

Erin Allmann Updyke

"E. F., male, age 49, physician began investigations of tularemia in Delta, Utah, July 23, 1919. His exposure differs from the other cases to be reported in that in addition to exposure to laboratory animals, he took blood and pus on two occasions from a human case which terminated fatally. On the 30th day of his investigation, August 23, 1919, E. F. became ill in the late afternoon, feeling tired and weak and having a temperature of 102.2 degrees. His fever continued until the 24th day. During the first 12 days of his illness, he packed up his laboratory equipment and animals in Utah with great difficulty and proceeded with them to Washington DC. And after his arrival, made a futile attempt to continue work. The next 14 days he spent in the hospital lying on the bed but not confined to the bed.

The departure of the patient from the hospital on the 28th day was attended with some forced exercise which resulted in a secondary rise of temperature which lasted four days, after which it remained normal. The second month was spent in a hotel, lying on the bed most of the time. The third month was one of slow convalescence. Throughout the illness there was an absence of localized pain or tenderness except that on the 16th day of illness, a sore throat developed on the right side. Practically the only complaint was that of languor or weakness and a desire to remain quiet on the bed."

TPWKY

(This Podcast Will Kill You intro theme)

Erin Allmann Updyke

Gosh.

Erin Welsh

Well yeah.

Erin Allmann Updyke

It's so long.

Erin Welsh

I know, it's such a long... And then if you kept reading this paper, there were like when it recurred or whatever relapsed or I don't know what the technical term is for tularemia.

Erin Allmann Updyke

Yeah.

Erin Welsh

But yeah. But the thing that I really like about this firsthand account is that the initials E. F., that stands for Edward Francis as in *Francisella tularensis*.

Erin Allmann Updyke

Oh Francisella.

Erin Welsh

Yeah.

Erin Allmann Updyke

Oh wow. Aw, poor guy.

Erin Welsh

I know, I know. And it took him like a long time apparently, according to one paper I read, to realize that this was tularemia, that what he was experiencing was tularemia. But then in retrospect he was like oh yeah. And then he tested his blood and the blood of several other laboratory workers and found that indeed it was tularemia.

Erin Allmann Updyke

Oh dear. Oh my gosh.

Erin Welsh

Yeah. So that was from a paper that he and a colleague wrote in 1922.

Erin Allmann Updyke

Wow.

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 tularemia.

Erin Welsh: Yeah. This is kind of a classic one I would say.

Erin Allmann Updyke: And my guess is that a lot of people have never heard of it.

Erin Welsh: Which is interesting because like I knew the name tularemia and then I had this vague association with rabbits in my head and that was it. But there is so much more to this.

Erin Allmann Updyke: I know. And it's such a big name in terms of public health because it is a potential agent of bioterrorism and all. So yeah, it's very interesting that I also knew very little about it. And I think there's probably a lot of people who have never even heard of it.

Erin Welsh: Yeah. And by the end of this episode, you'll be going how did I not know about this?

Erin Allmann Updyke: I hope so. That's the goal.

Erin Welsh: Yeah. Okay. But let's get into the episode starting with-

Erin Allmann Updyke: Quarantini time.

Erin Welsh: Quarantini time. What are we drinking this week?

Erin Allmann Updyke: We're drinking A Drop'll Do Ya.

Erin Welsh: We are. So named because the infectious dose is like 10 to 50 individual bacteria.

Erin Allmann Updyke: Yeah. 10 bacteria. What?

Erin Welsh: It's scary. But the recipe is not, it is a very... Did you like that segue?

Erin Allmann Updyke: Yeah, I sure did.

Erin Welsh: It's a very delicious and fairly simple kind of take on a Mojito with watermelon and of course mint and lime, a little bit of simple syrup and some vodka this time instead of rum.

Erin Allmann Updyke: Why not? Change it up. We'll post the full recipe for that quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com and our social media.

Erin Welsh: Oh I liked that.

Erin Allmann Updyke: Thanks.

Erin Welsh: And on our website, you can find all kinds of things including but not limited certainly, because I don't have the website in front of me, to things like our sources for each and every one of our episodes, our transcripts, our merch links, links to music by Bloodmobile, links to our bookshop.org affiliate account, our Goodreads list, Patreon, more stuff. Check it out.

Erin Allmann Updyke: Wonderfully said, Erin. On that note, shall we get started?

Erin Welsh: Let's do it right after this break.

TPWKY: (transition theme)

Erin Allmann Updyke: Francisella tularensis is a gram negative facultatively intracellular coccobacillus bacterium and the causative agent of course of tularemia. It turns out that there are four subspecies of Francisella tularensis, subspecies tularensis, subspecies holarctica, mediasiatica, and novicida.

Erin Welsh: That one I saw sometimes put in its own species and sometimes a subspecies.

Erin Allmann Updyke: Yeah.

Erin Welsh: And I was like there's probably some drama behind this but...

Erin Allmann Updyke: There is some drama and from what I can tell it was like in 2006 they made it a subspecies and then 2010 people were like no way, it's its own species! But then after that they're like nah, it's a subspecies. So that's how we'll call it.

Erin Welsh: Yeah.

Erin Allmann Updyke: In any case, we're not going to talk about that one very much because it's only Francisella tularensis subspecies, tularensis which is endemic to North America, that is the most virulent and the cause of the most severe disease. And holarctica is found throughout Eurasia and in North America and is the other major subspecies of Francisella tularensis that causes disease in humans. So those are the two subspecies that I'm gonna be focused on. They're also sometimes called type A and type B in the literature. But realistically, I'm just going to be talking about Francisella tularensis or I might even just say tularemia for the rest of this section.

Erin Welsh: Sounds good.

Erin Allmann Updyke: Great. So like we said at the top Erin, I kind of knew that this was going to be an interesting episode because I at least knew that tularemia was a potential like agent of bioterrorism or a potential bioweapon. But as I often do with this podcast, I really underestimated just how interesting of a bacterium this is.

Erin Welsh: We're always underestimating. How? Why?

Erin Allmann Updyke: You would think that we would learn by now.

Erin Welsh: Yeah.

Erin Allmann Updyke

Well let's get into it, shall we? So like I said off the top, this is a facultatively intracellular bacterium. What that means is that it can live both freely in the environment as well as live in and replicate within other ie host cells. And we'll talk a little bit more about that, what cells it's replicating in in detail. But as far as hosts go, this is a bacterium that can infect hundreds of animal species, mammals and birds and many different species of invertebrates which end up serving as arthropod vectors.

Erin Welsh

It was giving me Chagas disease vibes in that regard.

Erin Allmann Updyke

Ooh yeah, totally, totally. But even Chagas disease it's mostly just really just one vector.

Erin Welsh

Right, exactly.

Erin Allmann Updyke

Yeah, multiple species but one vector.

Erin Welsh

Yeah. Meanwhile tularensis just like any time anywhere, anything, let's make it happen.

