

TPWKY

This is Exactly Right.

Erin Allmann Updyke

"On one occasion I spent the night with the brigade machine gun officer and the signals officer in one of the captured German dugouts. We tossed down for the night in the hopes of getting some sleep but it was not to be. We no sooner laid down than hordes of lice got up, so we went round to the medical officer who was also in the dugout with his equipment and he gave us some ointment which he assured us would keep the little brutes away. We anointed ourselves all over with the stuff and again laid down in great hopes but it was not to be because instead of discouraging them it seemed to act like a kind of hors d'oeuvre and the little beggars went at their feast with renewed vigor."

Erin Welsh

"A full day's rest allowed us to clean up a bit and to launch a full scale attack on lice. I sat in a quiet corner of a barn for two hours delousing myself as best I could. We were all at it, for none of us escaped their vile attentions. The things lay in the seams of trousers, in the deep furrows of long, thick wooly pants and seemed impregnable in their deep entrenchments. A lighted candle applied where they were thickest made them pop. After a session of this my face would be covered with small blood spots from extra big fellows which had popped too vigorously. Lice hunting was called 'chatting', in parcels from home it was usual to receive a tin of supposedly death-dealing powder or pomade but the lice thrived on the stuff."

Erin Allmann Updyke

"We had to sleep fully dressed. Of course this was very uncomfortable with the pressure of ammunition on one's chest restricted breathing. Furthermore when a little warmth was obtained the vermin used to get busy and for some unexplained reason they always seemed to get lively in the portion of one's back that lay underneath the belt and was the most inaccessible spot. The only way to obtain relief was to get out of the dugout, put a rifle barrel between the belt and rub up and down like a donkey at a gatepost. This stopped it for a bit but as soon as one got back into the dugout and was getting reasonably warm, so would the little brutes get going again."

TPWKY

(This Podcast Will Kill You intro theme)

Erin Allmann Updyke

That's really funny.

Erin Welsh

(laughs) So those were all accounts of lice during trench warfare during WWI.

Erin Allmann Updyke

It sounds truly awful, Erin.

Erin Welsh

I just can't imagine and I also have some numbers that I'll share later on just to kind of put an even more horrific spin to this.

Erin Allmann Updyke

Yeah. Lice, fleas, all the little things that just don't stop biting you. Ugh.

Erin Welsh

I know, I know.

Erin Allmann Updyke

Yeah.

Erin Welsh

By the way those were from various soldiers from WWI and we will post the full names and links and whatever on our website. And also 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 welcome to a very weird episode today.

Erin Welsh: Yeah. We did not intend for this episode to be...we had no idea what we were getting into. We thought this was gonna be a run of the mill episode.

Erin Allmann Updyke: Yeah.

Erin Welsh: And it's not but that's okay.

Erin Allmann Updyke: We were very wrong but that means we learned something new.

Erin Welsh: Yeah, lots of new things.

Erin Allmann Updyke: Yeah.

Erin Welsh: So what are we covering today, Erin?

Erin Allmann Updyke: Well it's a good question. We're covering the genus Bartonella which causes a whole bunch of diseases, some of which listeners you may have heard of like cat scratch disease for example, also trench fever, hence the lice in trenches firsthand accounts. And also Carrion's disease.

Erin Welsh: Yeah.

Erin Allmann Updyke: Which you may not have heard of because I hadn't really.

Erin Welsh: I hadn't either but I learned a lot about it and I think it's actually gonna be fun to do.

Erin Allmann Updyke: I'm excited about. I think it's gonna be at least something new.

Erin Welsh: Yeah, yeah. And so this episode is gonna be formatted a little bit differently, just as an explanation. What we're gonna do is we'll go through the biology, history, biology, history, biology, history in sort of like three mini episodes almost.

Erin Allmann Updyke: Yeah.

Erin Welsh: And then we'll wrap it up with a current status and that's kind of how it'll be.

Erin Allmann Updyke: It's like three episodes for the price of one. You know what I'm saying?

Erin Welsh: Yeah. Look at it that way. Certainly the work felt like three episodes for the price of one.

Erin Allmann Updyke: Yep, 100%. So speaking of which I think it's about quarantini time.

Erin Welsh: It is. So what are we drinking this week?

Erin Allmann Updyke: We're drinking A Game Of Cat And Louse.

Erin Welsh: I love this name.

Erin Allmann Updyke I also do too even though cat scratch is really fleas more than lice but it's still really good.

Erin Welsh I know. Yeah.

Erin Allmann Updyke What's in A Game Of Cat And Louse, Erin?

Erin Welsh In A Game Of Cat And Louse is gin, peach nectar, sparkling water, some lemon juice, and then garnish it with a little fresh sprig of rosemary.

Erin Allmann Updyke Yum.

Erin Welsh Yeah.

Erin Allmann Updyke We'll post the full recipe for that quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com and on all of our social media channels as always.

Erin Welsh As always. And business. Our website, you can find lots of things. You can find transcripts, you can find our references to all of the episodes, you can find a Goodreads list, a bookshop.org affiliate account, a link to all of our promo codes that we talk about in the ads, Patreon. I mean I'm probably missing many things, merch, but if I missed it just go to our website and you'll be able to find it there.

Erin Allmann Updyke (laughs) It's true there's a lot there.

Erin Welsh Yeah. All right. Should we get started on this very unusual episode?

Erin Allmann Updyke Yeah, I'm excited about it. Let's take a break and then dive into the first of three minisodes.

Erin Welsh Yeah.

TPWKY (transition theme)

Erin Allmann Updyke So suffice to say I severely underestimated the genus Bartonella.

Erin Welsh Oh, same. Same, same.

Erin Allmann Updyke So just up front what I'm gonna do in this biology section is kind of go over the genus and all of the general things that we know about the genus Bartonella and the many species of bacteria that cause disease in humans and other animals and just sort of go over the similarities and then focus on one specific species and that is Bartonella bacilliformis. And that's, Erin, what you're gonna then cover, etc etc. Okay. And what makes this even more confusing is that even though we're gonna focus on three specific bacterial species, there's like 5 or 6 or maybe 7 depending on how you count them different diseases that they cause.

Erin Welsh Yeah. And there are some species that are not human-specific or like not commonly human pathogens but do infect humans but we're not gonna go into those.

Erin Allmann Updyke Yep. So let's talk about them all in general, shall we?

Erin Welsh	Yes.
Erin Allmann Updyke	So in general the genus Bartonella are small, fastidious which we know means difficult to grow in culture-
Erin Welsh	Love that word.
Erin Allmann Updyke	I know, it's such a good word. Gram-negative, rod-shaped bacteria. There are dozens of species, over 30 that we've identified so far. But again we're gonna focus on three today. But know that there are others that can cause some of these same diseases and there's probably more that we just don't know about yet. And I think that Erin, you're gonna talk a little bit more about the overarching evolutionary history.
Erin Welsh	Mm-hmm, yeah.
Erin Allmann Updyke	But it does seem that there are a lot of species that are relatively specific to certain mammals. Like there are some species mostly found in rats and others mostly found in cows or cats, etc.
Erin Welsh	Yeah.
Erin Allmann Updyke	And there's two species that we'll focus on today that are specific to humans and then another species that commonly infects humans even though it's a feline species.
Erin Welsh	Simple.
Erin Allmann Updyke	Simple, no problem. No one's confused yet. In general these bacteria are transmitted to these usually mammalian hosts by blood feeding arthropod vectors. But of course they're not simple so it's not like just one type, sometimes it's sandflies, sometimes it's lice, sometimes it's fleas, maybe it could even be ticks, some people are saying. Oh goodness. And if anyone listening has heard of cat scratch disease you might already be scratching your head - scratching - like I'm sorry I thought that cat scratch disease was from cat scratches? And we'll get there people, we'll get there. But for the most part these are vector-borne pathogens. But to make it even more confusing, unlike many vector-borne pathogens that we've covered on this podcast that are picked up in the bloodstream and then spit out in their next blood meal to infect another host, these ones are sometimes transmitted that way like when it's sandflies but sometimes they're picked up in a blood meal and then replicate in the guts and then are pooped onto the mammal and then have to be scratched into a bite wound. So these are complicated bacteria.
Erin Welsh	Yeah.
Erin Allmann Updyke	And then once they get inside their mammalian host, to be even more complex, Bartonella exist as intracellular bacteria. So they don't just live inside us and replicate like say Staph or Strep or many other bacterial species but they're more like Legionella that we just talked about or chlamydia, gonorrhea, etc.
Erin Welsh	Rickettsia.
Erin Allmann Updyke	Rickettsia. They go inside of our cells and replicate the way that viruses do. In mammals, not in the arthropod vector.
Erin Welsh	It's kind of impressive.

