

Erin Welsh	"On the first day of August 1576, Cocoliztli began extremely strongly in Tecamachalco. It could not be resisted. For this reason, many people died. Young people, married people, old people, men and women and children. In two or three days, they died of hemorrhage. Blood emerged from their noses, from the ears, from the eyes, from the anus, and women bled between their legs and for us men, blood emerged from our members. Others died from diarrhea which took them suddenly, they died quickly from this."
TPWKY	(This Podcast Will Kill You intro theme)
Erin Allmann Updyke	That's awful.
Erin Welsh	Oh yeah. This episode is loaded with quotes, Erin.
Erin Allmann Updyke	Okay, okay.
Erin Welsh	That particular quote was from an anonymous Nahua author of the 'Anales de Tecamachalco' from the epidemic of Cocoliztli in 1576.
Erin Allmann Updyke	Okay.
Erin Welsh	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 are doing a medical mystery.
Erin Welsh	We are. It's our first one in many episodes.
Erin Allmann Updyke	It's been years.
Erin Welsh	Yeah.
Erin Allmann Updyke	I think.
Erin Welsh	Definitely. over 50 episodes. The last one was sweating sickness?
Erin Allmann Updyke	Sweating sickness.
Erin Welsh	Yeah.
Erin Allmann Updyke	No, no, dancing plague?
Erin Welsh	I don't know.
Erin Allmann Updyke	I don't know. Could be either.

Erin Welsh: It's one of those. But yeah, this has been on our list for a while which I feel like we say about every topic. But I'm really excited that we're covering it because there is so much to get into. And wow, once I started pulling the string on this, I just couldn't stop.

Erin Allmann Updyke: Like a sweater?

Erin Welsh: Yeah.

Erin Allmann Updyke: It just came all the way unraveled.

Erin Welsh: Yep.

Erin Allmann Updyke: I can't wait. I am thrilled because... So listeners, you may recall or you may not because again it's been a number of years, we are going to do this episode in a different way. And the way that Erin and I have researched for this episode is very different than our usual. I know nothing about this story, about Cocoliztli at all. But I have been given a list of contenders of possible pathogens that may have caused this and then we're going to try and solve it in just the next hour and a half, this medical mystery that's been going on for hundreds of years.

Erin Welsh: I mean I hope that people aren't looking for full resolution like I always do when I watch Unsolved Mysteries and at the end I'm upset that it's still unsolved.

Erin Allmann Updyke: But what do you mean?

Erin Welsh: It's in the name of the show. So brace yourselves. You'll know a lot more and maybe be able to come to some conclusions yourself. But yeah, this will be an unsolved mystery at the beginning, middle, and end.

Erin Allmann Updyke: I can't wait.

Erin Welsh: Yeah.

Erin Allmann Updyke: I'm really excited about it. And to get us started, I believe that it's quarantini time.

Erin Welsh: It certainly is. What are we drinking this week?

Erin Allmann Updyke: It's Anyone's Guess. That's the name of it.

Erin Welsh: Thanks to John for that title, appreciate it.

Erin Allmann Updyke: So creative.

Erin Welsh: And in It's Anyone's Guess, it's delicious and it's got a lot of ingredients which I think sometimes can be fun. It's got some dark rum, it's got pineapple juice, orange juice, lemon juice, and passion fruit juice.

Erin Allmann Updyke: Ooh, so tropical.

Erin Welsh: Lots and lots of juices.

Erin Allmann Updyke	Yeah.
Erin Welsh	It's delicious.
Erin Allmann Updyke	We'll post the full recipe for that quarantini as well as the non alcoholic and equally delicious placeborita on our website thispodcastwillkillyou.com and our social media.
Erin Welsh	We certainly will. On our website, you can find all sorts of things such as transcripts, links to bookshop.org and Goodreads list. You can find music by Bloodmobile, merch, we've got some cool new merch coming out for you. You know there's more stuff, sources for our episodes. That's enough, right?
Erin Allmann Updyke	It's a lot, there's a lot there. Check it out.
Erin Welsh	Yeah.
Erin Allmann Updyke	Thispodcastwillkillyou.com .
Erin Welsh	Can we get started, please?
Erin Allmann Updyke	Please! I can't wait.
Erin Welsh	Okay, all right.
Erin Allmann Updyke	I am primed to take notes while we talk. I'm so excited.
Erin Welsh	Okay. Let's just take a quick break and then we can get right to it.
Erin Allmann Updyke	Okay.
TPWKY	(transition theme)
Erin Welsh	In the year 1584, 75 years after Hernando Cortés first arrived in what is now Mexico, Antonio de Ciudad Real and Fray Alonso Ponce, both Spanish, traveled through much of Mexico and wrote what they saw of this once densely populated and vibrant land. Quote: "In times past that town had a large population, according to the older people, and now it just seems like ruins of houses. And for the many fruit trees there are in the surroundings among which the Indians usually have their towns, especially being in the hot lands like it is. But with the Cocoliztli, there was such a very large pestilence and mortality in that land that everything was destroyed. And now there are scarcely 200 inhabitants." End quote.
Erin Allmann Updyke	Whoa.

Erin Welsh

Yeah. And while they name dropped Cocoliztli specifically there, it was far from the only factor in the tremendous population losses and cultural devastation experienced by indigenous populations in Mexico following first contact with European colonizers in the 16th century. And if you'll just allow me to get on a soap box for a little bit, even though the focus of today's episode is on just one of those factors, Cocoliztli, which we'll spend a lot more time about, I don't want to lose sight of that fact that this cultural and population devastation was multifactorial, that we can't take this disease, Cocoliztli, or these epidemics out of their historical context without considering everything else that was going on at the time. The retrospective diagnosis is a tricky enough business as it is and ignoring all of the social and political factors that played a role in the spread of disease, it's only going to further limit our ability to say anything about whether Cocoliztli was rodent associated or waterborne.

For way too long, many historians have overemphasized the effects that pathogens alone had on the population declines of indigenous peoples living in the Americas following European contact. The concept of quote unquote "virgin soil epidemics", as in the idea that these pathogens that Europeans were more acquainted with and brought with them to the New World, that these pathogens were more devastating to immunologically naive populations, this concept has been overly used in the construction of these like Eurocentric Jared Diamond-esque histories where the strong conquered the weak and took what was rightfully theirs because nature, ie pathogens, determined that they were the victors. Right?

Erin Allmann Updyke

No. Oh no, no.

Erin Welsh

Focusing on the role that germs alone played in mass mortality events in the Americas ignores the decisions that European colonizers made to subjugate and oppress the indigenous populations. Enslavement, forced labor, over burdensome taxation, complete upheaval of everyday life, and repression of traditional cultural practices. Germs weren't acting alone here, in more ways than one. Like yes, there were devastating smallpox epidemics, that cannot be ignored, that cannot be debated. And yes, there were also horrific measles outbreaks and influenza epidemics and so on and so forth. But it's not like in those 80s action movies where the bad guys take turns fighting the one good guy. It's like multiple pathogens were all circulating at the same time. All the bad guys were fighting all at once.

And this isn't to downplay the enormous mortality rates that we see during these epidemics, upwards of 60%-80% of the entire population in some cases. But it's just to try to present a more nuanced view of where those numbers, those mortality rates, might be coming from. Death from disease, absolutely. Maybe increased by malnutrition or co-infection with another pathogen or weakened health from forced labor or fewer people to care for the sick. Like societal collapse. The layers of protection from getting sick or dying from illness in many cases had been entirely stripped away. And I think sometimes that can get lost in looking at these epidemics from like a purely biological, microbiological, and epidemiological focus I guess.

And I think this is especially important to remember when we're trying to go through and guess which pathogen might be responsible for Cocoliztli and be like wow, there's no known pathogen that causes such high mortality rates. Like well of course, because it's not just one lone pathogen. But anyway, keeping all that in mind, now let's turn to Cocoliztli. What were the Cocoliztli epidemics? In short, they were a series of epidemics of undetermined cause that swept through much of Mexico and the rest of Mesoamerica during the 16th, 17th, 18th, and possibly even the 19th centuries. At least 13 distinct epidemics according to one paper I read. But today, I'm only going to be focusing on the two most devastating Cocoliztli epidemics. One that began in 1545 and the other in 1576, since they have the most documentation and had the most apparently impact on the population. But to better understand how these epidemics happened when they did and the impact they had, let's do a little bit of stage setting.

In 1519, the Spanish conquistador Hernando Cortés and his crew landed in Mexico where they claimed the land for the Spanish crown and proceeded to travel inland until they reached Tenochtitlan, the massive capital of the Aztec Empire or specifically the Mashika people. Aztec is kind of a political term I learned that means really just the three tribes that controlled a lot of Mexico at the time. And one of these tribes, the most powerful, was the Mashika. Anyway, shortly after arriving in Tenochtitlan and being showered with please go away gifts of silver and gold and textiles, the Spanish then took the Mashika emperor of the city as prisoner, Montezuma, for a year until he was killed. And skipping over a whole lot of history here, that really sort of kicked off the beginning of Spanish colonial rule in Mexico. Like that is not even beginning to get into, that's not even surface level. There's so much more history there but basically things changed very quickly in that Aztec Empire, from political organization to wealth distribution, cultural practices to daily life.

Agriculture shifted under Spanish rule as domestic animals were introduced and the dominant crops switched from maize, squash, amaranth, beans, and peppers, to wheat so that the Spanish could make European style bread. Lakes were drained to prevent flooding or to provide more arable land for farming, taxation or tributes grew enormously in demand, pretty much beyond anyone's means. And as a result, nutrition really suffered especially since there were a series of droughts throughout the 16th century that we'll talk maybe a little bit more about later on. Many indigenous people were enslaved or forced to do labor or displaced from their homes and land. Even clothing changed apparently, with an emphasis on European style clothing along with fewer baths, since it was the Spanish belief at the time that bathing daily was bad for your health.

