden further of this disease. But it remains the second leading cause of disability worldwide and a huge cause of stigmatization and ostracization in so many parts of the world, predominantly in parts of the world that are incredibly impoverished and have limited access to healthcare already. So that's lymphatic filariasis.

Erin Welsh

Sources?

Erin Allmann Updyke

Sources. People can read so much more.

Erin Welsh

There is so much more out there. I have a bunch of sources but I want to shout out in particular *The Cambridge World History of Human Disease*, which had some great info on the history of lymphatic filariasis. And then there's a great paper on *Wolbachia* by Bouchery et al from 2013 called 'The symbiotic role of *Wolbachia* and *Onchocercidae* and its impact on filariasis'.

Erin Allmann Updyke

I had a few papers for this. One of my favorites for just general biology was a 2010 paper in *The Lancet* titled 'Lymphatic Filariasis and *Onchocerciasis*'. And another one titled 'Lymphatic Filariasis' that was in the journal *Nursing Clinics* from 2019. And if you want to know more about that math modeling study which was an excellent read, that is from *Parasites and Vectors* 2022 and it was titled 'A Refined and Updated Health Impact Assessment of the Global Program to Eliminate Lymphatic Filariasis'. But we will post all of our sort from this episode and every one of our 100 something or other episodes on our website thispodcastwillkillyou.com under the EPISODES tab.

Erin Welsh

Thank you to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Allmann Updyke

Thank you to our incredible audio mixers over at Exactly Right.

Erin Welsh

And thank you to you, listeners. We hope that you learn something new.

Erin Allmann Updyke

Yeah. And a special shout out to our patrons as always, thank you so much for your support.

Erin Welsh

You are amazing. Well until next time, wash your hands.

Erin Allmann Updyke

You filthy animals.