Erin Allmann Updyke

I know. It very cool. They're facultatively intracellular.

Erin Welsh

Yeah.

Erin Allmann Updyke

It's very, very awesome. So that was all the really complex part. Let's talk about what they all have in common once they're in mammalian hosts because it's actually kind of simple and tells us a lot about the diseases that they tend to cause. So in mammals Bartonella tend to infect two different cell types, two different kind of tissue types. Red blood cells, erythrocytes, and endothelial cells which are the cells that line our blood vessels and can also be found in places like lymph nodes, they can also infect white blood cells. And those two cell types, infecting and causing damage to those two cell types actually explains a lot of what we see in terms of the actual symptoms of disease.

Erin Welsh

Right.

Erin Allmann Updyke

So at least that's one thing that they tend to have in common, asterisk, cat scratch disease is weird. Okay? All right. So that was all of the general details. Let's focus now on one species, Bartonella bacilliformis. Listeners you may have never heard of this because I had never even heard of it. This is a particular species that is human-specific, so it doesn't infect as far as we can tell other mammals, at least not naturally, and it causes a disease known as Carrion's disease. My accent is probably terrible on that. But also sometimes Carrion's disease is called two different diseases because this is biphasic illness. So there's an acute stage and then a potential chronic stage and these two phases are completely different.

Erin Welsh

That is fascinating and I don't understand it and I kept confusing the two phases and yeah.

Erin Allmann Updyke

Well hopefully when I explain it the two phases will make at least a little bit more sense.

Erin Welsh

Okay.

Erin Allmann Updyke

So this particular species is vectored by sandflies in the same genus that we talked about with leishmaniasis of all things, Lutzomyia sandflies.

Erin Welsh

Yep.

Erin Allmann Updyke

And part of the reason that many listeners may have never heard of it is that it's very geographically limited to certain parts of the Andean valleys in South America. So Peru, Ecuador, and Columbia. And only parts of those countries.

Erin Welsh

It's like a really narrow altitudinal range, right?

Erin Allmann Updyke

Yes and it's where this particular sandfly species is found.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah. So let's go over the symptoms of this one disease, Carrion's disease, which is sometimes called two different diseases. In the acute stage which happens the first time that somebody gets infected and the symptoms start usually about 60 days after infection so it's a really long incubation period.

Erin Welsh: Whoa. I did not know it was so long.

Erin Allmann Updyke: Yeah. And some estimates that I saw ranged from 10-200 days. And I wonder how much of that variability just has to do with how little we really know about this disease, quite honestly.

Erin Welsh: Yeah. This was the one that was the most difficult to get information on I think.

Erin Allmann Updyke: Absolutely. So the acute stage of Carrion's disease is sometimes called Oroya fever. What it looks like is a headache, some general feeling cruddy like malaise, maybe some joint pain, bone pain, and that will progress to chills and a fever. But then over the course of 1-4 weeks this becomes much, much worse. People infected become pale, jaundiced, they might have difficulty breathing, they might become confused. And this can progress to multi organ failure and death. And some reports say that the mortality rate is anywhere from 40-88% if untreated.

Erin Welsh: Yeah. Which blew me away.

Erin Allmann Updyke: Yeah, same. And I'm gonna talk about it in a little bit more detail in a second. But first I wanna talk about what's happening in this acute phase of the disease because it goes back to what we already know about this genus of bacteria. What's happening in this acute phase is that these bacteria are multiplying inside of our red blood cells, we know that that's one of the cells they like to infect. But in the case of this particular species, *Bartonella bacilliformis*, these bacteria replicate rapidly and enormously into like huge numbers and then they end up bursting open those red blood cells. So this can cause a severe hemolytic anemia. That combined with secondary bacterial infection is what often causes death.

Erin Welsh: Why is there secondary bacterial infection?

Erin Allmann Updyke: I'm not entirely clear but likely it's just how overwhelmed the immune system is already makes you more susceptible to secondary infection.

Erin Welsh: Okay.

Erin Allmann Updyke: You have an overwhelming bacteremia, so so much bacteria in your blood already, your immune system's probably just not able to fight off other organisms.

Erin Welsh: And so in that very wide incubation period, once symptoms do start to appear, what's sort of the timeline there?

Erin Allmann Updyke: From what I could gather a number of weeks. So 1-4 weeks is when these symptoms sort of start and then progress.

Erin Welsh: Okay.

Erin Allmann Updyke: But I wanna get into it a little bit more because there's actually some evidence from some more recent outbreaks that have happened in non-endemic areas that the mortality rate might actually be a lot lower. Not just because of good treatment which can certainly help but it's likely the case that there's actually a lot more subacute or subclinical, like not symptoms or barely any symptoms where people get infected but they don't even really know that they're sick that happens that we didn't know about when it was just the people coming in really, really sick and then dying. Does that make sense?

Erin Welsh: Yeah, no, I saw that also and it made me wonder why does that happen? Why are there certain people... Because from the history section it doesn't seem to be people who are already immunocompromised, doesn't seem to be people who are in advanced age that are more likely to die.

Erin Allmann Updyke: Right.

Erin Welsh: It just seems sort of random almost.

Erin Allmann Updyke: Right, yeah I honestly don't know. This was a disease that was really difficult to get super clear information on likely because it is pretty rare.

Erin Welsh: Mm-hmm. And then those non-endemic areas, that is where it might be a different species of sandfly or...?

Erin Allmann Updyke: Potentially different species of sandfly which could mean like a variant of the pathogen itself. So who really knows, quite honestly.

Erin Welsh: Yeah.

Erin Allmann Updyke: But in those outbreaks though what they found is that over 75% of a population had antibodies. So lots of people were getting infected but only about 14% had symptoms of Oroya fever, this initial infection. And then about 17% went on to develop the chronic form. And what's even more interesting is that only 5% had this biphasic illness where they first had Oroya fever and then they went on to develop chronic form. But a lot of people had the chronic form, quote unquote "chronic", without ever having symptoms of Oroya fever.

Erin Welsh: Okay. That is very interesting. So one of the questions that came up while I was reading was that it seems that this is human-specific and so that means that there would be no reservoir animal that we've found yet. And so are people just reinfesting the flies forever? Like how has this not burned through unless it is this high rate of subclinical cases that lead to just persistent pathogen presence.

Erin Allmann Updyke: Right. Exactly. And honestly that probably is what it is based on how Bartonella exist in so many other reservoir species, right. It's very common to have a chronic bloodstream infection that kind of you'll have a lot of bacteria in the bloodstream and then the numbers will decrease and it'll sort of cycle like that even without having any symptoms.

Erin Welsh: Yeah.

Erin Allmann Updyke: But speaking of symptoms, the chronic, quote unquote "chronic" disorder that you can get which can happen - I didn't get a timeline on how long after initial infection this tends to happen. But what can happen over a course of time is a disorder known as verruga peruana. And this is a cutaneous, so a skin disease and you get these little vascular tumors really, these little lumps or bumps or nodules. They look like little red or sometimes purple, almost black raised moles. Like not quite warty-looking but almost like a very red or purple lumpy lump just stuck onto your skin.

Erin Welsh: Right, yeah.

Erin Allmann Updyke

And they can actually have quite a lot of different appearances. Sometimes that's what they look like and they're little and tiny like less than 3 millimeters and just all over your body, especially on your arms and legs. Sometimes they can be a bit larger or you can have multiple little nubbins all in one. Or sometimes it can manifest with deeper kind of subdermal nodules and when those are present near a bone, like say right on top of your shin for example, those can be kind of painful. But the reason that these are red to purple to dark black on color is because they're actually derived from vascular tissue. So these little lesions are made from blood vessels that proliferate.

Erin Welsh

That's wild.

Erin Allmann Updyke

Uh huh. But it's not that wild when you know that this bacteria infects the lining of our blood vessels. So it's basically just the bacteria causing proliferation of blood vessels in which it lives.

Erin Welsh

That is ridiculous.

Erin Allmann Updyke

Uh huh.

Erin Welsh

Wow.