Erin Allmann Updyke

Okay.

Erin Welsh

Now all of these changes did not take place everywhere or at the same time throughout Mesoamerica but life certainly changed for everyone. And I came across a paper about Cocoliztli by Marr and Kiracofe from 2000 where the authors wrote that quote "certainly the policies of the Spanish colonial regime were harsh in many ways but no more so than those of the Aztec imperial regime had been." End quote. I mean wrong. And I think to claim that is to kind of undermine the drastic effects that the Spanish regime had on life for indigenous peoples. So anyway, when Cortés and his crew landed in 1519, Mexico was home to a population of around 22 million people. And the major city Tenochtitlan had approximately 250,000-300,000 occupants, which was five times the size of London at the same time.

Erin Allmann Updyke

Oh wow.

Erin Welsh

With an incredibly intricately connected society. But within the century, millions upon millions of people would be dead from a combination of disease and the major upheaval of Spanish rule. And the first disease to make itself felt was smallpox, which began to spread in 1520, only a year after Cortés arrived. 8 million people died during the smallpox epidemic.

Erin Allmann Updyke

Oh god.

Erin Welsh

Out of a population of 22 million. Yeah.

Erin Allmann Updyke

That's-

Erin Welsh

Unfathomable.

Erin Allmann Updyke

Yep.

Erin Welsh

And again, this was not just from smallpox alone but also from the general collapse of their society. Measles, epidemic typhus, influenza, and other diseases all followed, described by witnesses as distinct diseases even though they may co-occur. And although the 1520 smallpox epidemic has probably received more attention historically because of how it affected the transition of power from Aztec to Spanish rule, the Cocoliztli epidemics that followed were no less terrifying or devastating. So finally getting to Cocoliztli.

In 1545, Cocoliztli struck for seemingly the first time. Over a dozen early Spanish and indigenous contemporary accounts describe a deadly disease that swept through Mexico and the rest of Mesoamerica. Bernardino de Sahagún, Franciscan scholar who witnessed this epidemic, wrote quote: "In the year 1545 there was a huge and universal pestilence where in all of New Spain, most of the people who lived there died. At the time of this pestilence I was in Mexico City, in the part of Tlatelolco, and I buried more than 10,000 bodies. And at the end of the pestilence, I became ill and almost died." End quote. Importantly, Sahagún also lived to see the second epidemic of Cocoliztli in 1576 which he described as being very similar to the one in 1545. And he ultimately died in a third Cocoliztli epidemic in 1590.

Erin Allmann Updyke

Okay, okay.

Erin Welsh

Yeah. The symptoms of the illness were described as quote "acute onset of fever, vertigo, and severe headache, followed by bleeding from the nose, ears and mouth. It was accompanied by jaundice and severe abdominal pain and thoracic pain, as well as acute neurological manifestations." End quote.

Erin Allmann Updyke

I'm listening so intently, Erin.

Erin Welsh

I can hear you typing. I love it.

Erin Allmann Updyke

I know, I'm sorry. It doesn't pick up in the mic but I'm taking notes. Fever, vertigo, headache, bleeding. Okay, jaundice. Okay.

Erin Welsh

And we can go over all of this at the end also.

Erin Allmann Updyke

Oh we will.

Erin Welsh

Yeah.

Erin Allmann Updyke

Okay.

Erin Welsh

In general, the duration of the disease was described as short, about 3-4 days.

Erin Allmann Updyke

Okay.

Erin Welsh

And was said to have mainly affected the indigenous population. However sources vary on that point, which is maybe something that we'll get into later when going through the possible pathogens. Children and young adults were said to be the most affected, although again sources are not entirely consistent on this point.

Erin Allmann Updyke

Okay.

Erin Welsh

But this is supported by evidence from burial grounds in southern Mexico where the Mixtec peoples lived. And these burial grounds show that A) young people were disproportionately buried and B) bodies were stacked vertically, suggesting that the deaths happened too quickly for individual graves to be dug, which was the norm. So definitely like this is considered an epidemic graveyard.

Erin Allmann Updyke

Okay, okay.

Erin Welsh

And the bleeding seems like a key feature of this disease since it shows up in many of the contemporary illustrations of the epidemic. So one features a man in a full body rash as blood or vomit flows from his face. And others also feature bleeding from the face. And written descriptions also mention the blood. Quote: "A pestilence in which blood poured from the nose," end quote. And someone who was writing about the 1545 Cocoliztli epidemic like 60 years after it happened wrote that quote "blood flowed from the mouth, eyes, nose, and anus" end quote, of all people, poor and noble alike, and that the bodies were eaten by dogs and coyotes.

Erin Allmann Updyke

Oy, okay.

Erin Welsh

I think just like emphasizing the speed with which this killed and how many people are killed. Another Franciscan friar and eyewitness to both the 1545 and 1576 Cocoliztli epidemics used the term pujamiento de sangre, meaning abundant bleeding or full bloodiness, and said it was characterized by blood fevers.

Erin Allmann Updyke

Okay.

Erin Welsh

Notably though, this same author used the Spanish word for typhus, tabardillo, for the 1576 epidemic. And remember he saw both of them. But in general, this 1545 Cocoliztli epidemic was described by most eyewitnesses as distinct from other European introduced diseases including smallpox, measles, epidemic typhus, pertussis, and malaria. So in total, an estimated 5-15 million people died, said to be about 80% of the indigenous population.

Erin Allmann Updyke

Is that in these two outbreaks combined or just in the 1545 outbreak?

Erin Welsh

Just 1545.

Erin Allmann Updyke

Holy!

Erin Welsh

Yeah. There's a lot more detail on the 1576 one, so we'll get into that one in a second.

Erin Allmann Updyke

Oh my.

Erin Welsh

Yeah. 80% is what most estimates say.

Erin Allmann Updyke

80% of the indigenous population at the time.

Erin Welsh

Yeah.

Erin Allmann Updyke

Okay. I want to ask a million questions but I feel like you're going to answer them.

Erin Welsh: It's possible but it's also possible that I won't at all. But yeah, this 1545 epidemic lasted... It's kind of unclear, it probably varied from region to region but it seems like I've read 1.5 years to 4 years as the total length of time, more often 4 years.

Erin Allmann Updyke: And that's, okay, so like from 1545-1549 basically.

Erin Welsh: Yeah.

Erin Allmann Updyke: So over that time period, 80% of the population died presumably from this or related to it.

Erin Welsh: Right.

Erin Allmann Updyke: There's comorbid, etc.

Erin Welsh: Comorbid and also just sort of like societal collapse. Because this was such an intricately connected society, when you don't have... Let's say people who are sick can't then harvest food.

Erin Allmann Updyke: Right, okay.

Erin Welsh: And then people who get sick who can't turn that food into ingredients. And then people who can't turn ingredients into meals and then people who can't... It just like becomes this thing where if you're sick, then who's caring for you? So I think that's where we have to kind of remember where those mortality numbers are coming from.

Erin Allmann Updyke: Right. Because it's not necessarily all directly attributable to disease.

Erin Welsh: Right, exactly.

Erin Allmann Updyke: And/or to this one specific disease.

Erin Welsh: Right. And you can't assume care, even like palliative or supportive care or something.

Erin Allmann Updyke: Right.

Erin Welsh: Yeah.

Erin Allmann Updyke: And then this... But despite that, that is the number that's attributed to this outbreak which took place over four years.

Erin Welsh: It is the population losses during this epidemic, yes.

Erin Allmann Updyke: And can I ask a question?

Erin Welsh: Yeah.

Erin Allmann Updyke: Was it like sporadic, evenly distributed across those four years? Do we know was it like mostly at the beginning or mostly at the end? Was it like every spring for example or something like that? Or is it just like it was these four years and that's the most resolution that we have?

Erin Welsh: So for the 1545 one, more or less that's the most resolution that we have. I think it probably started out very strong and it seems to have sort of swept through towns very quickly and very dramatically. But we do have more information in general for the 1576 one.

Erin Allmann Updyke: Okay.

Erin Welsh: So let's get into that.

Erin Allmann Updyke: Okay, please.

Erin Welsh: But also I will say that the 1545 one did start in August.

Erin Allmann Updyke: It started in August, okay.

Erin Welsh: Yeah.

Erin Allmann Updyke: In August in Mexico, okay.

Erin Welsh: Okay. So there would be other appearances of Cocoliztli in the years following that 1545 epidemic but it really came back with a vengeance in 1576. Quote: "In the year 1576, a great mortality and pestilence that lasted for more than a year overcame the Indians. It was so big that it ruined and destroyed almost the entire land. The place we know as New Spain was left almost empty. It was a thing of great bewilderment to see the people die. Many were dead and others almost dead, and nobody had the health or strength to help the diseased or bury the dead. In the cities and large towns, big ditches were dug and from morning to sunset, the priests did nothing else but bury the dead bodies and throw them into the ditches without any of the solemnity usually reserved for the dead because the time did not allow otherwise. At night they covered the ditches with dirt. It lasted for 1.5 years and with great excess in the number of deaths." End quote.

Erin Allmann Updyke: Wow. Okay.