Erin Allmann Updyke

So I am going to focus on what the disease tularemia looks like in humans and therefore how the life cycle ends up spilling over into human populations, how we get infected. But this is by no means primarily a disease of humans. It's fortunately quite a rare disease of humans and primarily a zoonotic disease of many different wildlife species. And like we mentioned early on, Francisella is also so highly infectious. So as I talk about how it gets into us and does all of these party tricks, keep in mind that as few as 10 individual bacteria can cause infection in humans.

Erin Welsh

Did you just describe causing disease in humans as party tricks?

Erin Allmann Updyke

Yes. Is that not a party trick for a bacteria?

Erin Welsh

I guess technically, yeah. Look what I can do. Yeah.

Erin Allmann Updyke

Look at me, mom. So let's get into the nitty gritty of how this bacterium lives its life, how it infects our cells, and what it actually looks like when we get sick. To begin, the life cycle of Francisella tularensis is a little bit difficult because we don't fully know the ecological niche of this bacterium at all. We don't know the major natural reservoir hosts or the major environments even that are conducive to the growth of this bacterium. And keep in mind like I said there are several different subspecies that can all persist in the environment and live intracellularly inside of host cells. Because it's a pretty difficult bacterium to grow in the lab in culture, there is some thought that perhaps in the environment it's not just persisting on its own, maybe it's in a host like an amoeba or a protozoa. Who knows? It's unclear. But it can infect and be a pathogen of a whole bunch of different animal species. One paper I read said over 250, other papers said over 190. So like a lot of animals.

Erin Welsh

A lot.

Erin Allmann Updyke

Including mammals and birds and arthropods.

Erin Welsh

Which is amazing.

Erin Allmann Updyke

I know.

Erin Welsh

Like just the different, like how diverse the animal species are-

Erin Allmann Updyke

Right.

Erin Welsh

That this bacterium can infect.

Erin Allmann Updyke

All of our different cell types, different immune systems that it's having to evade. It's really impressive.

Erin Welsh

Yeah.

Erin Allmann Updyke

When it comes to spillover from animals into humans, the two biggest groups of animals that are commonly found infected and thought to be kind of like the culprits of spillovers are lagomorphs, so rabbits and hares, and rodents, so things like mice and rats but also prairie dogs, voles, even aquatic rodents like muskrats and beavers and things. And I had to look up to make sure that all of these things were really rodents, what a diverse group rodents are.

Erin Welsh

Really, truly.

Erin Allmann Updyke

Yeah. But in many of these species, this bacterium seems to cause an acute infection and make all of these animals quite sick. So it's perhaps less likely that any of these species that we commonly find *Francisella tularensis* in are actually the natural reservoir host in the environment. So we don't really know. But then how do we actually get exposed? If these are the animals getting infected, we should at least have an answer for how humans get sick. And it turns out that that's more complicated too.

Erin Welsh

Of course it is.

Erin Allmann Updyke

Like we alluded to already, *Francisella tularensis* has been shown to be transmitted not by one or two or three but many different arthropod vectors. And by that I mean it can be transmitted by ticks, a whole bunch of different species, horse-flies or tabanids, a bunch of different species, and mosquitoes, a whole bunch of different species. Normally when we talk about vector-borne diseases on this podcast, I have this whole section on the life cycle of the pathogen in the vector, right? We go over a mosquito sucks up contaminated blood, the pathogen travels through the guts, bursts out, goes to the salivary glands, the mosquito bites another host and injects the pathogen, blah, blah, blah. That's how most vector-borne diseases work with whatever species or few species that are able to serve as vectors. But this is not that.

Erin Welsh

Are there different vectorial capabilities among these different vector species? Like are some mosquitoes better than others? I'm sure that there are probably differences between the two subspecies of *tularensis* of human health importance. Yeah.

Erin Allmann Updyke

Yeah, great question. Who knows? So different geographical regions do have different arthropods that seem to serve as the primary vector. For example, in Russia and Finland and Sweden, it's mostly various species of mosquito. Throughout most of the rest of Europe it's thought to be primarily tabanids, so horse-flies and ticks, and in the US there are a few species of tick and tabanids that seem to be the primary vectors. It's not strictly based on just which subspecies of *Francisella tularensis* we're talking about, since in Europe we really only see subspecies *holarctica* and in North America we see both *holarctica* and *tularensis* as well as a little bit of the other ones that are less important for human infections.

But what's really interesting is that when it comes to the life cycle of Francisella in these arthropods from one paper that I read, they noted that it has never been demonstrated that this bacterium is found in the salivary glands of any arthropod. And so it's thought that maybe the spread is just mechanical. You have mouth parts becoming infected when a fly or a mosquito bites. But ticks are found infected throughout their life cycle. So if a tick gets infected as a larva, they remain infected as they become a nymph and an adult, etc. And we really have very little data on like what is going on in these ticks, which ticks are really the best vectors, and all of that. We just simply don't know. Because here's the thing, transmission doesn't stop there. Vector-borne transmission is one way that people can become infected.

Erin Welsh

Right.

Erin Allmann Updyke

But human infection with tularemia is also associated with waterborne transmission from contaminated water sources and perhaps the scariest and most severe possible route of transmission is aerosolized bacteria that we inhale and this can come from contaminated soil or grasses or even directly from animal carcasses that were infected themselves. This is the way that makes Francisella tularensis a potential bioweapon agent, that combined with a very low infectious dose.

Erin Welsh

Right. Do we know how long Francisella tularensis is, like how durable is it in the environment?

Erin Allmann Updyke

Excellent question. It's been isolated. I love when you ask a question that I actually have the answer for it right away. It's like that rarely happens, so love it. It's been isolated from water and mud that has been stored like in laboratory conditions in a fridge, nice and cold, for up to 14 weeks. So pretty long time.

Erin Welsh

Yeah.

Erin Allmann Updyke

It's been isolated from tap water after three months and then in like dry straw for six months.

Erin Welsh

Oh my god.

Erin Allmann Updyke

Yeah, it's a long time. It's unclear how long it might persist under real environmental conditions, like not ideal conditions, especially in the World Health Organization's estimates of what would happen in the case of a bioterrorism attack where you're just aerosolizing dried bacteria and spreading it, then you'd probably have a lot more like UV decay and things wouldn't probably persist quite as long is the thought. We don't know really.

Erin Welsh

So that is definitely an interesting thing in the column of mechanical transmission for non tick arthropod vectors.

Erin Allmann Updyke

Yeah. It's maybe? There's also been suggested that maybe it's water that becomes contaminated and that's a reservoir where flies and especially mosquitoes during their larval stage could become infected, so not necessarily from biting a host. But we really just don't know. And so there's a lot of these different theories.

Erin Welsh

What route of transmission is the most common or like how is that pie sliced?

Erin Allmann Updyke

That's such a good question. I don't really know because surprisingly the epidemiological data that I found didn't really break out infections by different type. As we'll see, there's different symptoms that you see depending on the route of transmission. One paper that I read suggested that the form that you see after vectoral transmission or like direct contact with a mucous membrane or like a wound say, which would be a very similar route of transmission from like an infected animal through the skin, through a break in the skin, that that might account for up to 90% of cases. But I didn't see that number reported in very many papers so I'm not sure.

Erin Welsh

Interesting.