Erin Allmann Updyke

I know. And so these continue to develop, often over the course of 3-6 months. You can imagine that because these are literally made from blood vessels it's very easy if you scratch them for them to open and bleed pretty profusely, more than a normal mole would bleed if you scratched it, especially on the arms and legs. But in general they tend to heal on their own even without antibiotic treatment.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah it's very interesting. And I think a large part of the reason they are able to heal on their own is because in general with this disorder, verruga peruana or the chronic form of Carrion's disease, these nodules tend to be limited to the skin and maybe a little bit deeper into the subcutaneous tissue or maybe rarely the muscle but they don't go any deeper than that. That's important for a different disease that we'll talk about later. Okay? Was that enough? That was a lot, Erin.

Erin Welsh

No I feel like this is going to be instead of three minisodes this is gonna be-

Erin Allmann Updyke

Like three full maxisodes?

Erin Welsh

Three full maxisodes. (laughs)

Erin Allmann Updyke

(laughs) But so that kind of sums up the genus that is Bartonella and then Bartonella bacilliformis in specific. I think that that particular species is a good example of not only how severe this disease can get but also why it's able to cause the diseases that it causes, right?

Erin Welsh

Mm-hmm.

Erin Allmann Updyke

We'll go over the other two species that most commonly cause disease in humans later. But Erin, first off, can you walk us through the history of this disease?

Erin Welsh

I can. And we don't even have to take a break first.

Erin Allmann Updyke

Yes!

Erin Welsh

(laughs) So like you, Erin, I wanted to start out with a general overview of the group of bacteria that we're talking about today because even though the human histories of each of the three species we're talking about are very distinct from one another, being in the same genus of course means that they share an evolutionary history. And it turns out that evolutionary history is actually pretty interesting.

Erin Allmann Updyke

Of course!

Erin Welsh

So the genus Bartonella is a fairly, like you mentioned, diverse group of bacteria that tends to though not always show high host specificity for its mammalian host or arthropod vector. And sidenote, it wasn't always known to be diverse. Until 1993 the genus consisted I think of just Bartonella bacilliformis.

Erin Allmann Updyke

Yeah which is so fascinating to me. I didn't realize how recent it was that we even knew that cat scratch fever or cat scratch disease and trench fever were caused by bacteria in the same genus. Like it's super recent!

Erin Welsh

Yeah it is really recent and part of that recency, like we knew about some of those pathogens before but this was just like merging with another genus. And so it was sort of just like this restructuring of naming and grouping and it does make looking at old papers more difficult and whatever but it make sense. And so here they all are together. So anyway even though we're only focusing on a few Bartonella species there are a whole lot more where those came from with Bartonella species infecting many other mammal species. But they didn't start out that way. This group, the Bartonellaceae is nested within the Rhizobiales which is a group of nitrogen-fixing soil bacteria.

Erin Allmann Updyke

Oh, fun.

Erin Welsh

Yeah. And so researchers think that Bartonella probably started out as an environmental pathogen and Bartonella bacteria are closely related to some plant pathogens and symbionts and then that environmental pathogen turned into an insect gut symbiont which then turned into a vertebrate pathogen.

Erin Allmann Updyke

Oh my goodness.

Erin Welsh

Yeah. And this last transition from insect gut symbiont to vertebrate pathogen is believed to have happened around the Cretaceous-Paleogene boundary previously known as the K-T boundary.

Erin Allmann Updyke

Okay.

Erin Welsh

Which is about 66 million years ago so like when all the dinosaurs died in the big extinction event and also around the time when there was like a big beginnings of mammal diversification as well.

Erin Allmann Updyke

Right, right. Okay.

Erin Welsh

And so what might have happened is that these arthropods that were hosting Bartonella began to evolve to be able to feed on the blood of these mammals and then the Bartonella species inside them began to evolve to be able to infect those blood feeding arthropods and then through that the blood of mammals.

Erin Allmann Updyke

I love this so much Erin, I had no idea.

Erin Welsh

I know!

Erin Allmann Updyke

What?

Erin Welsh

It is so cool, it is so cool. And so then after that it was like, 'Alright, I found my vector, I found my mammal, I'm good to go. Let's just follow this evolutionary train right down the line.'

Erin Allmann Updyke

Right. Yeah.

Erin Welsh

And so that's when a lot of these fairly tight vector-host-pathogen relationships began to form.

Erin Allmann Updyke

Oh my gosh that is so cool, Erin.

Erin Welsh

Yeah. I really like that. (laughs) There was a recent paper looking at the patterns of diversity within Bartonella that suggested that bats were among the first mammals to be infected and that both bats and rodents were key in Bartonella both diversifying and spreading like millions of years ago. And then more recently though in terms of evolutionary history there was another paper that talks about the role that humans have had in this recent spread of Bartonella species through the movement of domestic or human-associated animals, so like dogs, cats, cows, rats, etc. And that's fairly unsurprising. But what is cool is that we've seen not necessarily like... We've seen some spillover events and we've seen kind of like these not quite host switching events but more like Bartonella species that are fairly host-specific being able to infect other mammals that occupy the same ecological niche or geographic area.

Erin Allmann Updyke

You mean like cats and people?

Erin Welsh

Exactly.

Erin Allmann Updyke

Oh! Okay.

Erin Welsh

But Bartonella I think is a cool group of bacteria because in addition to tell us how different animals migrated and spread geographically, its very long history and broad host and vector diversity, it makes it a great group to study things like vector-host pathogen coevolution or the evolution of host specificity or especially something that I was thinking a lot about during this episode was the trade-offs between being a generalist pathogen and one that is specialist.

Erin Allmann Updyke

Yeah. Yeah.

Erin Welsh

Cause if you're a species of pathogenic bacteria it may seem like on the surface that if someone gave you the choice, do you wanna be able to infect as many host species as possible or do you wanna just put all of your eggs in one basket? You would probably be like, 'Eh, I think I'm gonna diversify here, that's gonna be the best way to go.' But that's not necessarily the case. We all know like in life you can't make everyone happy and along those same lines you can't infect everyone successfully either because being well adapted to one species may make you more visible to the immune system of another and there's a lot of other trade-offs that you can go into in terms of specificity vs generalist.

Erin Allmann Updyke

Right.

Erin Welsh

And I've also seen it predicted overall that single host pathogens will be more successful than multi host pathogens. But it's also not necessarily as clear cut as that, especially in light of widespread land use change and climate change, like having the ability to exist in multiple different species might make you a little bit more resilient to change, for instance. So anyway. And so this is why these trade-offs and the fact there isn't a clear answer is why we do see some pathogens putting all their eggs in one host and others are spreading their eggs across many hosts.

Erin Allmann Updyke

Literally and figuratively.

Erin Welsh

Yeah. (laughs) And so the same goes for Bartonella, right. You'll find ones that are generalist, especially those whose vector species tend to be more generalist biters as well like many of the rodent ectoparasites, and some that are very host specific, infecting only one mammal species or just ones that are closely related. Which brings me to Bartonella bacilliformis. This Bartonella species despite being the deadliest in humans by far and the first one to be described in general, not just on this podcast but in history, actually has quite a small history. And that kind of makes sense based on what you said. It's very localized, it's fairly rare occurrence-wise, and yeah. And so let's go into the biggest outbreak that we know about to date.

Erin Allmann Updyke

Okay.

Erin Welsh

In the 1870s construction on a railway linking Lima and La Oroya began and a good number of the laborers that were working on the lines weren't actually from the area, they had come in from elsewhere. And they during this construction began dying by the thousands.

Erin Allmann Updyke

Whoa!

Erin Welsh

Like absolutely astonishing numbers. It was estimated that more than 7000 of the 10,000 workers building this railroad died of this unknown disease.

Erin Allmann Updyke

Whoa! Okay, that's just a straight up mortality rate of 70%.

Erin Welsh

Yeah!

Erin Allmann Updyke

Yeah.

Erin Welsh

I just was blown away, I was like wait a second, are you sure?

Erin Allmann Updyke

Yeah. Oh my goodness.

Erin Welsh

Yeah. And so like you said, this disease sort of took this typical course or I guess it's not so typical now that I've heard the biology but of first this febrile hemolytic anemia which was often the fatal part of it and then if they survived, skin nodules. But it turns out that this unknown disease wasn't quite as unknown as unknown as people thought. Later looking back in history showed that there was some pottery from Ancient Peru, like 2000 years old, that seems to depict some of the symptoms that the workers were having, like the skin nodules.

Erin Allmann Updyke

Okay.