Erin Welsh: That is a quote from Fray Juan de Torquemada who was a Franciscan historian and he was describing the epidemic in Mexico City. The epidemic, this epidemic began in June in central Mexico and quickly made its way across the land, reaching as far north as parts of what is now the Southern US and as far south as the Peruvian Andes. But the vast majority of cases were concentrated in like a 400 mile radius in Mexico, where it spread from the dry plains of the north to the densely populated subtropical valleys of central Mexico, leaving almost no place unscathed. Except for perhaps the coastal areas according to some. The spread seemed to slow by October 1578, so it's like two years after, but then increased again in August 1579, ending finally in the middle of 1581. The effect was truly devastating. In Mexico, more than 2 million people died during this epidemic, half of the population, 51.36% to be precise. And we can be so precise because censuses were conducted a few years before the epidemic and a few years after.

Erin Allmann Updyke: Wow.

Erin Welsh: Yeah. This epidemic in general like I mentioned is much better documented, so get ready for lots of quotes.

Erin Allmann Updyke: Okay.

Erin Welsh

The mortality rate was not consistent across all areas. So one region southwest of Mexico City, Tepeaca, lost 86.6% of its population of 60,000. While Cholula east of Mexico City lost only 40% of its 15,000 inhabitants. Only 40%.

Erin Allmann Updyke

Unbelievable number.

Erin Welsh

Yeah, yeah. One eyewitness described its erratic spread. Quote: "It appears as if it is a living thing and that it goes in search of towns so that none remain." End quote. The Bishop of Michoacán wrote quote: "Almost half of the natives of this province have been taken. When the pestilence enters a town for 10 months or a year, it jumps from barrio to barrio and from house to house. And it was without order, even though divine disposition would have had it well ordered. Because it struck one neighborhood and then jumped to another far away, sparing the one closer by. And in the same home, it took some and spared others, only to return four or six months later to claim the healthy. This was observed by all." End quote. He added that quote "these poor Indios are half what they were in number and the half that return are wasted, weary, and miserable because everyone has either succumbed to the pestilence or escaped it. And even today, the sorrowful ones who survived are still preoccupied with their loved ones who continue to suffer." End quote.

So the Spanish who seem to be less affected by the disease, although asterisk, did keenly feel its impacts in other ways, namely economical. The accountant of the Royal Treasury of New Spain wrote quote: "The illness and death of the natives have been so so great that they have been completely diminished, so much so that in many pueblos in this great land, fewer than half the population remains, and in others less than a third. And so our profits are less than they were. The absence of natives in these lands is so great that it seems unfathomable that they could have been brought to this point. The profits are far less and our expenses ever greater because of the tremendous hardship. And the whole land is in misery, affliction, and need." End quote.

Erin Allmann Updyke

That quote, like your tremendous hardship because your profits are down, that's gross.

Erin Welsh

Yeah, I know.

Erin Allmann Updyke

This tremendous hardship of having to care for people. My goodness. Erin, this is truly astounding.

Erin Welsh

Right? Yeah. I mean I know I just keep saying it over and over again but it's just like it's unfathomable and there's so much here and I think it's also fascinating, number one how well this is documented.

Erin Allmann Updyke

Right.

Erin Welsh

And two, how much more is still being uncovered because for a long time the main accounts that were used were written by Spanish colonizers. And only more recently do we have people, the Nahua people, who also wrote down histories, like those are being translated and then taken into account in these retellings. And so-

Erin Allmann Updyke

Interesting.

Erin Welsh

It's very interesting.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah. But Cocoliztli, this epidemic especially threatened Spanish rule and colonial order because of sheer population loss, not just economically but also culturally. Fewer people to convert to the new religion and to rule over. And so okay, at this point we've established that this is a pretty deadly disease. Now let's go through how this one was described.

Erin Allmann Updyke

Yeah.

Erin Welsh

Again, the Nahuatl word Cocoliztli or Huey Cocoliztli was used to mean pestilence or great pestilence. And the Spanish also used mal pestilencia, pestilence universal, bad or universal pestilence. It was discussed as distinct from the other known epidemic diseases and was generally seen as something new, something unfamiliar. Some reports describe young people being disproportionately affected while others say it attacked all ages. No animal deaths, domestic or wild were mentioned. When it comes to symptoms, there's actually a medical description by Dr. Francisco Hernández who was the physician in chief of New Spain. It's very long, so brace yourself. But I think you're going to find it very interesting. And yes.

Erin Allmann Updyke

I'm going to try and memorize it.

Erin Welsh

Quote: "The fevers were contagious, burning, and continuous, all of them pestilential, in most part lethal. The tongue was dry and black, enormous thirst, urine of the colors sea green, vegetal green, and black, sometimes passing from the greenish color to the pale. Pulse was frequent, fast, small, and weak, sometimes even null. The eyes and the whole body were yellow. This stage was followed by delirium and seizures. Then hard and painful nodules appeared behind one or both ears along with heartache, chest pain, abdominal pain, tremor, great anxiety, and dysentery. The blood that flowed when cutting a vein had a green color or was very pale, dry, and without serosity.

In some cases, gangrene and sphacelus," AKA necrosis, "invaded their lips, pudendal regions, and other regions of the body with putrefact members. Blood flowed from the ears and in many cases blood truly gushed from the nose. Of those with recurring disease, almost none was saved. Many were saved if the flux of blood through the nose was stopped in time, the rest died. Those attacked by dysentery were usually saved if they complied with the medication. The abscesses behind the ears were not lethal. If somehow their size was reduced either by spontaneous maturation or given exit by perforation with cauteries, the liquid part of the blood flowed or the pus was eliminated and with it the cause of disease was also eliminated, as was the case of those with abundant and pale urine.

At autopsy, the liver was greatly enlarged. The heart was black, first draining a yellowish liquid and then black blood. The spleen and lungs were black and semi putrefacted. The bile was observed in its container, the abdomen dry, the rest of the body anywhere it was cut was extremely pale. This epidemic attacked mainly young people and seldom the elder ones. If old people were affected, they were able to overcome the disease and save their lives. The epidemic started in June 1576 and is not over in December when I am writing these lines. Very few with abdominal distention were saved. At the beginning the blood was expelled by some without severe disease, then by very few. Vital energy was consumed quickly." End quote. A lot to unpack there.

Erin Allmann Updyke

Was there a time frame in that description that I missed?

Erin Welsh

There was not. But again, in general 3-4 days, 3-5.

Erin Allmann Updyke

Wow, okay. Okay, okay.

Erin Welsh

Yeah. Other symptoms that I saw mentioned or key observations by other eyewitnesses include the fact that it was pus that would drain out of those swollen lymph nodes if cut and that bloodshot eyes were common and insatiable thirst was also mentioned, lung hemorrhage was seen at autopsy. But again, bleeding does seem to be a main feature. And the phrase 'blood emerged from our noses' and variations on that appeared many times throughout accounts of this epidemic. Epidemics of Cocoliztli continued possibly until as recently as the early 19th century, although the name used in these later epidemics was matlazahuatl, a net-like rash. And it's unclear if the new name meant new disease or was used in recognition of a new symptom or was just something else, people don't know.

But in any case, Cocoliztli, especially the 16th century epidemics, has stumped researchers for decades. The symptoms described along with the high mortality rate don't seem to match any known pathogen today. But don't worry, there are still plenty of hypotheses to go around. Historically epidemic typhus has been a popular guess and more recently hemorrhagic fever, possibly associated with rodents. This rodent association is because both the 1545 and 1576 epidemics occurred during brief intense rainfall, preceded by long periods of mega drought, which is very similar to the Four Corners 1993 hantavirus outbreak where deer mice proliferated after that same drought-rainfall cycle. Others that have been proposed include plague, specifically pneumonic, anthrax, leptospirosis, malaria, diphtheria, pertussis, louse-borne relapsing fever, and malaria. All of these I just mentioned were proposed based on epidemiological characteristics or descriptions of symptoms, not physical evidence, not yet for those anyway.

But there is one candidate pathogen for Cocoliztli that has gotten a lot of attention recently and that is *Salmonella enterica* subspecies *enterica* serovar *Paratyphi C*, longest name for an organism ever maybe. But a few years ago researchers detected *Salmonella enterica* *Paratyphi C* DNA in 10 individuals that were buried during the 1545 Cocoliztli epidemic in Oaxaca in southern Mexico. Now the researchers who published this paper are not claiming that this pathogen was solely responsible for the Cocoliztli epidemics but instead suggests that it may have acted in concert with other circulating pathogens at the time. But before we start debating which pathogen is the best candidate if any, let's maybe learn a bit more about the ones proposed, keeping in mind 1) what these diseases looked like, 2) how they're transmitted, 3) case fatality rates, 4) environmental factors, 5) Old World vs New World origins, and 6) that this could have been the work of many factors acting simultaneously. And now Erin, I turn it over to you.

Erin Allmann Updyke

Oh yeah. So let's take a quick break and then let's get into some of these candidate pathogens. I have so many thoughts already. So let's take a beat and then get real deep into it, shall we?

Erin Welsh

Let's do it right after this break.

TPWKY

(transition theme)

Erin Allmann Updyke

I am bursting right now. And part of what I think I am bursting with is how much I can understand how this has stumped everyone because nothing, nothing fits.

Erin Welsh

No.

Erin Allmann Updyke

When we did dancing plague, I remember feeling like oh at least some of these definitely don't fit and some of them like kind of fit a little bit maybe.

Erin Welsh

Yeah.

Erin Allmann Updyke

This I'm like hmm. So let's get into all of these different proposals. I have feelings about it and I'm going to have some more questions for you to be able to try and parse out some of this.

Erin Welsh

Great, let's dig in.

Erin Allmann Updyke

So the list that you told me, Erin, or at least the ones that I definitely researched included hantavirus, epidemic typhus, pneumonic plague, leptospirosis, bartonellosis, measles, smallpox, malaria, an unknown hemorrhagic fever virus, my personal favorite.