Erin Allmann Updyke

Yep. Honestly almost the only way that this is not transmitted, and this is a good thing, is directly person to person. So human to human transmission is incredibly rare, if not entirely nonexistent, which is very good.

Erin Welsh

Yeah. Can you imagine?

Erin Allmann Updyke

It would be terrifying. Absolutely terrifying. So once we are exposed, again to even incredibly low bacterial loads, *Francisella tularensis* exists mostly intracellularly and it predominantly infects our macrophages which are white blood cells. But it is capable of infecting a really wide range of cell types both in animals as well as in humans, which kind of makes sense when we think about just how many animals it's infecting overall. It's just really versatile.

Erin Welsh

Yeah but like how? How is it so good at doing this when most other bacteria are not?

Erin Allmann Updyke

Yeah. Yeah, great question. Do you want to guess my answer?

Erin Welsh

We don't know.

Erin Allmann Updyke

Yeah. We know some things.

Erin Welsh

Okay.

Erin Allmann Updyke

Part of what they do is they disrupt what's called the phagosome. And so this is when something like a macrophage especially engulfs a bacterium in order to try and our immune response get rid of these bacteria or other substances that are potentially pathogenic or just nonself, they form this structure called the phagosome. It's just like phages eat, right. So what *Francisella tularensis* is able to do is kind of like stabilize this phagosome initially, prevent it from doing its normal thing of killing those bacteria, and then escape and replicate in the cytoplasm. While we don't fully understand all the mechanisms by which they do this, it's not entirely uncommon compared to other intracellular bacteria. A lot of other intracellular bacteria are able to do kind of similar things. One thing that's interesting and cool about *Francisella tularensis* is that after they've burst out of the phagosome, replicated a whole bunch in the cytoplasm, they then induce apoptosis, aka cell death in the cells that they've infected, which allows for them to be released, go throughout the body, and infect further cells.

Erin Welsh

Virus style.

Erin Allmann Updyke

Exactly. And the exact mechanism by which they induce this cell death, we don't know, but it does seem to be unique to *Francisella tularensis*, meaning it's a different method than other intracellular pathogens like *Coxiella*, *Legionella*, *Salmonella*, etc. So yeah, we don't fully understand and that actually continues in terms of we don't fully understand our immune response to this pathogen either, which then has implications for our development of things like vaccines.

Erin Welsh

Question.

Erin Allmann Updyke

Answer maybe.

Erin Welsh

If you become infected with one of these subspecies, do you then have immunity to the second subspecies or to reinfection with the first?

Erin Allmann Updyke

It's a good question. I don't know the direct answer to that. What I can tell you is that the initial vaccines that were developed were based on the subspecies *holarctica*.

Erin Welsh

Yeah.

Erin Allmann Updyke

And they provided at least some protection against the *tularensis* subspecies which is of course the more virulent subspecies and the one that people really wanted to be able to develop a vaccine against.

Erin Welsh

Yeah.

Erin Allmann Updyke

So yes, at least some. How long does that immunity persist? Unclear. And that's been one of the big issues is trying to develop a vaccine that really does a good job of protecting against *tularensis*, subspecies *tularensis*, rather than just *holarctica*. And in the past the vaccines that have been developed have been mostly based on *holarctica* because it's safer to work with because it's less pathogenic.

Erin Welsh

Right, okay. Gotcha.

Erin Allmann Updyke

So yeah, that's what it's doing. Let's get to what does this illness actually look like? What is tularemia, right? In general, after exposure the incubation period initially is about 3-5 days. Symptoms often start with a fever and then some nonspecific symptoms like chills, malaise, headache. But there are multiple different forms of this disease that vary based on the route of transmission. So in addition to just nonspecific symptoms, let's look at all of the different kind of types of tularemia. The first and what like I mentioned is in some papers at least reported as the most common, like up to 90% of cases, is called the ulceroglandular form or less commonly there can be a glandular form without the ulcer at the beginning. What does this mean? This happens with vector-borne transmission, so from a tick or a mosquito or a fly that bit you on your skin somewhere, or from direct contact with an infected animal with like a break in the skin.

What you see with this form of tularemia is at the site of the bite or the infection, an ulcer. So it usually starts as a papule, like a little bump that then progresses to a pustule, like a blister with pus in it that looks inflamed, maybe warm, maybe tender, and can often kind of open to form this open ulcer. It might just look like a bug bite, it might not be that gnarly looking of an ulcer and it usually heals within a week or so. But if it doesn't, then what that means is that this infection has spread to the lymph nodes nearest the bite, which will then start to get enlarged. That's the glandular part of the name. These lymph nodes will get swollen and tender and if this infection becomes severe, you can have such severe swelling of these lymph nodes that they actually begin to drain pus from the lymph nodes to the skin, which is very, very serious.

Erin Welsh

It sounds so painful.

Erin Allmann Updyke

I know. And on top of that you're having these systemic symptoms, right. Like just fever and chills and feeling very sick in general. That's the ulceroglandular or in rarer cases you can have just the lymph nodes without that ulcer to begin with. Then there's the respiratory form, respiratory meaning that most commonly you have inhaled an aerosolized bacteria which is often happening from farming activities where hay or grasses or something are mowed or dealt with or from hunting activities where you're dealing with carcasses and maybe aerosolizing something from a carcass. Now if you have a respiratory infection from *Francisella tularensis* subspecies *holarctica*, usually it's a pretty mild flu-like nonspecific respiratory illness. But with subspecies *tularensis*, what we see are those fevers, chills, add on a cough, very severe chest pain, it can progress then to hemoptysis, so that's coughing up of blood. You might also see even more systemic symptoms like nausea and vomiting, diarrhea, so this GI tract becoming involved. Commonly one thing that we see is what's called pulse temperature dissociation which is something we talked about way, way, way, way back.

Erin Welsh

Yeah. I was like this sounds familiar. What episode?

Erin Allmann Updyke

I can't remember and I was going to try and look through but it would have taken a long time because we covered Dengue, Legionella, leptospirosis, leishmaniasis, typhoid, yellow fever, all of those can do this. Maybe it was typhoid because that's pretty classic or maybe Dengue. Okay but what does that mean?

Erin Welsh

Yeah.

Erin Allmann Updyke

So a typical physiologic response to fever when anyone has a fever is that our pulse will increase. So as our body temperature increases, our pulse increases, that is a typical physiologic response. So what a pulse temperature dissociation means is that you see a relative bradycardia, meaning your heart rate in comparison to your temperature is low, our pulse does not increase in compared to our temperature. So it appears slow. It's not that the pulse actually decreases.

Erin Welsh

That is fascinating. I want to know so much more about this.

Erin Allmann Updyke

Yeah, I know nothing more, unclear what the cause is.

Erin Welsh

Okay. So we don't understand how this works but what are the implications of this?