Erin Welsh

And it was also probably described in some of the journals written during the Spanish invasion of South America. But this large outbreak which gave rise to the name Oroya fever brought a lot of attention to the disease and in 1885 a Peruvian medical student named Daniel Carrion gave it its other name, Carrion's disease when he inoculated himself - I see you frowning already, you know what happens.

Erin Allmann Updyke

I usually am so good but it was like in the front of every paper.

Erin Welsh

Every paper, yeah.

Erin Allmann Updyke

I know.

Erin Welsh

That's just how it is.

Erin Allmann Updyke

Yeah.

Erin Welsh

Well we'll share with the group. (laughs) Daniel Carrion inoculated himself with some, I put 'juice from an infected skin lesion', I don't know if it was blood or pus or what juice.

Erin Allmann Updyke

Yeah.

Erin Welsh

Something from someone who had that second phase of the disease and then he died of this febrile anemia, so like the first phase.

Erin Allmann Updyke

Yeah.

Erin Welsh

His death through this very tragic experiment also showed that the two diseases were linked and likely caused by the same thing which up until that point had not been known for sure.

Erin Allmann Updyke

Okay.

Erin Welsh

And then in 1909 Alberto Barton, hence Bartonella, Barton, a physician from Peru published a paper describing bacteria in the blood cells of people with Oroya fever. But this on its own apparently wasn't good enough, this 'I found bacteria in the blood cells of people who had this disease' and also Daniel Carrion dying, that wasn't good enough. And so a group of researchers from Harvard University went down in 1913 to conduct some experiments involving human quote "volunteers".

Erin Allmann Updyke

Oh.

Erin Welsh: In which they basically repeated Carrion's fatal experiment. Only the person didn't die and so the researchers were like, 'I mean are they really related then? Are these really the same disease?'

Erin Allmann Updyke: Oh my.

Erin Welsh: Yeah. And so eventually however it was accepted that both Oroya fever and Carrion's disease or verruga were caused by the same bacterial species. Still though many questions remain like we talked about right. We have no non-human vertebrate reservoir. It historically was thought to be really restricted to just that Verruga zone but as you mentioned there have been outbreaks, like sporadic outbreaks of cases outside of that zone.

Erin Allmann Updyke: Yeah.

Erin Welsh: So like is it a new species, are there new strains, etc. We're gonna need some updates on this if you have any.

Erin Allmann Updyke: (laughs) We'll see, Erin.

Erin Welsh: Well for now let's just head to the next on the list.

Erin Allmann Updyke: Okay. Oh that was a good history, Erin.

Erin Welsh: Oh thanks.

Erin Allmann Updyke: I really, truly had no clue what we were getting into.

Erin Welsh: I know, I know. (laughs) We'll take a quick break before we get into the next one.

Erin Allmann Updyke: I think that's a good plan.

TPWKY: (transition theme)

Erin Allmann Updyke: So our second species of Bartonella of the day is Bartonella quintana and this causes the disease that many more people have probably heard of and that is trench fever. So this particular species is transmitted not by sandflies but by the human body louse, *Pediculus humanus corporis*. You like that?

Erin Welsh: I do.

Erin Allmann Updyke: I love, I mean I don't love body lice but I find lice to be really, truly fascinating. Talk about species-specific.

Erin Welsh: Yeah.

Erin Allmann Updyke: There's a body louse and a head louse and they are different.

Erin Welsh: I did not know that until this episode.

Erin Allmann Updyke

Yeah. So this is transmitted by the body louse, not the head louse, so don't freak out when your kid brings home lice. They're different.

Erin Welsh

Although it can be transmitted through head lice.

Erin Allmann Updyke

Yeah it probably can. Anyways.

Erin Welsh

But it's rare, that's not what usually happens.

Erin Allmann Updyke

(laughs) But like with Bartonella bacilliformis, there is no known natural animal reservoir for Bartonella quintana. So as far as we can tell this is a human-specific disease which makes sense if it's being transmitted by the human body louse. And like Oroya fever, the acute stage of Carrion's disease, trench fever is a bloodstream infection. So this is a disease that happens when these bacteria replicate and proliferate inside of our red blood cells. The symptoms though look a little bit different. The symptoms are a periodic relapsing fever most often. And this can range from fairly mild to pretty severe in terms of symptoms but in general the onset is sudden and starts about a week after infection although the incubation period can be up to 25 days and starts with a fever that tends to last classically 5 days but I saw some papers that said like 1-3 days. So everything in medicine that's called 'classic' is probably not 100% true. I'm gonna make someone angry but that's the case. But this fever is associated with severe headache, often dizziness and for some reason that Erin do not ask me why, shin pain.

Erin Welsh

Okay so I do have a question about shins though.

Erin Allmann Updyke

Okay Erin, what's your question?

Erin Welsh

That is in the quote unquote "classic" description of the disease.

Erin Allmann Updyke

Yes.

Erin Welsh

Which, spoilers, was first described in WWI. And so I was wondering if it was something about the conditions of the trenches or what it was like to be in the trenches. Like do people who have trench fever today still describe severe shin pain?

Erin Allmann Updyke

Good question. That's a very good question. In most of the descriptions that I've read, they likely go off of some of those more classic descriptions rather than... I didn't read a lot of individual case reports to know what specific people's symptoms were today but other papers that I read said more generally bone pain. And joint pain is also really common which makes sense because that's where your blood cells are coming from. So it does make sense that there would be bone pain, maybe it's not always specific to your shins and maybe in WWI it was something to do with that rather than specifically just this.

Erin Welsh

Yeah, okay. Interesting.

Erin Allmann Updyke

Yeah, it's a good question. So in general this is a disease where these fever episodes often recur and when they recur, it might be every 4-6 days or so because some people say the fever lasts 5 days or sometimes these episodes recur every 5ish days, trench fever is often sometimes called 5 day fever or quintan fever.

Erin Welsh

Right.

Erin Allmann Updyke: Sidenote, you know what interesting Erin? Trench fever, recurrent febrile illness where bacteria is infecting your red blood cells. Malaria, recurrent febrile illness where parasites are infecting your red blood cells.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah.

Erin Welsh: So that's what they noticed during WWI and they tried to treat them with quinine but to no avail.

Erin Allmann Updyke: It didn't work. Yeah. I just thought that was an interesting little sidenote.

Erin Welsh: Which also brings me to another question.

Erin Allmann Updyke: Okay.

Erin Welsh: Why is it relapsing?

Erin Allmann Updyke: It's a really good question, there's another disease that is louse-borne relapsing fever that's caused by a different species of bacteria, it's a *Borrelia* species.

Erin Welsh: Right.

Erin Allmann Updyke: I'm not entirely sure why. And this comes back to the fact that we don't have good animal models for these illnesses.

Erin Welsh: Yeah.

Erin Allmann Updyke: So the specifics of a lot of this pathophysiology I just don't have answers to. Yeah. But unlike *Bartonella bacilliformis*, the cause of Carrion's disease, trench fever, *Bartonella quintana*, does not cause a severe hemolytic anemia. So it's generally self-limited, doesn't have a huge mortality rate. Certainly people have died from it. But it can also cause a chronic infection like we've seen with *bacilliformis*, it can also cause an asymptomatic infection entirely and it can go on to cause some pretty severe infections, much more severe than trench fever. So there's a whole other disease called bacillary angiomatosis. Yeah. 'Bacillary' just refers to involving a rod-shaped bacterium, so that's the bacterium in this case and an angioma is an abnormal growth either on the skin or internal organs that is due to the formation of new blood vessels or the dilation of existing ones. Does that sound familiar?

Erin Welsh: Uh huh, it certainly does.

Erin Allmann Updyke: Yeah. So bacillary angiomatosis was discovered in HIV-positive patients. So primarily it's a disease of immunocompromise and it has been found to be caused often by *Bartonella quintana* and other species of *Bartonella*.

Erin Welsh: Uh huh, oh yeah.

Erin Allmann Updyke

That we'll get to a little bit more later. So what is it exactly, what does it look like? It's lesions not so dissimilar to verruga peruana but dissimilar enough that bacillary angiomatosis is a very severe illness. These lesions are most often and most obviously on the skin but unlike with verruga peruana, they're not limited to the skin. The damaging part is that these same lesions, these tumors made from blood vessels essentially can be found on any other internal organs and you can imagine these are blood vessels, they can bleed quite intensely. And so that bleeding itself can be life threatening as well as just having these growths that can get large on other internal organs. So bacillary angiomatosis is a much more severe disease that can also be fatal.