Erin Welsh

It's just like choose your own adventure, like just attribute traits that have not been observed in one virus. But that's fine, yeah.

Erin Allmann Updyke

And of course Salmonella enterica Paratyphi C. Some of these I think we can very quickly and very easily discard.

Erin Welsh

As the main contributor, yeah.

Erin Allmann Updyke

As the main contributor. Because they not only just don't match symptoms-wise but like you importantly mentioned, these were things that circulated and were described very differently.

Erin Welsh

Right.

Erin Allmann Updyke

Right. So that includes something like smallpox, where one of the predominant symptoms of smallpox and something Erin that you really didn't mention at all in that list of symptoms is a rash.

Erin Welsh

Yeah. Okay, rash. Interesting. So there was that one illustration of the 1545 epidemic that did depict someone with a full body rash. But in general, it was not consistently mentioned and in 1576 there was that Franciscan scholar who used the word tabordillo which I think means cloak rash or something like that, it refers to the rash from typhus, from epidemic typhus. But that long quote from the physician didn't describe it.

Erin Allmann Updyke

Right.

Erin Welsh

And in general it didn't seem to be a main feature of the disease.

Erin Allmann Updyke

Right, yeah. So I feel like based on that, smallpox is just all the way out, it just doesn't fit.

Erin Welsh

It doesn't fit.

Erin Allmann Updyke

Same thing with measles quite honestly.

Erin Welsh

Yeah.

Erin Allmann Updyke

And on top of that measles, which okay, side note, one of my favorite things about researching for this episode is that we have covered all of these things.

Erin Welsh

Did we do Bartonella?

Erin Allmann Updyke

We did Bartonella, Erin.

Erin Welsh

I forgot.

Erin Allmann Updyke

The literal... Because there's a few more things that I have on my list that you gave me. And literally the only ones that we haven't covered are unknown hemorrhagic fever. Okay? And Parvovirus B19, which it's not that either.

Erin Welsh

Right, right.

Erin Allmann Updyke

But we'll get there. Everything else we've talked about, so this is really fun and most of my sources are see our previous episodes.

Erin Welsh

Nice.

Erin Allmann Updyke

But okay, smallpox is out. Measles, we did measles a very, very long time ago now. Measles, while it spread through populations and absolutely caused a lot of morbidity and mortality, the mortality rate is nowhere near what we're seeing with Cocoliztli. The mortality rate of measles was far, far lower. And on top of that, the symptoms really are just nothing like these symptoms that are being described.

Erin Welsh

I do remember from our measles episode there being in entirely naive populations, measles having a much higher mortality rate. But A) again I still think that the symptoms don't... Like where's the hemorrhage? Is there a hemorrhagic form of measles?

Erin Allmann Updyke

Not that I know of.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah. And like so much of measles is a very characteristic measles rash.

Erin Welsh

Right, right.

Erin Allmann Updyke

I think the things that make it seem like measles are just the rapidity which it seems to have swept through a population. Except that like the duration of disease with measles also tends to be longer.

Erin Welsh

Yeah. Well and I think it's interesting that you say the pattern of spread because I think keeping that in mind for transmission route.

Erin Allmann Updyke

So that's what I wanted to get, I wanted to ask you a little bit more questions.

Erin Welsh

Okay.

Erin Allmann Updyke

But let's knock a few more off this list first.

Erin Welsh

Yeah, yeah.

Erin Allmann Updyke

Because I think there's some other easy ones.

Erin Welsh: Okay.

Erin Allmann Updyke: So it's not smallpox, it's not measles. It's not malaria.

Erin Welsh: No. Cyclical fevers vs continuous high fever.

Erin Allmann Updyke: Cyclical fevers.

Erin Welsh: Yeah. I mean and not to mention a lot of other things.

Erin Allmann Updyke: A lot of other things, the mortality is not happening within a number of days, that's just not how measles works.

Erin Welsh: It doesn't seem mosquito-borne, like that just doesn't match the pattern of spread.

Erin Allmann Updyke: Yeah. Hepatitis B was one that you mentioned to me via text message, Erin.

Erin Welsh: I saw that mentioned last minute in a paper that I came across.

Erin Allmann Updyke: Yeah. It was like yesterday evening and I was like great, more work. I love it. So Hepatitis B, again we did this episode, y'all. Hepatitis B causes chronic illness. And it absolutely accounts for even to this day hundreds of thousands of deaths every year. But it's a chronic infection, it's not something that is acutely killing people, at least not at this scale. So it's not Hepatitis B. It's not Parvovirus B19, it seems to me. This is one that we haven't covered so I'll just briefly mention it. And even just doing this little dive on it for this episode made me want to do Parvovirus.

Erin Welsh: I definitely want to do Parvoviruses, yeah.

Erin Allmann Updyke: Yeah. So Parvovirus B19 is one specific Parvovirus, these are DNA viruses. They're transmitted person to person by respiratory droplets. They can be quite infectious and tend to infect kids more than adults, mostly because you develop immunity to it. But the disease that we tend to see in majority is a pretty mild illness though it can cause an aplastic anemia. And I think maybe that is where there is this potential, looks like there's a connection. Because a lot of the symptoms that you described, not necessarily with regards to hemorrhage, but in that 1576 description of everything being pale and the blood being pale and etc. To me, that means we're not having enough red blood cells for one reason or another. Aplastic anemia means that your body stops making red blood cells. And that's because in the case of Parvovirus B19, it's replicating and destroying your red blood cell precursors, replicating in and destroying your red blood cell precursors.

Erin Welsh: Interesting.

Erin Allmann Updyke: And so it can cause this transient usually anemia where you basically can't make any more red blood cells, which can be really dangerous. But again, it doesn't happen in everyone, it's not killing people outright, it's not causing this massive amount of hemorrhage, etc, etc.

Erin Welsh: Right. And it does make me think based on that description and the amount of hemorrhage that was happening that the paleness may have been due to that more than aplastic anemia. But I like that, that's interesting.

Erin Allmann Updyke: Yeah. And it sounds to me like there's multiple things going on in the description.

Erin Welsh: For sure.

Erin Allmann Updyke: So I want to get into like my thoughts on it and then talk about the more likely candidates.

Erin Welsh: Okay.

Erin Allmann Updyke: What were some of the others that you told me that seemed easy to say 'I don't think it's that'?

Erin Welsh: Bartonella, did we already talk about that one?

Erin Allmann Updyke: We haven't talked about Bartonella yet, let me scroll through my nine page table.

Erin Welsh: Leptospirosis and pertussis and diphtheria.

Erin Allmann Updyke: Oh my gosh Erin, you did not tell me diphtheria and pertussis.

Erin Welsh: Okay well we can rule those out. There were no respiratory symptoms described.

Erin Allmann Updyke: There were no respiratory symptoms described. So because of that, I actually think that pneumonic plague is not likely to be a cause of this. And it's interesting because some of what was described in that 1576 outbreak sounded a little bit like bubonic plague.

Erin Welsh: With the lymph nodes?

Erin Allmann Updyke: With the lymph nodes and these ulcerated nodes behind the ears. You have a pretty decent chain of lymph nodes back there. And pneumonic plague, which is a form of plague caused by *Yersinia pestis*, see season one for more details.

Erin Welsh: Yeah.

Erin Allmann Updyke: Bubonic plague would cause these very inflamed lymph nodes, these buboes, though generally throughout the body and not necessarily only in one place. And it was pneumonic plague that was the most deadly. And with pneumonic plague, generally the symptoms very much were pneumonia-like, you had symptoms predominantly in the lungs and people tended to die from respiratory failure and not from hemorrhage like it sounds like happened here.

Erin Welsh: Yeah.

Erin Allmann Updyke: I will say that pneumonic plague is something that killed people very rapidly when it happened, often in as little as 24 hours. And the untreated fatality rate for pneumonic plague is nearly 100%.

Erin Welsh: Yeah.

Erin Allmann Updyke: So is it possible that there was plague going on that was causing bubonic, pneumonic, even septicemic plague? I mean it certainly seems possible that that was circulating.

Erin Welsh: I mean and this is what I find interesting though because plague was a known entity.

Erin Allmann Updyke: That was going to be my question, is how much, and I would have to go back and listen and re-remember, how much plague was kind of already well described and well known during the kind of Spanish conquistador takeover?

Erin Welsh: Well okay, that's a good question. And this is me grasping at wisps of memories from season one. The Black Death happened in the middle of the 14th century.

Erin Allmann Updyke: Right.

Erin Welsh: And it didn't just go away, like it remained in pockets, it would rear up every now and then. There there were epidemics of plague that happened on a regular basis. And so I think given it's sort of like formative impact on medicine-

Erin Allmann Updyke: Yeah.

Erin Welsh: I would think that it would have been described or recognized as plague.

Erin Allmann Updyke: I agree.

Erin Welsh: Like it was well known, it was familiar. And the other thing too, and maybe this is a little unfair, but like most papers seem to also kind of discard it or like mention it as this was one of the ones considered or has been suggested.

Erin Allmann Updyke: Yeah, right.

Erin Welsh: So like maybe we should be giving it a more fair shake but I think that we have.

Erin Allmann Updyke: Yeah. I don't think it fits.

Erin Welsh: I don't think it fits.

Erin Allmann Updyke: Yeah, I don't think it fits. Bartonellosis is an interesting one. So bartonellosis, we did this Erin in a very nontraditional episode way because we covered all of the different kinds of Bartonella.

Erin Welsh: Yes. I remember that because we were like what have we done?

Erin Allmann Updyke: Yes.

Erin Welsh: Yeah.