Erin Allmann Updyke

Great question. Part of the implication is just that it gives clinicians a sign to think there's only a few pathogens that tend to cause this, so it can help narrow down a diagnosis. In terms of what is this doing in our bodies, it's kind of a little bit unclear but probably not a good sign because what it means is that this infection has significantly altered the way that our physiology responds to infection and has disrupted that process. So like what does that mean? It means that our body is not working the way that it is supposed to. So we can see this in up to 42% of cases with respiratory tularemia and the case fatality rate of respiratory tularemia if left untreated can be upwards of 30%. And so it kind of tracks that this is a sign of a pretty severe infection.

Erin Welsh

It is fascinating how differently this infection can manifest based on how you get exposed.

Erin Allmann Updyke

Yeah. And there are a few other forms as well because like we mentioned, there's a few other possible routes of exposure. When people are infected from contaminated water sources it can cause like an oropharyngeal infection, so more of a mouth and throat infection and a GI infection, nausea, vomiting as the primary symptoms. And it can also cause an oculoglandular infection if the eye is the first route of entry, right, a mucous membrane, which then leads to a conjunctivitis, so infection of the eye and drainage from the eye and then the lymph nodes where your eye drains. All of these different forms, while they are very different especially initially, can then lead to a systemic bloodborne infection which can then lead to sepsis and septic shock and death.

Erin Welsh

So the difference in severity between the two subspecies tularensis and holarctica, is that due to which type of infection they are most likely to cause or is it just like the damage that's done or the likelihood of that turning into a blood infection? Like where does that difference come into play?

Erin Allmann Updyke

That is one big question that especially vaccine researchers and things are trying to answer. We don't fully know what these virulence factors are and what the big determining factors are on why subspecies tularensis is so much more virulent than subspecies holarctica. We don't really know. Both of them can cause all of these different types of infection and I don't have enough data to be able to say like holarctica is much more likely to cause X than Y, except that overall holarctica causes much less severe disease.

Erin Welsh

Right, okay.

Erin Allmann Updyke

Compared to tularensis. So that's a lot. When it comes to animals by the way, because I mentioned a lot of the species that we associate with tularemia, actually get quite sick from this pathogen. And in a lot of cases tularemia has a pretty high mortality rate in animals like rabbits and rodents and things. But the symptoms of this are going to vary so much by different animal species that I'm not going to go into detail on all of them. But in general, it's not super dissimilar to humans and that there's a lot of fevers, there's a lot of lethargy, it can be kind of a long infection. And again there's a potentially pretty high mortality rate.

Erin Welsh

What about our domestic animals? We've talked a lot about wildlife but our cats, dogs, horses, cows, gerbils, obviously gerbils, yes, but when would a gerbil encounter a wild animal to get tularemia?

Erin Allmann Updyke

On a farm maybe.

Erin Welsh

I really can't think of any other domestic animals. Tortoises?

Erin Allmann Updyke

I never saw reptiles listed so I don't know about that. Cats and dogs, yes. Cats far more likely to become infected and get sick compared to dogs, dogs get a lot less sick from tularemia. And then among livestock, I think it was sheep that tend to get the most sick of all of our livestock species.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah, yeah, yeah. But all of them potentially can get infected, it's just a matter of how sick they get. The good news is that so far at least antibiotics still work.

Erin Welsh

That's good.

Erin Allmann Updyke

That's good, that's good. But it can sometimes take prolonged courses of treatment. I didn't get into detail on this but like was kind of mentioned in the firsthand account, this is something that even if it's not fatal can cause a very prolonged illness that can also result in relapses where people become sick, kind of again get better, and then get sick again. I didn't look into detail in this, it didn't come up a lot in the papers that I read it, mostly it was a side note which is why it's a side note for me here. But I'm sure that there's some very interesting research in terms of the immune response and why this is possible, right. Is it because it's hanging out in our immune cells? It's infecting a lot of our white blood cells, does it hide in our spleen or our liver? What's going on? I don't know. But it's interesting.

Erin Welsh

It is, it is.

Erin Allmann Updyke

And terrifying.

Erin Welsh

Yeah. I feel like there are so many questions I have about like how does it do this?

Erin Allmann Updyke

Yeah.

Erin Welsh

And I think the intracellular part of it is always something that's just like so fascinating.

Erin Allmann Updyke

Yeah, it's obviously a huge part of the story of tularemia, right? Especially in that it's doing this living inside of cells in so many different species, right, across the entire animal kingdom. It's phenomenal.

Erin Welsh

Yeah.

Erin Allmann Updyke

But that is the biology of tularemia. So tell me Erin, how did we get here? Where did it come from? What's the deal?

Erin Welsh

Yeah, let's go through whatever I have right after this break.

TPWKY

(transition theme)

Erin Welsh

Chances are if you skim a scientific article about tularemia or *Francisella tularensis* published between say the 1930s and the 1970s or so, you're likely to come across some reference to this disease being quote unquote "an American disease" or something to that effect.

Erin Allmann Updyke

Ooh.

Erin Welsh

From a paper by Walter Simpson published in 1928, quote: "The history of tularemia makes fascinating study. It is in every respect the first American disease. The physicians of this country should be thrilled by the thought that not only was this disease discovered by American investigators but also because it's specific etiologic agent, the determination of its modes of transmission from animal to animal and from animal to man, the descriptions of its clinical manifestations and its pathology and bacteriology were made known by American workers. And leading all as the guiding spirit which has made this accomplishment possible is Edward Francis of the United States Public Health Service." It's a very long quote to kind of kick this off. But I feel like that kind of sums it up.

Erin Allmann Updyke

Yeah.

Erin Welsh

But yeah. This designation of tularemia as an American disease, first of all I just find it really interesting because I don't think that we've come across that before.

Erin Allmann Updyke

No.

Erin Welsh

It's like extreme patriotism about a particular disease. Usually it's like more like racism about disease or something.

Erin Allmann Updyke

Right, to like claim it like this one's ours.

Erin Welsh

Right. We stake our claim.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah. But this designation as an American disease would stick with tularemia for a really long time, like long after the bacterium or at least subspecies of this bacterium had been found to be globally distributed. But did *Francisella tularensis* originate in North America? Honestly I have no idea.

Erin Allmann Updyke

That's my line.

Erin Welsh

Yeah. We don't fully understand. But yeah, there's like quite a bit of really interesting and thorough research on the evolutionary relationships among *Francisella tularensis* subspecies and with other *Francisella* species and like the virulence genes potentially and when it acquired them and when it lost them and all of that cool stuff. But there doesn't seem to be a whole lot of consensus on which subspecies came first and from where especially. And it's no wonder because the ecologies of these bacteria are so different and their distribution is so wide ranging, honestly it's amazing that anyone has been able to make any sense out of it at all.

Erin Allmann Updyke

Yeah.

Erin Welsh

So this is what we think we do know about the two main subspecies that cause disease in humans. Like you said Erin, *Francisella tularensis* subspecies *tularensis* is the big baddie, can cause very deadly disease with the vast, vast majority of samples found in North America with one exception. In 1998, a paper reported that two isolates of this deadly *tularensis* subspecies were found in Slovakia near Bratislava. Isn't that interesting?

Erin Allmann Updyke

Yeah.

Erin Welsh

And as far as I could tell, that's been the only instance of this subspecies found outside of North America and how it got there and what it means is still a mystery.