Erin Welsh

How often does that occur? I guess if you are immunocompromised, how often does it occur?

Erin Allmann Updyke

It's a good question. I don't have solid numbers on it. The numbers that I saw in people living with HIV, the prevalence of Bartonella-associated infection is still quite low, like 1 in 1000 in some studies in Germany and Spain.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah. So it's still a very, very rare disease. It's not only associated with HIV, it also has been found in people who are organ transplant recipients and other cases of immunocompromise. In rare cases it has happened as well in people who are otherwise immunocompetent. Why? Great question, right.

Erin Welsh

Yeah.

Erin Allmann Updyke

We don't know. And then finally, because that's not quite all, Bartonella quintana has also come very recently within the last couple of decades to be recognized as an important cause of what used to be called culture-negative endocarditis. Endocarditis we've talked about a lot, this is an infection of the heart tissue itself which again, unsurprising considering this bacteria likes our endothelial cells. And so endocarditis associated with Bartonella as well as trench fever have both become important causes of disease today, not just in world wars but today among people experiencing homelessness. And so that's the majority of where we see Bartonella quintana infections today.

Erin Welsh

I actually have a bit of trivia too about endocarditis that I didn't include in my little history section.

Erin Allmann Updyke

Oh, tell me it.

Erin Welsh

So during WWI there was a condition that was called either disorderly action of the heart or soldier's heart which was a variety of like shellshock, like it was just this no one knew what was causing it. And one paper I read suggested that at least some of these cases might have been caused by this endocarditis caused by quintana.

Erin Allmann Updyke

Fascinating. Oh that's really interesting.

Erin Welsh

Yeah.

Erin Allmann Updyke

Erin, tell me more interesting things. What's up with this particular species of Bartonella? Where did trench fever come from?

Erin Welsh

I'll get right into it.

Erin Allmann Updyke	Okay!
Erin Welsh	This is fun.
Erin Allmann Updyke	Yeah, I'm really learning a lot.
Erin Welsh	Yeah. Okay on July 28th, 1914 WWI began. And this episode, I looked it up, I'm pretty sure, will actually be released on July 27th and so that'll be the day before the 107th anniversary of the start of the Great War.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah.
Erin Allmann Updyke	Timely.
Erin Welsh	Interesting. (laughs)
Erin Allmann Updyke	Totally planned.
Erin Welsh	Yeah, sure.
Erin Allmann Updyke	Yeah.
Erin Welsh	By September of 1914, trench warfare had begun on the western front starting with a battle in France. And when I say trench warfare had begun, I mean it had begun. Within a few months of this battle, 4000 miles of trenches were dug and maintained from the English channel to Switzerland.
Erin Allmann Updyke	Whoa.
Erin Welsh	Trench warfare was brutal, it was deadly, it was horrific and in these trenches soldiers would live, they would fight, they would die and many of them would get infected with trench fever. By June 1915 an unusual febrile infection was running rampant through the troops that spent a lot of the time in the trenches and it drew enough attention to end up in a report by British medical officer Major John Graham. Quote: "A private from an infantry regiment was admitted to a casualty clearing station suffering from a febrile illness of 3 days duration. Headache, dizziness, severe lumbago, a feeling of stiffness down the front of the thighs and severe pains in the legs referred chiefly to the shins. I have been receiving cases in considerable numbers, presenting clinical features which do not differ from those given above." And this was the first description of what would become known as trench fever, an illness that didn't often kill you, like rarely killed you but it would take a lot out of you, leaving you as a soldier unable to fight for up to 2 months at a time.
Erin Allmann Updyke	Wow. That's a long time.

Erin Welsh

It is a long time, yeah. After this first report, military physicians all over began recognizing it in the troops that they treated and after first being seen in British soldiers it popped up in French troops, then in Greece, Italy, and all across the eastern front. And it wasn't just limited of course to the Allied forces. Regardless of where you were from or who you were fighting for, if you found yourself in the trenches, you were likely to find yourself with trench fever at some point or at least the person standing next to you or digging the trench next to you was likely to have trench fever.

Erin Allmann Updyke

Yeah.

Erin Welsh

And while some soldiers viewed trench fever as a welcome relief because it took you off the front lines for like 60-70 days to recover.

Erin Allmann Updyke

Wow.

Erin Welsh

And actually one paper pointed out that it probably saved a lot of lives that way.

Erin Allmann Updyke

Yeah, that makes sense.

Erin Welsh

Yeah. Those higher up in the armed forces saw it as a massive problem in reducing the sheer numbers of available troops, this was just a numbers game. And it certainly did reduce these numbers. Official records were not kept on the overall incidence of the disease but I did see one estimate of about 1 million cases among the Allied troops alone which is quite a lot.

Erin Allmann Updyke

Yeah.

Erin Welsh

There were actually a lot of famous people with trench fever.

Erin Allmann Updyke

I feel like we haven't done 'famous people with this disease' in a while.

Erin Welsh

We really haven't. And there's a really funny... I'm sure there are more that are out there but I just came across an article that mentioned the names A. A. Milne, so Winnie the Pooh, he wrote Winnie the Pooh.

Erin Allmann Updyke

Oh! Okay.

Erin Welsh

J. R. R. Tolkien and C. S. Lewis.

Erin Allmann Updyke

Oh wow.

Erin Welsh

All got trench fever. I think Milne was actually taken off of the lines entirely because of trench fever.

Erin Allmann Updyke

Oh my gosh.

Erin Welsh

And yeah.

Erin Allmann Updyke

We can probably thank trench fever for Winnie the Pooh.

Erin Welsh

And Lord of the Rings.

Erin Allmann Updyke

And Lord of the Rings.

Erin Welsh

And The Lion, The Witch, and The Wardrobe.

Erin Allmann Updyke

We know things.

Erin Welsh

Yeah. Trench fever caused 1/5 to 1/3 of all illnesses in the British army and 1/5 in the central powers.

Erin Allmann Updyke

Wow.

Erin Welsh

It's a lot. And even once the war was over and the disease had run its long course, many people were still impacted by it. For instance 6000 men in Britain attributed their war disability to trench fever in 1920, so a couple years after the war ended. And while trench fever could not hold a candle to the morbidity and mortality caused by influenza or typhoid or cholera or dysentery or all of the other diseases that were flourishing under these war conditions, the sheer number of soldiers it took out of commission made it somewhat of a priority to figure out what was causing this disease and how it was being transmitted.

Erin Allmann Updyke

That's very interesting.

Erin Welsh

Preliminary research has already put forth body lice as the main suspect for transmission, the disease could be transmitted through the inoculation of blood from an infected person but not plasma alone. Infections continued to occur throughout the winter which ruled out flies or midges or mosquitoes which wouldn't be able to overwinter as well as the body louse. And units that had more body lice had more trench fever or unexplained pyrexia which is what it was often put down as before trench fever became a more popular term.

Erin Allmann Updyke

Okay.

Erin Welsh

And efforts to control lice had led in a few instances to reduction in the incidence of this pyrexia of an unknown origin. And by the way control efforts were like next to impossible. There would be like a steam disinfester or something where it was like rarely operational. If you were in the trenches, you were there, dug in for a long time.

Erin Allmann Updyke

Yeah.

Erin Welsh

And so it was like okay, the goal was to shower at least once every two weeks.

Erin Allmann Updyke

Oh gosh.

Erin Welsh

That was the standard and that is just not frequent enough to completely rid yourself of lice. Yeah and so there was a study in 1915 that found that 95% of soldiers were infested with body lice with an average of 20 lice per soldier with 5% of soldiers having 100-300 lice each.

Erin Allmann Updyke

Oh my god.

Erin Welsh

Can you imagine how itchy that would be?

Erin Allmann Updyke

No, it sounds terrible.

Erin Welsh

Yes. And so despite this evidence though in support of the body louse, there was still debate over the route of transmission. And so a couple of research commissions were set up by the British and the Americans in a very bureaucratic fashion which meant that the studies themselves didn't start until closer to the end of the war and the results would be published too late to do much to stop the spread of the disease.

Erin Allmann Updyke

Oh gosh.

Erin Welsh

But still the commissions made a few important and in my opinion impressive observations during a time when there were a lot of other deadly things going around. And when medical and microbiological knowledge and technology isn't anywhere close to what it is today. I should also note that this was done through the use of "human volunteers" quote unquote because like you mentioned, human body lice don't feed on non-primates and lab animals aren't susceptible to trench fever. So these studies found that it was indeed the body louse responsible for transmission or more accurately louse poop.