Erin Allmann Updyke: I still feel that way. But what's interesting is that because there are so many different bacteria, so many different species of Bartonella that cause a pretty wide variety of disease including... So Bartonella bacilliformis is what causes Carrion's disease. Carrion's disease today is limited to the Andean valleys of South America. But there are many other species of Bartonella that cause things like trench foot, bacillary angiomatosis, of course Bartonella henselae which causes cat scratch disease. And the symptoms don't quite fit, especially this hemorrhage. I really just keep coming back to the hemorrhage part of it.

Erin Welsh: Yeah, it's hard to ignore.

Erin Allmann Updyke

It's really hard to ignore. But the high fevers, the headaches, the jaundice that was mentioned in both of those descriptions, and the pallor which could in addition to being from just blood loss, be from a hemolytic anemia which can definitely be seen with bartonellosis, especially with bartonellosis from Bartonella bacilliformis which causes the most severe Bartonella that we see today. So could it be that there was a different species of Bartonella perhaps or the same species but causing infection in a slightly different way during that time? I don't know, maybe. The things that make me feel like it's less likely to be Bartonella is really that this was a more protracted illness. So while the mortality rate can be very high, according to some studies at least, Carrion's disease has an estimated mortality rate of anywhere from 40%-80%. Although some studies suggest that the infection rate in a lot of these outbreaks was actually much higher, which means that the mortality rate comparatively was lower.

Erin Welsh

Okay.

Erin Allmann Updyke

But it also is just a more protracted illness. This was something taking place over the course of 1-4 weeks and people were dying at the end of this very protracted illness, which is not what was described in Cocoliztli.

Erin Welsh

Okay. One interesting thing about Bartonella is that it's a bacterium. And I don't know, like I'm just not up to speed on how DNA analysis is done on ancient specimens. So I don't know if they would have been able to look for Bartonella or if it would have come up.

Erin Allmann Updyke

Yeah.

Erin Welsh

But definitely I know that they mentioned in the paper that the techniques that they used could detect bacteria, many bacterial species as well as DNA viruses but not RNA viruses. And so I do wonder if it was there they would have been able to find it. And that doesn't mean at all that it's not Bartonella just because they didn't find it. Like again, these are very few samples in one specific region, that doesn't mean that that is what happened all over Mexico. But anyway, just thought.

Erin Allmann Updyke

That's interesting.

Erin Welsh

But yeah, I think based on the duration, like I don't know.

Erin Allmann Updyke

It just seems less likely. I think that one is one that's maybe not quite as easy of a just dismiss it.

Erin Welsh

Yeah. We're getting to that stage.

Erin Allmann Updyke

Because it's interesting. Yeah.

Erin Welsh

Yeah.

Erin Allmann Updyke

Another one that I think based on symptoms is worth talking in a little bit more detail about but I still think is very less likely more based on kind of epidemiological data is leptospirosis.

Erin Welsh

Okay.

Erin Allmann Updyke	So leptospirosis is caused by the spirochete, <i>Leptospira</i> , many different species. This is a waterborne illness in general, it comes to us from the urine of other animals. And symptom-wise it seems like some things really do seem to fit. Fever is one of the first symptoms, there's generally a lot of GI symptoms like nausea and vomiting and diarrhea. Rashes tend to occur only pretty late in the course of disease, so they're definitely not like an everyone feature and they're not like a predominant feature, I guess. But what does tend to be especially in severe disease is signs of organ dysfunction like jaundice because of damage to the liver, like kidney dysfunction which tends to be what ends up killing people.
Erin Welsh	Okay.
Erin Allmann Updyke	Like hemolytic anemia.
Erin Welsh	Okay.
Erin Allmann Updyke	Right. So a lot of things are kind of ticking boxes. We do also see in leptospirosis when it's severe disease, signs of bleeding, signs of hemorrhage. And this is usually because of a decrease in platelets. But in general, it's mild bleeding, it's petechiae, like little pinpoint purple spots. You can however see more severe bleeding, like massive gastrointestinal or pulmonary hemorrhage, and pulmonary hemorrhage tends to be what kills people in the case of leptospirosis. But this is not something that happens for everyone who gets leptospirosis.
Erin Welsh	Yeah.
Erin Allmann Updyke	The time course of leptospirosis is generally pretty long and it's usually not until a kind of biphasic second round of disease that people get very, very sick.
Erin Welsh	Okay.
Erin Allmann Updyke	Where they actually end up dying from the disease.
Erin Welsh	Whereas this was like clearly seemed to be happening over the course of 3-4 days.
Erin Allmann Updyke	A couple of days.
Erin Welsh	Yeah.
Erin Allmann Updyke	And the other thing that I think makes leptospirosis so much less likely is that you specifically mentioned that no animals seem to have died.
Erin Welsh	Right.
Erin Allmann Updyke	Leptospirosis is something that infects lots and lots of different animals and humans are dead end hosts.
Erin Welsh	Yeah.
Erin Allmann Updyke	And so I mean on the one hand, could it be that this... I just wouldn't expect for it to be something that could spread across an entire region so easily and so rapidly without having some kind of animal involvement.

Erin Welsh: Yeah, I feel like it would have to have been transmitted human to human. And since leptospirosis, humans are a dead end host, you would have to have a continuous reintroduction of the pathogen into the water supply.

Erin Allmann Updyke: Yeah.

Erin Welsh: That's harder to imagine happening.

Erin Allmann Updyke: Yep. I agree. I agree.

Erin Welsh: All right. So now are we left with-

Erin Allmann Updyke: We're left with, oh wait, epidemic typhus.

Erin Welsh: Yeah.

Erin Allmann Updyke: That's our last one besides the other three. So epidemic typhus you mentioned a number of times. And I think part of the reason that makes me think it's not epidemic typhus is just that epidemic typhus was known it seems.

Erin Welsh: Yeah.

Erin Allmann Updyke: But in addition to that symptom-wise, epidemic typhus which is caused by *Rickettsia prowazekii*, so a rickettsial intracellular bacterium spread by lice, so not quite person to person but person to person in that you're transmitting lice person to person.

Erin Welsh: I mean in historical epidemic typhus outbreaks, we see massive spread and massive mortality.

Erin Allmann Updyke: Of course.

Erin Welsh: And mortality associated with malnutrition.

Erin Allmann Updyke: Yes.

Erin Welsh: Like we talked about.

Erin Allmann Updyke: I remember talking about that in a lot of detail. Yeah, pre antibiotic mortality rates were as high as 60% in epidemic typhus which fits with this. A sudden onset of fever and headache and abdominal pain are the kind of key symptoms along with central nervous system dysfunction, which could include seizures like you mentioned and could include delirium and a lot of other things. But that's kind of where the overlap seems to end. There's really not a lot of description of hemorrhage at all when it comes to epidemic typhus. There is not the hemolytic anemia, there's not the jaundice, there does often tend to be a rash and rash is something that is often described as associated with epidemic typhus. And we talked in that typhus episode about the difficulties with those historic descriptions of rash because rash appears very differently on different colored skin. And so it's thought that maybe rash was actually less common or maybe more common, etc. But in any case, rash is definitely something that is described as associated with typhus. And the disease here tends to last for 2 to 3 weeks. So again, we're talking about something that tends to have a much longer course of illness.

Erin Welsh: Yeah.

Erin Allmann Updyke

So I think less likely to be epidemic typhus. Okay, so we're almost done with this long list and we've come to the few that I think are either the best contenders or that we, like you said, maybe have a little bit of evidence to suggest, maybe. Okay. So let's go through these last couple and then we'll regroup, shall we? So one of the last is hantavirus. Hantavirus, there are many different hantaviruses. Hantaviruses are RNA viruses. So like you mentioned, we would never know, at least not as of this point.

Erin Welsh

Yeah.

Erin Allmann Updyke

And they're generally spread by aerosolized rodent excrement. So like rodent pee has to get in your face in order to get a hantavirus. Symptom-wise, because there are many different types of hantaviruses that have been found in different parts of the globe, some of the symptoms do seem to fit fairly well and certainly Sin Nombre virus has a mortality rate of 40%-50% or even higher than that in some outbreaks that we've seen. The symptoms tend to be fevers, headaches, dizziness, body aches, so it can present kind of like more like the flu than what it sounds like the descriptions of this particular outbreak of Cocoliztli were. But it can also have nausea, vomiting, abdominal pain, diarrhea. And when hantaviruses cause severe disease, there's a couple different forms or a couple of different manifestations that they can take.

One, which is what tends to be caused by Sin Nombre virus, is a cardiopulmonary disease which causes death within 24-28 hours, within a day usually. And the symptoms are caused by vascular permeability, by your blood vessels just leaking everywhere and fluid and blood just leaking out of these leaky blood vessels. So while we don't necessarily tend to see like pure hemorrhage, we certainly see leaky blood vessels in hantavirus infections, in Sin Nombre infections specifically. In other hantaviruses like Hantaan virus and Puma virus, we do see more hemorrhage potentially and we tend to see a cardiorenal syndrome more than a cardiopulmonary syndrome. Because I know Cocoliztli, we didn't really see pulmonary, we didn't really see lung involvement described but we did see potentially kidney involvement described. And so we do see that in a cardiorenal form of a hantavirus. But what we tend to see is just that your kidneys stop working and you stop making pee and then you die because of kidney failure. So I don't know, it doesn't fit that well.

Erin Welsh

Okay. But it's something.

Erin Allmann Updyke

It's something. Also though this is something that is spread by rodents.

Erin Welsh

Right. So far for the most part with like one possible exception or two, we do not see human to human transmission of hantaviruses.

Erin Allmann Updyke

Correct.

Erin Welsh

Which doesn't mean that it can't happen or didn't happen in the past.

Erin Allmann Updyke

Yeah.