Erin Allmann Updyke

Where was it? Like what kind of sample?

Erin Welsh

That's a good question, I don't remember.

Erin Allmann Updyke

Interesting.

Erin Welsh

Yeah. But the paper will be on our website.

Erin Allmann Updyke

Okay.

Erin Welsh

So if you want to check it out. But the other subspecies of human health importance, again like you mentioned Erin, subspecies holarctica, that's been found throughout the northern hemisphere. And so I feel like if you had to guess which came first, you might be more inclined to guess the one that is globally distributed. But in fact most papers think that the tularensis subspecies, the one only found in North America* is actually older and that the holarctica species evolved from it. And researchers think this because of the genetic diversity of the two subspecies. Tularensis is much more diverse than the holarctica they've tested. And in fact, holarctica is so unexpectedly not diverse that they think there was some sort of bottleneck event that was just like okay, everyone is now the same.

Erin Allmann Updyke

The same, yeah. That is interesting.

Erin Welsh

But the bottom line and what nearly every one of these papers ends with, and rightly so, is that there's a whole lot more Francisella tularensis diversity out there just waiting to be explored.

Erin Allmann Updyke

Yeah.

Erin Welsh

And so this story will probably change or at least more details will emerge as that research is done. So we don't know where in the world Francisella tularensis first emerged nor do we know when in history or prehistory this pathogen, these pathogens, first made their appearance. Or at least I didn't find it in the papers that I read. But as I was hunting for papers on Google Scholar, I came across at least three papers proposing that Francisella tularensis was the causative organism for several different ancient plagues. Each paper went into a particular plague, all of the papers were by the same individual author, and all were published in the same journal, Medical Hypotheses. And these were like wide ranging plagues, I'll make that point.

Okay, so that right away kind of stuck out as a little suspicious but interesting enough to look into. And so I started to skim these papers and the biology proposed in them didn't really make much sense at least as far as what we know about tularensis. So then I was like okay, what's going on with this journal? So I googled it. Turns out that it uses quote unquote "unconventional peer review", which I looked into it more, isn't very rigorous, which is intended to be that way because they're publishing the papers that no one else will publish. And it has been known to publish articles denying AIDS as well as articles on other horribly offensive and completely nonfactual topics. So I dug a little bit deeper to see if I could find any other mention of tularemia and the Hittite plague, which is the subject of one of these papers.

And I found an amazing book chapter called 'Beyond The Differential Diagnosis: New Approaches to the Bioarchaeology of the Hittite Plague' by Smith-Guzmán, Ros, and Kuckens. I'll put it on our sources on our website. But anyway I came across this chapter because it mentioned that the tularemia hypothesis had been disregarded because of a lack of biological plausibility. And then I kept reading because it provided this amazing 11 step, like step by step discussion of how you could incorporate so many different and varied methods to arrive at a likely causative agent for ancient epidemics, which often have very limited physical evidence. By the way, they concluded that malaria was a likely culprit for the Hittite plague. So this was kind of a long detour with not very much meat to it. But I really wanted to include it because I feel like it illustrates how hard it can be sometimes to tell whether something is a legitimate source or not.

Erin Allmann Updyke

Oh my gosh.

Erin Welsh

Like you can find these papers on PUBMED and on the National Library of Medicine Journal archive, it's on Google Scholar, right. So just because it's on Google Scholar doesn't mean it's necessarily legitimate. Or just like it just shows how crucial it is to keep doing that little bit of extra digging to help you decide if something is a good source. So keep going down that rabbit hole because at the end of it you'll get better at spotting these crappy sources and you get to appreciate the good ones.

Erin Allmann Updyke

And hopefully not get tularemia. Get it, rabbit hole? Sorry.

Erin Welsh

Wow.

Erin Allmann Updyke

I'm so sorry. I'm so sorry.

Erin Welsh

Moving on.

Erin Allmann Updyke

But I agree 100%.

Erin Welsh

Yeah. It was kind of like a nice refresher of oh yeah, okay, stuff like this is... Anyway, so that's all I've got for tularemia in ancient times which isn't really anything at all turns out. So instead let's move on to the discovery phase of this disease.

Erin Allmann Updyke

Let's.

Erin Welsh

The story begins with the 1906 San Francisco earthquake or rather the fallout from it. Not what you were expecting.

Erin Allmann Updyke

Not at all.

Erin Welsh

Yeah. To call this earthquake devastating would be an incredible understatement. An estimated 80% of the city was destroyed and 250,000 people were left without a place to live. As listeners of this podcast are probably well aware, these types of conditions are perfect for diseases to break out and just spread like wildfire. Since about 1900 or so, before the earthquake, San Francisco had been battling bubonic plague and things were just starting to seem under control when the earthquake struck. Soon after the earthquake, rats swarmed the wrecked city, sparking this renewed fear of this deadly disease. And there is a lot more to the story of rats and bubonic plague and racism and discrimination in San Francisco that I'm not going to get into in this episode. But one of the things that came out of this threat of plague after the earthquake was the push for more research on the ecology of this disease, of bubonic plague.

So the director of the US Public Health Service plague lab, George McCoy, decided to investigate some of the reservoir animals for plague in North America, particularly ground squirrels, curious whether the plague bacteria they harbored was in any way different from those in rats. So to answer this he went out trapping in Tulare County, California. At this point, the causative agent of bubonic plague, *Yersinia pestis*, had already been described. But McCoy was having trouble isolating this bacterium from some of his ground squirrel samples, even though they had symptoms of plague like these swollen lymph nodes, like lesions. Yeah. And so eventually after tinkering with the culture media recipe, McCoy and his colleague Charles Chapin were able to isolate a new microbe from the squirrels which they named *Bacterium tularensis*, after Tulare County.

Erin Allmann Updyke

Wow.

Erin Welsh

Eight years later in 1919, a researcher at the US Public Health Service named Edward Francis was sent out on his first field assignment to study an outbreak of something called deer fly fever in an area of rural Utah. Francis set to examining each person who was sick, taking samples from them, trying to grow microbes from the samples to figure out what was making them sick. And it didn't take him too long to figure out that the likely causative agent was *Bacterium tularensis*. So he called the disease tularemia.

Erin Allmann Updyke

Wow. Straightforward.

Erin Welsh

Yeah. Well yeah, I mean, there also was a little bit of this unfortunate situation where Francis got to know the bug all too well. Yeah, he picked up tularemia from someone who later died of tularemia and you know the rest from the firsthand account. But his illness, Francis's illness kicked off what would be an unlucky trend among tularemia researchers and many of them would get sick with the thing that they were studying over the next years, decades really. So I want to read you a quote from the same paper describing Francis's illness. Quote: "All of the men, six in number, who have been intimately connected during the past two years with the laboratory investigations of tularemia, which the public health service has been conducting, have contracted this disease. Such a record of morbidity among investigators of a disease is probably unique in the history of experimental medicine. Fortunately there were no fatalities." Endquote.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. And then this paper goes on to describe how some of these researchers that got tularemia had worked with deadly pathogens for decades and knew all of the PPE tricks and whatever. Some of them worked under rougher conditions in terms of like a field lab and others were working in like state of the art labs and still they got sick.