Erin Allmann Updyke

Yeah.

Erin Welsh

It wasn't carried in the serum but in the blood itself. All it took was one louse who became infectious 5 days after feeding on an infected person and could remain infectious for at least 4 months.

Erin Allmann Updyke

Wow.

Erin Welsh

Even though I don't know how long, I thought the average lifespan of a body louse was like one month.

Erin Allmann Updyke

I was just about to ask you how long does a body louse live. I don't know the answer to that.

Erin Welsh

I thought I saw in one paper it was comparing the different life spans of the vectors of different Bartonella species and I thought a body louse was pretty short. But maybe if you keep them, if you maintain them maybe that one month is like-

Erin Allmann Updyke

Under ideal conditions.

Erin Welsh

Yeah. (laughs) Four months is like your pet louse, one month is like...yeah.

Erin Allmann Updyke

Your trench louse.

Erin Welsh

Yeah. And they also found that a person with trench fever could infect lice for at least 443 days after first showing signs of illness.

Erin Allmann Updyke

Whoa!

Erin Welsh

Yeah. And that the pathogen which was still unknown did not seem to be able to be transmitted vertically from parent louse to offspring.

Erin Allmann Updyke

I mean 443 days, I feel like that explains why the commission took so long to get these results published. They were just like still infectious, still infectious, not done yet.

Erin Welsh: For sure, yeah. They're like well, we're still going at least 443 days.

Erin Allmann Updyke: Are our louses still alive? (laughs)

Erin Welsh: And so while this information would have been nice to know during WWI at least it would be useful in the next war, not that people knew there was going to be a next war.

Erin Allmann Updyke: Right.

Erin Welsh: But WWII didn't have as much trench warfare as WWI and also the use of DDT had substantially reduced the infestation rates with lice. And so it just wasn't much of a problem at all, trench fever.

Erin Allmann Updyke: Okay.

Erin Welsh: And even though a lot was known about the disease and its transmission, the causative agent of trench fever was still unknown and wouldn't be described until 1961.

Erin Allmann Updyke: Wow.

Erin Welsh: Yeah, by J. W. Vinson which I think gave his last name to another species of Bartonella, vinsonii maybe.

Erin Allmann Updyke: Okay.

Erin Welsh: I think that infects dogs. I might be wrong. Anyway.

Erin Allmann Updyke: That sounds familiar.

Erin Welsh: Yeah. Who initially named it Rickettsia quintana, so quintana like you mentioned is from 5 day fever. But later studies showed that it wasn't a Rickettsia even though it seemed like one because it could be cultured, meaning it wasn't obligately intracellular and so it was put in the genus Rochalimaea which was changed to Bartonella when the two genera were merged like I mentioned earlier in 1993. And once the organism could be cultured, different antibiotics could be tested to see which were effective and sporadic outbreaks became more manageable. But the bacterium didn't disappear just because there was no more trench warfare. Starting in the 1990s trench fever has made a substantial comeback as I'm sure that you will talk about Erin and already have touched on a bit. But before we get to that I need to go back a little bit or a lot bit because I started trench fever in kind of the middle of the story. Although the conditions during WWI trench warfare were pretty perfect for the proliferation of Bartonella quintana, the relationship between the bacterium and humans goes way back.

Erin Allmann Updyke: Okay.

Erin Welsh: We already know that Bartonella in general evolves with their vertebrate hosts but in the case of Bartonella quintana we also have hard proof of this. Researchers found Bartonella quintana DNA in the dental pulp of someone who died 4000 years ago in southeastern France, very cool. Dental pulp and pathogen DNA is the best.

Erin Allmann Updyke: Dental pulp. It is almost as good as coprolites.

Erin Welsh: Oh god do I love a coprolite, yeah. (laughs) And then there was also studies showing evidence of infection in Napoleonic soldiers from around 1812. And those soldiers there was actually a 20% prevalence with this pathogen.

Erin Allmann Updyke: Wow.

Erin Welsh: Yeah.

Erin Allmann Updyke: Man, so 4000 years minimum.

Erin Welsh: Uh huh. It's gonna get even cooler.

Erin Allmann Updyke: Stop, how?

Erin Welsh: Okay so there's been other archeological research that has found evidence of infection all across Europe and in some other places. And so the fact that it was first described in WWI was probably just because of the conditions, right. Previously it was probably grouped in with just fever, like general fever in the pre-germ theory days.

Erin Allmann Updyke: Right.

Erin Welsh: And actually one paper made a note that this lack of distinction among fevers may have been why in some years mortality from fever was really low.

Erin Allmann Updyke: Oh.

Erin Welsh: So like if there was a lot of trench fever going around-

Erin Allmann Updyke: Then everyone had a fever but nobody was dying.

Erin Welsh: Mm-hmm, yeah.

Erin Allmann Updyke: Fascinating. Okay.

Erin Welsh: Okay. So Bartonella quintana and humans have been cozy with one another for probably as long as the human body louse has been with humans. But how long is that?

Erin Allmann Updyke: Ooh, tell me.

Erin Welsh: Apparently around 72,000 years.

Erin Allmann Updyke: Stop.

Erin Welsh: Which is when it diverged from the head louse. And that's also around the same time, Erin, that the use of clothing increased and as humans began their out of Africa migration, so it kind of spread with humans as humans moved and started wearing clothing.

Erin Allmann Updyke: Oh. Em. Gee.

Erin Welsh: Isn't that very cool?

Erin Allmann Updyke: Dude, lice. I'm telling you, very cool.

Erin Welsh: I know!

Erin Allmann Updyke: Very cool.

Erin Welsh: So Bartonella became specialized on humans and the human body louse for the most part more recently though it has been detected, the Bartonella quintana, in a couple of monkey species including macaques.

Erin Allmann Updyke: Ooh.

Erin Welsh: Yeah. And researchers were actually able to inoculate macaques and produced chronic bacteremia.

Erin Allmann Updyke: Okay.

Erin Welsh: So it's unclear how prevalent natural infection is with this bacterial species in different species of monkeys but it's possible that the bacteria spilled over into humans from nonhuman primates either more recently or a long time ago. It seems like it would be a long time ago, I don't know for sure. But regardless of how exactly quintana came to be, this pretty specialist bacterial species is a contrast to our next and last Bartonella species, Bartonella henselae.

Erin Allmann Updyke: Ooh I'm excited about this one.

Erin Welsh: Me too.

Erin Allmann Updyke: So we need a break first or should we just go there?

Erin Welsh: I think let's take a break and then wrap it up.

Erin Allmann Updyke: Great, okay. Quick break.

TPWKY: (transition theme)

Erin Allmann Updyke: Okay. So now it's not where we go off the rails but I think we're on a different train on the same rails.

Erin Welsh: Oh yeah.

Erin Allmann Updyke: Right? Yeah, okay.

Erin Welsh: We've hopped in a new car.

Erin Allmann Updyke: Definitely new car, definitely.

Erin Welsh: Train car.

Erin Allmann Updyke
Yeah, new car. So Bartonella henselae aka cat scratch disease. So this is a species of Bartonella that commonly infects cats, feral and domestic. And between cats it seems to be transmitted by the cat flea, Ctenocephalides felis, which makes sense based on what we know so far about Bartonella, right. These tend to be vector-borne species. But humans for the most part become infected from contact with a cat directly, specifically from scratches or bites.

Erin Welsh
Wait a second.

Erin Allmann Updyke
Uh huh.

Erin Welsh
But how?

Erin Allmann Updyke
(laughs) In many parts of the world like 50% of cats have evidence of infection with Bartonella henselae, current or past infection.

Erin Welsh
Yeah, sure.

Erin Allmann Updyke
And just like Bartonella species that we've talked about that are specific to humans can maintain chronic bacteremia without any symptoms of disease potentially, that's what happens in cats. So in cats, they get infected from fleas, like cats have fleas and in general they don't have any symptoms of disease but they can maintain a chronic state of having these bacteria in their bloodstream that can then somehow, Erin, be present in their claws or in their mouth.

Erin Welsh
Yeah that's the part that I'm struggling with.

Erin Allmann Updyke
I mean I don't have a great answer to it.

Erin Welsh
Is it in their saliva?

Erin Allmann Updyke
I think maybe perhaps it could be in their saliva but also cats' gums bleed a lot. Have you ever looked inside a cat's mouth?