Erin Welsh

But based on the ones that circulate that we recognize today, no.

Erin Allmann Updyke

No. So that brings us to *Salmonella paratyphi*, or rather *Salmonella enterica* subspecies *enterica* serovar *Paratyphi C*.

Erin Welsh

There are multiple paratyphis.

Erin Allmann Updyke

There really are. And it's shockingly difficult to get information on symptoms of Salmonella enterica subspecies enterica serovar Paratyphi C because all of the papers described say you can't tell the difference between Salmonella typhi and Salmonella paratyphi when it comes to the symptoms of disease, at least in so far as we know today.

Erin Welsh

Okay.

Erin Allmann Updyke

So we did typhoid relatively recently and the classic description of symptoms of typhoid start with a fever. But there's a few things about typhoid that really stick out to me as not fitting with your description of Cocoliztli. Some of them include the fact that this fever, you mentioned in those descriptions that the fever was constant, but the fever of typhoid is usually described as not just constant but getting progressively worse day after day.

Erin Welsh

Okay.

Erin Allmann Updyke

And rising over the course of a couple of weeks.

Erin Welsh

Right.

Erin Allmann Updyke

So already we don't quite fit. Also classic typhoid, and we talked about this in our typhoid episode, has a relative bradycardia.

Erin Welsh

Right.

Erin Allmann Updyke

Which means that your heart rate does not increase with that fever. And the description from the 1576 outbreak very nicely specifically said that you see really high heart rates. And in typhoid, it's less likely for that to happen. Additionally, rash is a really common description of typhoid infection and this rash, it tends to be salmon-colored, little spots, starting on the trunk and then kind of spreading outwards from there. And then it's usually not until the third week of this illness that you start to see GI symptoms like abdominal pain or diarrhea. And that is when we can see some bleeding from the intestinal tract, we can see bloody diarrhea. And potentially this infection spreading to the bloodstream where you can get hepatosplenomegaly, which is again where your liver and your spleen starts to swell.

Erin Welsh

Yeah.

Erin Allmann Updyke

And that seems to have been described in that 1576 outbreak where you have your liver and your spleen becoming abnormally large and all of your organs just getting super messed up. But other than that, we don't really see a lot of bleeding. We don't really see a lot of neurologic manifestations. So we don't really tend to see the delirium, we don't really tend to see the seizures, that kind of thing is much less likely in typhoid. But certainly mortality rate ranged from 10%-30% for the most part if untreated with typhoid. But it is spread fecal-oral, so easily spread person to person. And there's of course the carrier state, ie Typhoid Mary.

Erin Welsh

Yeah.

Erin Allmann Updyke

Meaning that it would be really easy for this to be something that could spread across a country.

Erin Welsh

Yeah.

Erin Allmann Updyke

Because people could be carrying it and asymptomatic for a really long time. But in general I feel like it's interesting, and we'll talk I know a little bit more about this, that this happens to be the pathogen that has been found in people who likely died during this outbreak because it seems to me like the least good fit in terms of symptoms.

Erin Welsh

So okay, I definitely think and the authors also acknowledge the possibility that this is just a circulating pathogen that was there that people had. I did a bit of digging.

Erin Allmann Updyke

I can't wait.

Erin Welsh

A little bit of Google Scholaring. And one thing that I think is interesting and that this sort of reminded me of is that a paper from even like the 1980s or up to the 2000s that describes typhoid fever is going to I think look at a case of typhoid fever in a very different setting than historically. And this also applies to typhus, to hantaviruses, etc. Another thing that I also wonder about is like virulence plasmids. How, and I don't remember this from our typhoid episode, like whether there are different subspecies or serovars that contain different virulence plasmids and some are much more deadly or can cause different suites of symptoms or whatever. But yeah. Okay, talk to me about hemorrhagic fever viruses. And then we'll sort of do like a compare and contrast.

Erin Allmann Updyke

Okay, okay, okay. So the last kind of group of possible infections would be a viral hemorrhagic fever of unknown type I guess, just one of these other ones. And what's interesting about this is that hantavirus is considered a viral hemorrhagic fever. It's under this class of viral hemorrhagic fevers.

Erin Welsh

Right.

Erin Allmann Updyke

There's a great paper that I'll link to that kind of groups all of these into a few different categories. So we have filoviruses which include of course Marburg and Ebolaviruses. We've talked about both of those. We have flaviviruses which we've talked about many of these, this includes the dengue viruses and yellow fever virus, as well as a few other tick-borne and mosquito borne viruses. The bunyaviruses which include Rift Valley fever that we have not yet covered, Crimean-Congo hemorrhagic fever virus, and of course the hantaviruses, which includes Sin Nombre virus, Hantaan virus, etc, etc, as well as a virus called, it's a really great name, severe fever with thrombocytopenia syndrome virus that is a tick-borne virus found in China.

Erin Welsh

That's not all one word, is it?

Erin Allmann Updyke

No, no, no. It's literally just like the name of the syndrome, virus.

Erin Welsh

Okay, okay.

Erin Allmann Updyke

Yeah. Okay? And then there are arenaviruses and we have not covered any arenaviruses on this podcast.

Erin Welsh

Are you serious though?

Erin Allmann Updyke

I know. But these include Machupo virus, which is the causative agent of Bolivian hemorrhagic fever.

Erin Welsh

Right.

Erin Allmann Updyke Guaranito virus which causes Venezuelan hemorrhagic fever. Sabia virus, Lassa virus, Lujo virus, Chapare virus, a lot of different viruses that have been found across the globe in different specific regions that have caused hemorrhagic fevers of various types. Most of these, especially when it comes to arenaviruses, we really don't have a good handle on.

Erin Welsh Okay.

Erin Allmann Updyke We don't have a good handle on their reservoirs.

Erin Welsh Okay.

Erin Allmann Updyke We don't have a good handle on infection, like how things are spread. So just like in my pocket, I'm banking on an arenavirus.

Erin Welsh Okay. For Cocoliztli?

Erin Allmann Updyke Yes.

Erin Welsh Okay, okay.

Erin Allmann Updyke Yeah. But that's just me and I still have a lot of questions for you, Erin.

Erin Welsh Yeah.

Erin Allmann Updyke So how about we pause here, we take a break, and then we get into some more of the details about the epidemiology of these outbreaks so that we can try and parse this apart, shall we?

Erin Welsh Yes, let's do it.

TPWKY (transition theme)

Erin Allmann Updyke Can I just start by asking you a question?

Erin Welsh I was going to start by asking you a question.

Erin Allmann Updyke Oh okay, okay. Who asks first?

Erin Welsh You can ask.

Erin Allmann Updyke Okay, I feel like I should have asked this earlier but like when you were going through the symptoms and this outbreak, so I know that the outbreaks themselves lasted for a number of years, like a year and a half, couple years, four years. And people when they got infected were dying incredibly rapidly. People were dying in a number of days. But how quickly did this spread say through a family or through a town? What was the estimated incubation period here?

Erin Welsh Great question. I don't know.

Erin Allmann Updyke Ugh.

Erin Welsh	Maybe there are more accounts out there but none of the papers that I read mentioned an incubation period or like a possible estimated incubation period.
Erin Allmann Updyke	Wow, that was a whole entire column of my table and I really thought it was going to help parse things apart, Erin.
Erin Welsh	I know, I know. So it's difficult too because I think the movement of it seemed really erratic. It didn't seem to move in like an outward spreading radius. It would be like all of a sudden it was there. But also let's consider the time and communication and limitations in terms of like did that town get hit before this town? If there was two days difference or even a week difference, would that have been something detected or like even able to be observed, I guess?
Erin Allmann Updyke	Right.
Erin Welsh	Yeah. I know, I wish I had that answer. Okay, but let me ask you a question real quick.
Erin Allmann Updyke	Okay.
Erin Welsh	What causes nosebleed? What's happening in a nosebleed?
Erin Allmann Updyke	There's potentially a lot of different things that can cause a nosebleed but there's two different places in your nose that you tend to bleed from. Because your nose, your nasal mucosa, essentially the skin is very thin and there's a lot of vasculature there. So most nosebleeds come from the anterior vessels, the vessels that are closer to where your nose opening is.
Erin Welsh	Okay, yeah.
Erin Allmann Updyke	And you have this plexus of vessels that if that mucosa gets dried out or if there's any trauma to it can just very easily start to bleed from that plexus of vessels. This can also happen if you have say thrombocytopenia, that is you don't have any platelets to be able to clot any bleeding that happens there. So there's a lot of different things that can potentially cause that anterior bleeding. There's also posterior nosebleeds that happen farther back in your nose. And those tend to be more commonly from that type of bleeding disorder or disease in the blood vessels, say from atherosclerosis or something like that.
Erin Welsh	Okay.
Erin Allmann Updyke	And those posterior nosebleeds can be massive and like really difficult to stop.
Erin Welsh	Interesting. And so a lot of these nosebleeds, and I feel like I'm a little bit hung up on the nosebleed thing and maybe I shouldn't be, but like they do seem to be massive hemorrhaging out the nose. So could that be a combination of like some type of clotting issue combined with... Like what disease could do that or would do that? How? What's the pathogenesis?

Erin Allmann Updyke

Oh I feel like we have talked about a number of diseases that can cause nosebleeds. Generally when we see nosebleeds, it's not isolated nosebleeds if it's caused from say a hemorrhagic virus of some kind or something that's causing thrombocytopenia. But that would be one of the major things that I would think about. Thrombocytopenia is when we don't have enough platelets. And we've talked in a number of our episodes now about how essential our platelets are to be able to stop bleeding when it starts. So because your nose just happens to be a place much like your gingiva, like in our vitamin C episode way back when we talked about how you get bleeding from the gums because you just don't have any collagen left. And so it's not even about in that case not being able to stop bleeding, it's just that's a place that's really easy to bleed from.