Erin Allmann Updyke

Yeah, it's just so infectious.

Erin Welsh

Yes. You can take as many precautions and still there's like such a high risk of getting sick.

Erin Allmann Updyke

I read it's also especially in laboratory conditions because even just opening the culture flask, you're potentially aerosolizing things. So yeah, yeah, yeah.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

It's impressive and terrifying. Yeah. So at some point in between taking all of these samples and recovering from tularemia, Francis had also carried out extensive testing to try to figure out where this bacterium was hiding out in nature and how humans got exposed to it, which as we learned is like a number of ways. So not a simple answer. Yeah. Francis isolated the bacterium from jackrabbits and ground squirrels and also showed that deer flies, mouse lice, and bedbugs could play a role in transmission to humans. His extensive and groundbreaking work on the disease would later inspire the genus name to be changed to Francisella.

Erin Allmann Updyke

Love that.

Erin Welsh

Yeah. But the cases of deer fly fever that Francis was sent to investigate in 1919 didn't mark the very first outbreak of tularemia in humans of course, because as is so often the case once Francis and his colleagues published their findings, other likely past cases or past outbreaks of this disease came to light. The oldest of these dates back to 1818 and comes from Japan. A disease named yato-byo, hare disease, that appeared in people who had handled rabbit meat. In the 1890s in Norway, an illness called lemming fever was described and this is maybe a stretch but there's also a description of a tularemia-like disease in lemmings in Norway from the 1600s, like 1653.

Yeah. But even in the US there had been outbreaks or at least individual cases of deer fly fever prior to Francis's investigations in Ohio, Utah, California, probably other places. This was clearly not a disease that was new to humans nor was it limited to North America. After it came out that Francisella tularensis can cause disease in humans, cases and outbreaks began to be reported all over the globe, from Japan where in 1926 a widespread disease was linked to rabbits and concluded to be caused by Francisella tularensis, to Russia where four outbreaks between 1926-1929 involving over 1100 cases were determined to be tularemia.

Erin Allmann Updyke

Whoa.

Erin Welsh

And in these outbreaks in Russia, flooding had driven water rats, which I'm guessing are European water voles which are actually voles but look like rats. Anyway, this flooding had driven them out of their holes. And the Russian government offered rewards for every skin to try to reduce their numbers which led to a lot of exposure by killing all these rats.

Erin Allmann Updyke

Yeah.

Erin Welsh

We also see tularemia popping up in Turkey, Canada, Austria, Sweden, Italy, and many other regions. And over time a pattern began to emerge in who was most likely to get infected. Basically people handling wildlife, hunters, trappers, cooks, agricultural workers, and naturally war. Similar to what I mentioned earlier in terms of an increased rat population following the 1906 San Francisco earthquake, war also created tremendous opportunities for Francisella tularensis to thrive, largely through increases in rodent populations. For instance during WWII in the Soviet Union, a huge amount of arable land was not cultivated, harvests were delayed or destroyed, buildings were demolished, and poor sanitary conditions all resulted in a ton, a ton of increased contact between humans and rodents, with an estimated 67,000 cases between 1941-1942 in just one region.

Erin Allmann Updyke

What?

Erin Welsh

Along the eastern front there may have been tens of thousands of Russian and German soldiers may also have been infected during the war. And because this is a pathogen that infects wildlife, the increase in human cases and rodent populations also meant that *Francisella tularensis*, subspecies *holarctica* of course, became more established and disseminated in the environment causing a long term persistence in high caseloads.

Erin Allmann Updyke

Wow. Okay.

Erin Welsh

I read in a paper that in the 1940s there were an estimated 100,000 cases annually of tularemia in the Soviet Union.

Erin Allmann Updyke

Ay ay ay!

Erin Welsh

I know, I know. It was probably helped along by exposure routes, like breathing in dust that had been contaminated by dead rodents or their poop or contaminated water supplies. Like basically all the things that you would expect to see increase during times of war.

Erin Allmann Updyke

Ay ay ay.

Erin Welsh

Fortunately sanitary conditions improved in later decades, plus there was that vaccine that was developed and was widely administered, like mass vaccination campaigns in the Soviet Union. I think 60 million people ended up getting vaccinated between 1946-1960.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. And by the 1990s, annual cases there had decreased to 100-400.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah, yeah. But I'm getting ahead of myself there. The incredible increase in both the number of cases and the distribution of this pathogen prompted more research into *Francisella tularensis* throughout the 1930s and 1940s, its ecology, its clinical picture, exposure routes, the role of arthropod vectors like ticks, other animals it could infect, and so much more. And we already know from Francis' research in 1919 that this pathogen could be a dangerous one to work with. And so what do you think happened once more and more bacteriologists turned their attention to it?

Erin Allmann Updyke

Uh oh.

Erin Welsh

Yeah, more and more cases among these researchers. *Francisella tularensis* had earned a reputation as a deadly microbe that was disturbingly difficult to avoid in lab settings, so much so that in some countries, researchers just flat out refused to work with it. Other countries however saw a silver lining.

Erin Allmann Updyke

Oh dear.

Erin Welsh

The potential of *Francisella tularensis* as a biological weapon. Working in its favor are the following. There are seven, so buckle up. Number one, it's highly infectious, like you said as few as 10-100 bacteria needed to cause disease. Number two, it's easy to find in nature because of its wide distribution. Number three, it's easy to make a lot of. Number four, it can be aerosolized very easily as lawnmower associated outbreaks have shown, they started out on Martha's Vineyard, there's been some in Colorado. Yeah, it's really horrible.

Erin Allmann Updyke Terrifying.

Erin Welsh Yeah. Number five, it can spill back from humans into the environment and stay there for a long time continuing to pop up. Number six, only a few antibiotics work on it and resistant strains could in theory be easily engineered.

Erin Allmann Updyke Yeah.

Erin Welsh And number seven, no vaccine is currently available.

Erin Allmann Updyke Yeah.

Erin Welsh As early as WWII, countries such as Japan, the US, the USSR, and probably many others devoted a lot of time and effort into determining whether or not Francisella tularensis could be developed into a suitable biological weapon. And this wasn't the only pathogen considered of course but it was given really high priority for those reasons I mentioned. And some of this quote unquote "research" involved just straight up torture, right, injecting people with tularemia. One of the most publicized was the horrific torture carried out by the Japanese Research Unit 731 operating in Manchuria. And the US used human quote unquote "volunteers" in the 1950s who were infected with Francisella tularensis using different exposure routes, especially aerosol, and different levels of bacteria. And so this is how we know that the infectious dose is 10-50.

Erin Allmann Updyke I read that in several papers and it's disturbing how all of the papers that I read literally just say human volunteers. That's what they say.

Erin Welsh Yeah. So I don't know the circumstances of what that volunteering looked like. Were they given a consent form?

Erin Allmann Updyke Right.

Erin Welsh Were they given full disclosure about the risks associated with this?

Erin Allmann Updyke I mean 1950s, almost certainly not.