Erin Welsh
I mean but I just, the claws and the mouth... Cat fleas don't bite humans.

Erin Allmann Updyke
No, in general. And that is not how people get infected. It is possible, it is physically possible to get infected through a vector with Bartonella henselae but in general people get infected from cat scratches and bites.

Erin Welsh
I need more info on this. I am struggling.

Erin Allmann Updyke
(laughs) That's all I got for you, Erin. I mean that's not all I got for the biology but...

Erin Welsh
(laughs) I was like that is a really short one, wow.

Erin Allmann Updyke
Yeah no. Yeah I mean it is very interesting right because in general it's a bacteria that's found inside of cells, mostly in red blood cells and endothelial cells. But it finds its way into the saliva and claws of cats.

Erin Welsh
I'm baffled.

Erin Allmann Updyke: I mean maybe it's like when cats scratch or bite people, maybe there tends to be action more than just a little kitty scratch.

Erin Welsh: I'm gonna think about this as I'm trying to sleep tonight.

Erin Allmann Updyke: I don't have a great... Nothing that I read talked about it. Isn't that weird?

Erin Welsh: That's so strange.

Erin Allmann Updyke: So off the top clearly this is a weird one, right. It's different than other species we've covered. It's also a very different illness that is cat scratch disease. Okay? In general it is fairly mild and self-limited. It most often occurs in kids but that's probably more likely due to exposure than susceptibility, it also can happen to older people as well, in anyone any age. And it looks like this:

First about 3-10 days after a bite or scratch you'll get a little lesion on the skin, usually quite close to the wound. Just like a pustule or maybe a little scab, this will crust over. And then usually over the course of a few weeks you'll start to develop swollen lymph nodes. Just a few, like one, two, etc. just on one side, the side near wherever the bite was. So if you got bit on your arm then maybe the lymph nodes in your armpits, if you got bit on the cheek, maybe under your neck, behind your ear, wherever. And then maybe around that time as your lymph nodes start to swell you might have some mild symptoms like a fever or body aches or joint aches, just feeling cruddy. But really it's just these swollen lymph nodes and they can stay swollen for quite some time. It can often take about 7 weeks or more before they completely resolve. In some cases like 20% of the time they can persist for 6 months to 2 years.

Erin Welsh: Whoa.

Erin Allmann Updyke: Yeah. And about 10% of the time the swollen node will kind of burst out to the surface a bit so you'll have like pus draining from it.

Erin Welsh: Yikes, that sounds uncomfortable.

Erin Allmann Updyke: Yeah it's definitely uncomfortable but that's rare, that's like 10% or less. Usually it's some swollen lymph nodes, self-limiting, and it goes away. So it's already a lot of weird things. In humans this bacteria for some reason is infecting tissues in our lymph nodes rather than directly infecting our red blood cells.

Erin Welsh: Where does it go in cats?

Erin Allmann Updyke: It goes into their red blood cells but it doesn't cause disease and it doesn't cause any of the angioproliferative or the skin disorders that we've seen with other Bartonella, that doesn't happen in cats. Usually they have no symptoms whatsoever.

Erin Welsh: And it doesn't go into their lymph nodes.

Erin Allmann Updyke: Not enough to cause them to swell.

Erin Welsh: Okay.

Erin Allmann Updyke: But it gets even weirder because in people who are immunocompromised *Bartonella henselae* is a very important cause of bacillary angiomatosis, that disorder that we already talked about caused by *Bartonella quintana*.

Erin Welsh: Right.

Erin Allmann Updyke: And with *Bartonella henselae* it can actually be even worse because these vascular tumors can be found on the liver. This is sometimes called an entirely different disease, peliosis hepatis or bacillary peliosis, that just means these tumors on your liver.

Erin Welsh: Okay.

Erin Allmann Updyke: And in both immunocompromised as well as immunocompetent people very rarely *Bartonella henselae* can infect the nervous system and cause things like encephalopathy. There's a few cases of it causing neuropsychiatric disorders potentially. It's very bizarre.

Erin Welsh: Yeah this one is definitely the weirdest.

Erin Allmann Updyke: It is definitely the weirdest. And it's a zoonotic disease, right. This is a species of bacteria that's closely associated with cats, it can also infect dogs and in dogs it can actually cause endocarditis.

Erin Welsh: Okay.

Erin Allmann Updyke: But in cats it doesn't tend to cause any disease, none of these symptoms seemed to happen whatsoever. And so all of this is to say that that's part of why we really don't understand a lot about the pathogenesis of *Bartonella* in general, this species or otherwise. Because even here where we have a zoonotic species you would think well at least we have an animal model, it's in cats. 50% of cats are infected. But they don't manifest the same disease so we can't study this human disease in cats or in other animals.

Erin Welsh: *Bartonella* is like this is tip of the iceberg type thing where you're like oh, I see what's on the surface, this is going to be very straightforward.

Erin Allmann Updyke: Right.

Erin Welsh: And then it's like just kidding!

Erin Allmann Updyke: Right. We severely underestimated them.

Erin Welsh: Yeah.

Erin Allmann Updyke: So for the last and final time, Erin, can you tell me how we got here? Where *Bartonella henselae* came from? Like what's up with cat scratch disease?

Erin Welsh: I'll just dive right in yet again.

Erin Allmann Updyke: Please.

Erin Welsh

So I was trying to think of what is the take home for all of this. Is there any sort of unifying theme? And the only thing that I could really think of was that the growth of knowledge doesn't happen in a predictable way or rarely happens in a predictable way and that we may only recognize how things are connected in retrospect and rarely if ever at the time when we're examining them. And I think this can definitely be said for the two Bartonellas we've already talked about, bacilliformis and quintana, but I think it's especially true for our last Bartonella, henselae. So not only did it take until 1993 for this bacterium to be put in the Bartonella genus along with quintana during that reshuffle thing or merge, it was only 10 years before that that it was seen for the first time despite the disease itself, cat scratch fever, being known for 100 years and clinically described for 50 years.

Erin Allmann Updyke

Goodness gracious.

Erin Welsh

Yeah. So let's get into it. First off there is most definitely evidence of ancient infection with this bacterium, again using dental pulp. Researchers found Bartonella henselae DNA in 800 year old French cats from the 13th, 14th, and 16th centuries and it's likely that cats have been infected with this bacterium since cats have been cats or at least since the cat flea began biting cats.

Erin Allmann Updyke

Okay.

Erin Welsh

And since Bartonella henselae is also able to infect humans it seems also likely that humans have probably been prey to this pathogen since humans and cats began associating with one another which was around 7500 BCE. But the earliest description we have of anything resembling cat scratch disease or cat scratch fever is from 1898 when a physician described a condition similar to and thought to be in retrospect of course cat scratch fever in the context of oculoglandular syndrome. That's all, I don't really know.

Erin Allmann Updyke

Okay.

Erin Welsh

And the disease got its official clinical description only in 1950 by Robert Debré, professor of pediatrics at the University of Paris.

Erin Allmann Updyke

Okay.

Erin Welsh

Dr. Debré was no stranger to this disease having treated a 10 year old boy in 1931 who had a cold fistulated adenitis that healed quite nicely on its own. And the doctor though was struck in particular by the severe and numerous cat scratches on the same hand as the same side as the adenitis.

Erin Allmann Updyke

Oh gosh.

Erin Welsh

I know. The boy's mother said that although her son had been told not to play with the cats, she found him in his room with a bunch of the kittens and they were all hanging out together, he just could resist which I think is really cute.

Erin Allmann Updyke

Aw, I hope he had fun. I hope it was worth it.

Erin Welsh

Yeah, yeah.

Erin Allmann Updyke

It healed nicely.

Erin Welsh

Yeah, exactly. So initially Dr. Debré was convinced that this was like a form of tuberculosis but he was unable to isolate the tuberculosis bacterium. So then he figured okay, it must be some sort of bacterial infection from the cats. But again none of these bacterial assays or investigations turned up anything. The wound healed, the kid recovered, but the case stuck out in the doctor's mind. Over the next years Dr. Debré saw additional cases of adenopathy that cleared up on their own, all of them with cat associations and he took to calling it cat scratch disease. But despite a regular influx of cases he was never able to find or isolate a causative agent. And Debré wasn't the only one to recognize this strange illness. Lee Foshay, a professor of microbiology at the University of Cincinnati in Ohio had also noticed it. And when Debré visited Cincinnati in 1947 for I believe a conference they struck up a conversation when they realized they both had a special interest and experience dealing with this cat-associated illness.