Erin Welsh

Okay.

Erin Allmann Updyke

Your nose is very similar, same thing with your eyes. And you described maybe seeing bloodshot eyes. So the mucosa of your eyes is just another place where things are very thin and there's a lot of really small blood vessels. So if you have a tendency towards bleeding, because you say don't have any platelets to stop bleeding, then little tiny blood vessels breaking can lead to large amounts of bleeding.

Erin Welsh

Okay. Interesting. That makes sense.

Erin Allmann Updyke

It's the same thing in your GI tract.

Erin Welsh

Yeah. So it's not necessarily an indicator of any particular disease, it's just like this is maybe already when things have gone well wrong.

Erin Allmann Updyke

Yeah, I would say it's an indicator that your coagulation state is totally screwed up.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah.

Erin Welsh

Okay.

Erin Allmann Updyke

We saw it in, you can see it in DIC which we talked about, so DIC is disseminated intravascular coagulation. We talked about it in our sepsis episode, we talked about it in our snake bite episode. We've talked about it in a few other episodes. But basically just anything that's going to like completely screw up your body's ability to clot properly, you could potentially see nosebleeds. Now that being said, there are a lot of diseases that are considered like hemorrhagic diseases of some kind. We don't usually see described like actual, and we've talked about this in a few episodes, it doesn't usually mean that you're just bleeding out of places.

Erin Welsh

Right.

Erin Allmann Updyke

Like hemorrhagic doesn't often mean the way that you think of hemorrhage with trauma where blood is just gushing out of orifices.

Erin Welsh

Right. This is not Richard Preston's 'The Hot Zone'.

Erin Allmann Updyke

Exactly. But it sounds like it is in the case of Cocoliztli.

Erin Welsh

I mean yeah. And it's interesting too because this does appear in both Spanish accounts as well as indigenous Nahua accounts of the disease.

Erin Allmann Updyke

Yeah.

Erin Welsh

All right. So let's, before we get into more questions, let's just do a quick recap. So I have a list of the symptoms.

Erin Allmann Updyke

Yeah.

Erin Welsh

This is in not any specific order but these were the ones that were mentioned primarily in that account by that physician. So excessive thirst, continuous and high fever, headache, confusion, delirium, rapid pulse, nasal hemorrhage, bleeding from mouth, eyes, ears, genitals, tongue black and dry, swollen lymph nodes in neck, jaundice, chest pain, bloody stool, stomach pain, sometimes rash, autopsy showed enlarged liver, black heart, dry stomach, black lungs, urine green or black then pale, and no notable respiratory symptoms. The disease seemed to have a 3-5 day duration, incredibly high case fatality rate with the overall mortality rate of like 50% -80%. Again, not necessarily attributable to one pathogen alone.

And there was actually that one Franciscan scholar, Sahagún, wrote that quote "many died of hunger and because no one was able to care for them. In many cases, every member of a household fell ill without a single person left to give them even a cup of water to the sick." End quote. So it has also been described as disproportionately attacking young adults and adolescents. And it also has been said to have disproportionately affected the indigenous population. Not all accounts describe this and I do kind of want to get into this in a little more detail because I think it can help maybe resolve the question of Old World vs New World pathogen.

Erin Allmann Updyke

Okay.

Erin Welsh

If this disproportionate impact on indigenous populations was a true phenomenon, where was that coming from?

Erin Allmann Updyke

Right.

Erin Welsh

Was it socioeconomic factors? So one person described that people who were quote "rich, well dressed, and with a comfortable living were not affected by the disease." End quote. So was it just socioeconomic factors? And so it was a New World disease that everyone was in theory immunologically susceptible to but it was just that the indigenous population who had been suffering the greatest losses due to forced labor and mines, enslavement, ridiculous taxation, etc. Spanish witnesses did recognize this disproportionate impact and the living conditions and how it affected the rate of disease. Quote: "The reason why so many Indians die of pestilence is a god secret. I do not find any better answer than that in the past, the Indians were not as badly mistreated and oppressed as they are today with heavy workloads. They are skinny and delicate. The disease finds them overworked and without resistance. So they are finished." End quote.

Okay. So if we do New World, then for the most part socioeconomic factors and living conditions would explain the difference in susceptibility or attack rate or mortality rate. If it's an Old World pathogen, it's probably a combination of those things. Socioeconomic factors are still there, they're not going away. But it also might be something about if it's an Old World pathogen it's quote unquote "more familiar" to the immune systems of the Spanish colonizers. And there is a little bit of evidence in this respect because if socioeconomic status meant that you were not only protected from getting super sick if you did get infected but that it also prevented you from getting infected, then we would still see high death rates among those who were exposed to disease if that makes sense.

Erin Allmann Updyke

Yeah, right.

Erin Welsh

And so you have a bunch of these Spanish members of these religious orders who did a lot of the caring for the ill and a lot of the burying of the bodies, these priests and so on. And they are not described as having high death rates, nor are the Spanish physicians that performed so many autopsies without the slightest bit of PPE. So one author also suggested that maybe the reason for the disparity in these mortality or attack rates is that the route of transmission was somehow unique to the indigenous populations.

Erin Allmann Updyke

Right.

Erin Welsh

We don't know what the route of transmission was. But given that the Spanish colonizers and indigenous populations lived pretty similar day to day lives at that point or at least not terribly drastically different in terms of like completely separate lives, it doesn't necessarily seem like it was that. I don't know.

Erin Allmann Updyke

Yeah.

Erin Welsh

Because if the disease was transmitted through direct contact, lice, fleas, blood or other bodily fluids, respiratory droplets, mosquitoes or water, there's really no way that the Spanish would have just been completely spared if they had been as susceptible. So okay, that was my sort of New World, Old World thing.

Erin Allmann Updyke

Okay.

Erin Welsh

Route of transmission, we don't know. We can compare the spread of Cocoliztli to the other epidemics that were happening in the 16th century. And it seems very similar to those that were spread person to person like smallpox, chickenpox, and measles. We can go over some of the other possible routes of transmission too like waterborne or louse-borne or like a rodent reservoir, we kind of already touched on that. Geography, again we only have a few accounts to rely on but it seems like everywhere was impacted with the possible exception of some of the coastal areas. There are many different reasons why that could be, maybe a less virulent variant of the disease made it there, people were more immune, or the vector or reservoir wasn't as prevalent, or just something else interrupted transmission. Could be a whole lot of things going on.

Erin Allmann Updyke

Yeah. But was that trend like persistent across the years, I guess?

Erin Welsh

I don't know. I don't know.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

And then there's the environmental factors which this mega drought and then a period of intense rainfall. And so some researchers have suggested that as like evidence for rodent associated, like this proliferation of rodents. But could it also be contaminated water supply? Because we know that drought, excessive rainfall, and just in general like disruption and chaos in everyday life, water supply is one of the first things to get all screwed up. And so I think it's an interesting question about the symptoms. Does whatever disease that actually cause this have to include every one of those symptoms? Which symptoms do we concentrate on first? Which accounts are reliable? Like what if this physician never actually performed an autopsy and he's just hearing word of mouth? Then you have a physician who's looking at someone and saying these are the things you're experiencing vs someone who's like this is what I'm experiencing.

Erin Allmann Updyke

Yeah.

Erin Welsh

Like it's an interesting, I don't know, interesting questions. But yeah, let's sort of get into a few of these things. So I feel like the New World vs Old World discussion plays a role in the hemorrhagic fever virus potential.

Erin Allmann Updyke

It does, yeah. Because I think when I would think about a hemorrhagic fever virus as the causative agent, it doesn't seem likely that it would have been a hemorrhagic fever imported from the Old World to the New World for a few reasons. One because then I would expect, I don't know, something similar to have been reported somewhere else first. Right? But I think that that argument stands for any pathogen that was brought over, right. If it was something that was brought over, how could it be something brand new that hadn't been seen by the Spanish Conquistadors beforehand?

Erin Welsh

Yeah.

Erin Allmann Updyke

Right. And that is the part that I think makes it so hard to think could it have been anything that was brought over?

Erin Welsh

Right.

Erin Allmann Updyke

Unless it was something that was brought... I don't know.

Erin Welsh

Brought over and then mutated into a more virulent strain.

Erin Allmann Updyke

Right. Or something perhaps not brought from Europe but brought from Africa during slave trade that maybe was happening but we don't have as great of records on it perhaps. But that also still doesn't explain why Spanish colonizers seem to have been less affected.

Erin Welsh

Yeah.

Erin Allmann Updyke

Per se.

Erin Welsh

Unless it's just again down to-

Erin Allmann Updyke Socioeconomics and exposure and things like that?

Erin Welsh Yeah.

Erin Allmann Updyke Yeah.

Erin Welsh But so many of these hemorrhagic fever viruses that we do know are transmitted direct contact through bodily fluids, right?

Erin Allmann Updyke Many.

Erin Welsh And that happens a lot, not all the time, but a lot during caring for the sick and also taking care of the bodies of people who have succumbed to disease. And we don't see records of like the Spanish priests dying at higher rates.

Erin Allmann Updyke Right. Well and what's interesting is that that's a problem I think with lumping all of the hemorrhagic fever viruses together, right.

Erin Welsh Yes.

Erin Allmann Updyke The filoviruses like Marburg and Ebola, yes, are spread direct person to person through contaminated bodily fluids. The flaviviruses are often spread by mosquito vectors. So could this be something that was a hemorrhagic flavivirus of some kind that we don't know of? Because I don't think that it was Dengue or yellow fever for a number of reasons.