Erin Welsh No, I know, definitely not. Yeah, I think it's just sort of the fact that it's just like and they were volunteers.

Erin Allmann Updyke Right. It's just like brushed under. It's like oh we learned this from human volunteers. Like what? Sorry, back it up. More detail, please.

Erin Welsh Yeah.

Erin Allmann Updyke Yeah.

Erin Welsh

Yeah. But interest in this pathogen as a potential biological weapon continued to rise and of course with it was increasing concern about its actual use. And so this actually led the WHO to develop this model that you talked about earlier, Erin, to estimate just how bad an attack using the pathogen could be. And they incorporated things actually like meteorological conditions, decay rate of the bacteria in the air, antibiotic sensitivity or resistance, infectious dose, case fatality rate, etc. And they estimated that if 50 kg of an antibiotic resistant strain of *Francisella tularensis* was released in a metropolitan area with a population of 5 million people, 250,000 individuals would become incapacitated and 19,000 would die.

Erin Allmann Updyke

Yeah.

Erin Welsh

And I say incapacitated just because like you said earlier, Erin, there's this really long period of recovery with relapses in later months. And the CDC also performed its own cost estimate. I love that it's always cost.

Erin Allmann Updyke

Always.

Erin Welsh

Let's just equate human lives to monetary value.

Erin Allmann Updyke

I mean is that not America for you?

Erin Welsh

Yeah. And in 1997 dollars, they estimated that it would cost \$5.4 billion for every 100,000 people exposed in an aerosol attack.

Erin Allmann Updyke

Ooh!

Erin Welsh

Yeah.

Erin Allmann Updyke

Oh wow!

Erin Welsh

I mean now that we are equating human lives with money, that's really expensive.

Erin Allmann Updyke

Yeah, it really is.

Erin Welsh

Really expensive, yeah. Only smallpox and anthrax were estimated to be more expensive actually.

Erin Allmann Updyke

Wow.

Erin Welsh

And although the US officially ended its bioweapon development program in the early 1970s, research on antibiotic and vaccine resistant *Francisella tularensis* as a bioweapon allegedly continued in the Soviet Union until the early 1990s, although this has not been confirmed. But to this day, *Francisella tularensis* is on the very short list of category A select agents by the CDC which are organisms that quote "pose a risk to national security because they can be easily disseminated or transmitted from person to person, result in high mortality rates, and have the potential for major public health impact, might cause public panic and social disruption, and require special action for public health preparedness." And it really is a very short list. Anthrax, botulism, plague, smallpox, some viral hemorrhagic fevers, Ebola, Marburg, Lassa, Machupo, and tularemia. That's it. That's it.

Erin Allmann Updyke: I did want to point out one thing about that list, we have covered almost every single thing on that list.

Erin Welsh: I know, we're still missing Lassa and Machupo.

Erin Allmann Updyke: Lassa and Machupo. And that's it.

Erin Welsh: I know.

Erin Allmann Updyke: So wow, wow.

Erin Welsh: I know. And Marburg very recently.

Erin Allmann Updyke: Yeah, exactly.

Erin Welsh: Just a couple of episodes ago, I think. But yeah, I think that just underlines how seriously people take this bacterium and for very good reason. And because of this and because of all the other really fascinating aspects of the biology of tularemia that you explored, Erin, research on this pathogen is still an incredibly active field.

Erin Allmann Updyke: Yeah.

Erin Welsh: And we're learning so much more about this deadly microbe every year. So Erin, what can you tell me about tularemia today?

Erin Allmann Updyke: Ooh, I can't wait to get into it right after a short break.

TPWKY: (transition theme)

Erin Allmann Updyke: So like you mentioned Erin, tularemia, *Francisella tularensis* and all of its subspecies, has really only been found in the northern hemisphere. But in the northern hemisphere it's reported very widely, throughout North America, Europe, Russia, into Japan, China, throughout a lot of Asia. Not really reported in the southern hemisphere, although at least one subspecies has been found in Australia at least one time. I don't know. But throughout its range, tularemia is generally considered an emerging or reemerging disease. That is that over the last 20 years, it's being found in expanded geographic ranges, popping up in places that we didn't know that it was, either because it wasn't there before or because we just hadn't found it there before, hard to say which.

It's being found in new host species, same qualifiers, was it just not there or had we not found it? And it's popping back up in locations that it hadn't been seen for quite some time. And this is true really throughout its range. And throughout all of the northern hemisphere, it's not an even distribution across various countries or territories or regions. This tends to be an infection that's more common in rural areas of various countries but it's not entirely clear what all of the different determining factors are that go into when you're going to have say an episodic outbreak in animals or an epidemic in humans or even sporadic cases. And part of that comes back to that we don't really know what the environmental reservoirs are, we don't really know what the conditions are that facilitate this spread per se.

Erin Welsh: Yeah. It's so weirdly patchy.

Erin Allmann Updyke

Yes, very patchy.

Erin Welsh

And like I can only imagine how many variables would go into a model that would begin to try to estimate where and when and how. And yeah.

Erin Allmann Updyke

I love thinking about it though because it would be such a complicated model. The other thing too is that it's very patchy in terms of identification and reporting, right. Every different country or even different regions of different countries might have different things that they're doing to both actively surveil or passively surveil for this disease in animals and in humans and maybe are reporting it differently on a country by country level, right. One quote from a paper that I really liked that kind of sums up why it is so difficult to really understand what the kind of global prevalence and incidence of this disease is sums up like this. And I quote: "Thus a correct assessment requires extensive trapping of the primary mammalian reservoirs of *F. tularensis* such as rodents and lagomorphs and of vectors, ticks, flies, and mosquitoes. In most countries, such epidemiological investigations are not made currently since they are very time consuming and expensive." Endquote.

Erin Welsh

Well there you have it.

Erin Allmann Updyke

There you have it, right? We don't know, we're not doing it. We need a one health approach and we mostly don't have one.

Erin Welsh

Yep, yep.

Erin Allmann Updyke

But we do have some things. So let's go over some of the numbers that we do have, shall we? In the US, the most recent official like morbidity and mortality weekly report on this which sums up data from 2001-2010, reported 1208 cases in the US in that time. So that's an average, a median of about 126 cases per year. Now on the CDC website you can also find much more up to date data from every year since then. So from 2010-2020 the numbers seem to have gone up. Again, I can't tell you if this is statistically significant because the reports are not out. But just the raw numbers that exist tell us that over the most recent 10 years, the median number of cases is 214 compared to 126 the year before. And the range also is on the higher end, between 149-314 cases. So overall greater numbers every year.

Erin Welsh

Interesting.

Erin Allmann Updyke

It is interesting. In that time frame, the year with the greatest number of cases in the US was 2015 where there were 314 cases reported. Over 100 of these were in Colorado, Nebraska, South Dakota, and Wyoming. These are states that many years do see some numbers of tularemia but this was a huge increase in those states compared to like the prior 10 years combined. So this is part of what I mean when I say that this is an emerging and reemerging disease, we're seeing sporadic cases here and there in places where maybe it existed but not necessarily to the extent that we see today or in some years.