Erin Allmann Updyke

How fun.

Erin Welsh

I know, right? And they had even come up with basically the same name for it. So Debré called it cat scratch disease while Foshay called it cat scratch fever. Debré was super excited to find another person interested in it and especially so when he learned that Foshay had developed a diagnostic antigen test. And he suggested like, 'Oh, you know, let's put our minds together, we'll publish two articles about this disease, yours will be about the diagnostic test, mine will be about the clinical disease.' But Foshay was like, 'No, no, I'm not a clinician or a pediatrician, I'm a bacteriologist and a virologist and I won't publish anything until I find the causative agent.' So Debré was like oh man, bummer. This stinks.

Erin Allmann Updyke

(laughs)

Erin Welsh

And it took him a few years to get up the nerve to publish anything on cat scratch disease which he finally did in January of 1950. The publication of his description got the wheels turning for other people and additional work on the disease continued with more antigen diagnostic tests being developed and experiments infecting cats and humans. But like Bartonella quintana, much of the progress had to do with describing the disease itself rather than isolating the causative agent. But that changed when in 1983 the bacillus was discovered in lymph nodes of patients with cat scratch. I know, 1983.

Erin Allmann Updyke

83, my goodness. So recent.

Erin Welsh

I know! Yeah. And even then in 1983 the researcher was just able to say that this was a small gram-negative bacillus. It took 5 years for the bacterium to be successfully isolated and cultured. And then it was named first Rochalimaea henselae and changed to Bartonella henselae.

Erin Allmann Updyke

Right.

Erin Welsh

Henselae after Diane M. Hensel who isolated many of the original strains.

Erin Allmann Updyke

Okay.

Erin Welsh

This species like Bartonella quintana has made headlines over the past few decades as you mentioned due to its emergence as a threat for people who are immunocompromised and also as I saw in one paper as a possible occupational hazard for people who routinely work with cats like veterinarians.

Erin Allmann Updyke

Yeah, veterinarians. Definitely.

Erin Welsh: So Erin, let's wrap this very interesting and all over the place episode up by talking about where we stand with all of these Bartonella today.

Erin Allmann Updyke: Oh let's try but here's the problem, Erin. It was very difficult to find any kind of numbers in terms of overall infections which is what I usually try and find, like current status, etc.

Erin Welsh: To be honest I'm not surprised by that.

Erin Allmann Updyke: I know. And the other thing is that a lot of the papers that I found that did cite some numbers were like 10 years old. So we'll just go with what we've got which is, I'm not gonna lie, it's not great. Okay.

Erin Welsh: Yeah.

Erin Allmann Updyke: We'll start back at the beginning with Bartonella bacilliformis. From a 2009 paper that cited data from the Peruvian National Institutes of Health that was congregated from 2004-2006. So this is old data, y'all. But they cited over that 2 year period in the early 2000s more than 26,000 cases of bartonellosis.

Erin Welsh: Wow.

Erin Allmann Updyke: Yeah, it's more than I thought. And because the mortality rate can be high, this paper was saying that it can be estimated that just in Peru, and remember this is in at least three different countries, hundreds of people are likely dying every year from this disease.

Erin Welsh: And how effective is antibiotic treatment if you get it early enough?

Erin Allmann Updyke: It's a good question, it seems like it is effective especially because a lot of the mortality is from secondary infections so if you're able to tamp down the primary infection. But again I don't have numbers on that.

Erin Welsh: Okay.

Erin Allmann Updyke: Some other stats just to kind of get an overall sense of this. People have reported that in some endemic areas in Peru up to 45% of people that live in those areas under 21 show exposure. So they show evidence of having been infected at some point. So that kind of not only says this is a prevalent disease but also maybe there's more asymptomatic or mild infections than we thought. Right?

Erin Welsh: Okay.

Erin Allmann Updyke: So that's Bartonella bacilliformis. Bartonella quintana, so difficult to get numbers on. We know that it's a big problem for people experiencing homelessness, both trench fever as well as endocarditis. The best I could find is that in studies where they have tested people that have been found to be infected with lice, anywhere from 8-50% of people were seropositive for Bartonella quintana. So that doesn't tell us that much as far as actual numbers go but I think it does tell us that this is probably far more prevalent than we think.

Erin Welsh: Yeah, I mean absolutely and trench fever I think people think oh it must be a disease of the past but that is not the case.

Erin Allmann Updyke

Exactly. And like I said, in terms of bacillary angiomatosis that is very low prevalence, like 1 in 1000 of people living with HIV though it can happen in other people as well. and then we get all the way back around to Bartonella henselae. What's the prevalence of this? Who knows. The CDC estimates about 22,000 cases every year with about 2000 requiring hospitalization.

Erin Welsh

Wow, okay. That's more than I thought to be honest.

Erin Allmann Updyke

Yeah. It's more than I thought as well. We know that in a lot of places where they've tested cats, seroprevalence in cats can be quite high but even in some places where they've tested people they have found that anywhere from 5-30% of people are seropositive for Bartonella henselae. Lots of people are around cats. Also only about 25% of infection are actually strictly associated with cats.

Erin Welsh

What?

Erin Allmann Updyke

Like a known source, like here's my cat bite, here's my infection. Erin.

Erin Welsh

Yeah, henselae is by far the most strange.

Erin Allmann Updyke

It's a different car. Yeah.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah. And then the really tough thing is quite honestly there are so many more species of Bartonella and there are so many case reports out there of cat scratch disease caused by this new species or trench fever caused by this other species, etc etc. There are species of Bartonella associated with so many different mammals, many of these can potentially cause zoonotic disease, they can spillover into humans whether from whatever vector potentially. Right?

And so I think in terms of where is the research going, one of the biggest thing we have to get a handle on is really just the breadth and depth of this genus of bacteria worldwide. What is it's true distribution? What the heck are the details of how it causes disease? We really don't know a lot. For people who are interested, we do have more detail on how it causes neoangiogenesis like formation of new blood vessels and things, so we'll cite those papers. But we still don't know a ton. Vaccines, we don't have any. I will link on our website to a paper that was interesting that found potential targets because there's at least a theoretical possibility that people do mount a protective immune response to infection if they don't just become chronically infected.

Erin Welsh

Okay.

Erin Allmann Updyke

But it just comes down to both do we have the baseline knowledge that will be necessary first of all and is there any funding for it? And I don't know.

Erin Welsh

Yeah.

Erin Allmann Updyke

So that's a bunch of different diseases, a few different bacteria.

Erin Welsh

Yeah. Probably more than anyone bargained for.

Erin Allmann Updyke: Definitely. I mean we did try and warn them, three episodes.

Erin Welsh: Yeah. (laughs) Maxisodes, I like that.

Erin Allmann Updyke: Yeah.

Erin Welsh: Should we do sources?

Erin Allmann Updyke: We should, definitely.

Erin Welsh: Okay. I have a ton but I'm gonna shout out four that I found really helpful. One by Anstead from 2016, 'The centenary of the discovery of trench fever, an emerging infectious disease'. One by Carithers from 1970, 'Cat-scratch disease: notes on its history'. One by Ihler from 1996, 'Bartonella bacilliformis: dangerous pathogen slowly emerging from deep background'. And finally one from 2021 by McKee et al, 'Bats are key hosts in the radiation of mammal-associated Bartonella bacteria'.

Erin Allmann Updyke: Excellent. I had a lot of papers for this one. I think my favorite of just an overview of all of the different species of Bartonella was just called 'Bartonellosis', it was by Maguiña et al and I'll post that. And then there were a couple of others like 'Bartonella species: throwing light on uncommon human infections', there was one that was all of the different Bartonella species called 'Historical pathogens of emerging significance'. There's a bunch of good papers and we'll post every single paper on our website thispodcastwillkillyou.com under the EPISODES tab.

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

Erin Allmann Updyke: Thank you to the Exactly Right network of whom we are very proud to be a part.

Erin Welsh: And thank you to you, listeners. We really appreciate you listening, let us know you liked this one.

Erin Allmann Updyke: Yeah, was it fun for you? It was fun for us.

Erin Welsh: It was fun actually.

Erin Allmann Updyke: And thank you also to our patrons, we love you all so much. So much.

Erin Welsh: Yes we do. Well okay. Until next time, wash your hands.

Erin Allmann Updyke: You filthy animals!