Erin Welsh

I'm curious about those strong year to year fluctuations because it makes me think about like, okay, are rodent populations going up? And was it a really strong rainy year the year before where there's a lot of whatever, more nuts of a certain kind?

Erin Allmann Updyke

Oh Erin, Brian Allan would be so proud of you, you disease ecologist, you. But yes, that is one of the like possible thoughts on an explanation is that there may have been increased rainfall which promotes vegetation growth and potentially pathogen survival in the environment and then leads to increased rodent and rabbit populations. Again, very à la Lyme disease.

Erin Welsh

Yeah.

Erin Allmann Updyke

Where you have these very complex cycles that really require a very integrated approach to be able to understand. But even more complicated because it's not just one or two or a few species that we have to look at.

Erin Welsh

Right, right.

Erin Allmann Updyke

A vector and reservoir and etc. So that's the US. In Europe, the European Centers for Disease Control and Prevention also collects data on tularemia, it's a notifiable disease. But each country, each member state of the EU has different surveillance systems and different degrees of public awareness. But let's go over some numbers, shall we? Between 1992-2012, over 18,000 cases were reported to either the World Health Organization or the ECDC. The majority of these were in Finland, Sweden, and Turkey, like the highest numbers overall. And then there's a more recent paper from 2021 that reported that in that year, just over 800 cases of tularemia in humans were reported across 26 member countries. That was an increase over 2020 and increase over the average of 2017-2019, though in 2019 there was a large outbreak in Sweden, so the total number that year was over 1200. And then Erin, just because you mentioned Russia so much and those numbers back in the former Soviet Union, I did find one paper that reported in 2019 only 42 cases reported in Russia.

Erin Welsh

Wow.

Erin Allmann Updyke

Right?

Erin Welsh

Yeah.

Erin Allmann Updyke

Way better.

Erin Welsh

Way better. Those are some much, much better numbers.

Erin Allmann Updyke

Yeah, yeah. But in addition to this geographic variation, the other thing that we see with tularemia is seasonal variation, which isn't surprising since we do have a lot of arthropod-borne infection and environmental transmission really. So it's northern hemisphere summer months that tends to have the highest number of cases but this of course varies right across all of Europe and between Europe and North America, different states in the US report cases year round, others not so much, etc, etc. But that's at least what we know of the epidemiology of tularemia across its distribution. I do think that one of the things that's most interesting, scary about it is that we do seem to be seeing these increases, right, and how much of that is just better surveillance vs true increases? We don't know, we really don't know.

Erin Welsh

Right. And it seems like there's still so much that we don't know about the ecology, that getting an answer to that is not going to be possible without more research.

Erin Allmann Updyke

Exactly. Speaking of more research, in addition I think to this one health approach and a better understanding of not just the incidence and prevalence in humans but in animals and the ecology of this infection and all of that, I think that that's a really important part of the future research that is being done, that needs to be done. But the other part of this of course is the vaccines of which we don't have one currently, not one that's licensed. There was a vaccine, it was a live vaccine, it was effective, it was based on the holarctica subspecies but had at least some efficacy against the more virulent tularensis subspecies.

But part of the reason that it was never fully licensed in the US at least by the FDA is in part because we did not and still don't understand the mechanisms by which this vaccine-derived strain was attenuated, was made to be even less virulent. And because we didn't understand that and we still don't really understand the virulence of this pathogen, how does it make us so sick? Why does this one make us so much sicker than the other? There's a lot of concern that this could easily revert to a more pathogenic strain. So for longtime listeners, you might remember from our vaccines episode that there's a lot of different types of vaccines that exist and there's pros and cons to all of these. With live vaccines which are a live virus, these are a strain of virus that gives us a very robust immune response, really good, usually long lasting immunity, but without any illness, without a real infection per se.

But with live vaccines, there's the possibility that these vaccine-derived attenuated, less virulent strains can gain some of those variance factors back and then actually cause disease. And we see this on occasion with things like the live polio vaccine, for example. And that's why across the globe we really don't use that vaccine in most of the world. Because polio is no longer prevalent in most of the world, the risk-benefit analysis has changed. So we now use an inactivated injected vaccine for most people that are getting vaccinated with polio. When it comes to tularemia, the risk-benefit analysis is already going to be very different because this is a rare disease, right. So the risk of using a live virus that has the potential to revert to something more virulent is already, like that calculus is already different than something that's very prevalent. Does that make sense?

Erin Welsh

Yes. Yeah, no, it does.

Erin Allmann Updyke

So there's a lot of research being done. And in the US especially since 2001 when the anthrax letters came and were a thing and the fear of a bioweapon attack kind of increased again, there has been a ton of research on alternative vaccines, alternative live vaccines, killed vaccines, component vaccines, and all the different types of vaccines for tularemia. We still don't have one. All of the other vaccine types so far just haven't come to fruition in a way that has led to a vaccine coming to market essentially. But I do have a great paper, it's a little old now, it's from 2015, but it kind of goes over what we had so far and where we may go from here. But that's tularemia.

Erin Welsh

So much more to it than I thought.

Erin Allmann Updyke

I know!

Erin Welsh

I know I say that a lot but...

Erin Allmann Updyke

Yeah, I underestimated it, won't do that again.

Erin Welsh

Yeah, certainly not. I want to keep an eye on Colorado numbers in the next few years, see if this rainy spring will have any impact down the line.

Erin Allmann Updyke

Oh, we'll have to do an update episode, Erin.

Erin Welsh

Sources?

Erin Allmann Updyke

Sources?

Erin Welsh
I have so many because I think I just like pulled snippets from 1000 papers. I'm gonna shout out three right now but there are so many more out there. For the history I really liked a paper by Sjöstedt from 2007 called 'Tularemia: History, Epidemiology, Pathogen Physiology, and Clinical Manifestations'. And for the bioweapon aspects of tularemia, there's a great paper by Oyston et al from 2004 called 'Tularemia: bioterrorism defencee renews interest in Francisella tularensis'.

Erin Allmann Updyke
I read that paper too. I liked it a lot.

Erin Welsh
Yeah.

Erin Allmann Updyke
I had for the biology a couple of other also older papers but they were really nice. One from JAMA in 2001 that was called 'Tularemia as a biological weapon: medical and public health management', that was a fun one.

Erin Welsh
I read that one.

Erin Allmann Updyke
And then I had a whole bunch of papers updating the epidemiology in the US and in Europe and across its range. We'll post the sources from this episode and every one of our 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 Lianna Squillace for all of the wonderful sound mixing, we appreciate it so much.

Erin Welsh
We do. Thank you to Exactly Right.

Erin Allmann Updyke
And thank you to you, listeners. I hope you liked this episode.

Erin Welsh
Yeah, I hope you learned something new. That's pretty much our goal every single time.

Erin Allmann Updyke
Every time, literally.

Erin Welsh
Yeah, yeah. And thank you to our wonderful generous patrons. We appreciate you and your amazing support so very much.

Erin Allmann Updyke
So much.

Erin Welsh
Well until next time, wash your hands.

Erin Allmann Updyke
You filthy animals.