Erin Welsh It doesn't seem mosquito-borne.

Erin Allmann Updyke I mean I feel like I don't have a good enough handle on the spread of this thing.

Erin Welsh Yeah. I mean rapid, rapid and sudden.

Erin Allmann Updyke Right, rapid and sudden which I would say probably goes against the mosquito-borne because in general you're going to need time for it to be in the mosquito and then causing more infection, etc.

Erin Welsh Well and then where did it come from?

Erin Allmann Updyke And why would it... I would expect it to be more infection at the coasts because if you have a new mosquito coming in or honestly even a new infection coming in, it's going to come into the ports.

Erin Welsh Yeah.

Erin Allmann Updyke So any kind of imported infection, how did it not come through the ports and cause more disease in the coast than in inland?

Erin Welsh Yeah, yeah. I don't know.

Erin Allmann Updyke

But there's a lot of other hemorrhagic fever viruses as well. The arenaviruses and the bunyaviruses, like hantavirus, any of those... Well the arenaviruses can be transmitted a lot of different ways, including person to person. But some of them maybe not so much. A lot of them are from rodent vectors. So could it be that it was a rodent vector disease that somehow mutated to be able to be transmitted person to person?

Erin Welsh

Sure.

Erin Allmann Updyke

Sure.

Erin Welsh

I mean...

Erin Allmann Updyke

I mean maybe, it seems possible.

Erin Welsh

Yeah.

Erin Allmann Updyke

But I think that what that comes back to is how to prioritize when we're thinking about this hundreds of years ago outbreak or outbreaks is which of these symptoms do we trust, which of these symptoms were definitely caused by the pathogen that we think killed people in this case vs which of them were a secondary bacterial infection on top of something else?

Erin Welsh

Yep.

Erin Allmann Updyke

Although that seems less likely given the time course of this illness. I just can't get over how rapid this was.

Erin Welsh

Yeah. And to be honest, I don't know. And I think it also probably would have been worth me looking into what predominant understanding of disease there was. So like was it the humoral theory of disease? Are certain symptoms emphasized over others given those sorts of biases, right? Like if someone has a fever, is that a primary symptom or is that like okay, it's just a low grade fever. Is the bleeding... I mean that just seems so stark and so dramatic. But then there's stuff like rapid pulse, abdominal pain, a lot of these symptoms are very general.

Erin Allmann Updyke

Very general.

Erin Welsh

Or can be severe manifestations of many different types of infections.

Erin Allmann Updyke

But there's also I think enough descriptions that tell us that whatever this was, it was a pathogen that was very rapidly affecting a wide variety of our organs. And that was certainly causing a significant degree of what sounds like hemolytic anemia. Because in all of the descriptions there was jaundice, in all of the descriptions there was some amount of bleeding, be it bloody diarrhea or bleeding from the mucus membranes. And was it truly trauma level hemorrhagic? We don't know. But it's very likely that if you're having this degree of hemolytic anemia, that you're also having issues with your other blood cells, including your platelets, which means that you're going to be at risk of bleeding, even if it's just that your nose is constantly dripping and not truly a faucet coming out of it, right.

Erin Welsh

Yeah. I mean the illustrations show gushing.

Erin Allmann Updyke

Gushing, right.

Erin Welsh: Yeah.

Erin Allmann Updyke: But is that gushing in combination with vomiting or...

Erin Welsh: Right. Or is that like this is the degree with which we suffered.

Erin Allmann Updyke: Exactly. Yes. Good point. And so I think that all of those symptoms, including the changes in the color of the urine, to me that says this is affecting the kidneys in addition to affecting the liver and the spleen. The pulse being high and the fevers, that just means you're sick, right. That could be from anything. But all of these and the rapidity of the infection just sound so viral to me.

Erin Welsh: Okay. Before we go further, can I just do a little bit of a dive-

Erin Allmann Updyke: Yes.

Erin Welsh: Into the other end of things, the bacterial side of things?

Erin Allmann Updyke: Sure. Okay. Please.

Erin Welsh: Okay. Because I wanted to do a little bit of research about typhus and typhoid.

Erin Allmann Updyke: Okay.

Erin Welsh: So epidemic typhus was one of the earliest diseases to be proposed as the cause of Cocoliztli, Han Zinsser wrote about it in that book 'Rats, Lice, and History'.

Erin Allmann Updyke: Okay.

Erin Welsh: During the Cocoliztli epidemics, typhus was a recognized disease but most people did not use the name for typhus to describe what was happening. But there is a precedent for typhus being described with more superlative or extreme names, like those that emphasize the severity of infection. And there exists at least one description from the late 15th, early 16th centuries of typhus causing a severe nosebleed. The Italian physician Fracastorius wrote quote, "I have often seen cases where 3 lbs of blood burst from the nostrils, yet the patient died soon after." End quote. And so I got a little bit curious about typhus and nosebleeds. And so I just put the words nosebleed and typhus into Google Scholar. And what I actually got were primarily results for typhoid. And that's something I remember from doing those episodes, typhus and typhoid weren't really distinguished as separate diseases until like the early to mid 1800s or so.

Erin Allmann Updyke: Yeah.

Erin Welsh: Because they do have similar courses of disease and would also tend to proliferate during similar times of like chaos or unrest or war, even though they're transmitted differently, epidemic typhus via lice, typhoid fecal-oral. Also I kept coming across the phrase 'abdominal typhus' that actually means typhoid, which was very confusing for me. I was like but what is it? But I don't entirely know whether or not tabardillo, the Spanish word for typhus, was also historically used for typhoid or whether it was distinguished from typhoid. I don't know. But in any case, so going back to my Google Scholaring, what I found were a bunch of historical reports of nosebleed in people with this abdominal typhus, AKA typhoid.

A report of a typhoid outbreak associated with oysters that was published in 1939 describes nosebleed as a cardinal symptom of typhoid and says that in that particular outbreak, it was the most common symptom observed. And in young kids, delirium also seems to be a common symptom that was found in a different paper. But in this oyster paper, hemorrhage happened to be the most common complication. Another paper from 1934 describes a case study of typhoid fever with hemorrhagic onset. Quote: "On August 19th, 1933, at about 3 am, the patient suffered a sudden profuse nosebleed. A physician was consulted who packed her nose. The bleeding however continued and the patient was admitted to the hospital." End quote.

And typhoid, as we talked about, can be transmitted by asymptomatic carriers. I know that they're different diseases but Paratyphi C DNA has been found in an 800 year old skeleton of a woman in Trondheim, Norway. So that suggests an Old World origin of at least Paratyphi C. So I think that like I said, there's a lot that historically may have been reported and may have been attributed falsely to some of these diseases like typhoid. And searching for typhus and nosebleeds or typhoid and nosebleeds is certainly cherry picking Google Scholar. But I did just find that interesting because I was curious whether there had ever been something like that reported before. And then also I came across, when I was looking for nosebleeds I came across the fact that black tongue is often another characteristic of typhus/typhoid. I've seen it in both.

Erin Allmann Updyke

One or the other.

Erin Welsh

And maybe you could do this for literally any of the diseases, right.

Erin Allmann Updyke

Yeah.

Erin Welsh

Hantavirus nosebleed.

Erin Allmann Updyke

Oh I'm sure you would find it.

Erin Welsh

Exactly.

Erin Allmann Updyke

Ooh, can I try it?

Erin Welsh

Sure.

Erin Allmann Updyke

Yeah, it exists, Erin.

Erin Welsh

Yeah. So maybe all we learned from that whole dive was that nosebleed is not as specific a symptom as we thought and that these diseases can take on many different forms.

Erin Allmann Updyke

Definitely. I think that's definitely true. And again, what symptoms you have and what symptoms predominate are also going to vary depending on what the underlying immune state of a person or a population is.

Erin Welsh

Yeah.

Erin Allmann Updyke

But I still can't get over the rapidity aspect of it.

Erin Welsh

Well I mean that could be influenced by immune state as well.

Erin Allmann Updyke

Definitely. But it just seems like everything at least that we know about typhoid and typhus today are longer courses of disease.

Erin Welsh

Yeah, for sure. So is it something that changed? Was it a virulence plasmid? Was it a different serovar or was it just acting, sort of swooping in opportunistically when the person's immune system was suppressed from another pathogen?

Erin Allmann Updyke

Right.

Erin Welsh

Or just was there in the background not doing anything.

Erin Allmann Updyke

Right. I mean because what I think is interesting is in the paper where they found the Paratyphi in the dental pulp, I did read that paper, that's the only paper about actual Cocoliztli that I read. But one of the things that they said is that finding it in the dental pulp does suggest that the person or the people died with high levels of this bacterium in their bloodstream specifically.

Erin Welsh

Okay.

Erin Allmann Updyke

Because my first reaction was well we know that Salmonella enterica subspecies enterica, blah, blah, blah, Paratyphi and Typhi both can very easily establish asymptomatic infections and live within us, predominantly in our gallbladder, for weeks if not months if not years. And so finding it in a person isn't that interesting, right, on its own because this is something that circulates and can be present in people. But knowing that it's not likely to end up in someone's dental pulp upon death unless it was in their bloodstream is very interesting.

Erin Welsh

In an epidemic graveyard.

Erin Allmann Updyke

In an epidemic graveyard. However it's still, I mean it's so interesting to me how much the symptoms and the time course don't seem to fit.

Erin Welsh

Yeah.

Erin Allmann Updyke

Not to mention, and I think this is where I really wish that we had a little bit more granular data on how rapidly this was spreading through homes and through families, right. Because when you get down as well to the incubation period of something like a typhoid, we're looking at a much longer incubation period than we are for many of the viral hemorrhagic fevers. And again, viral hemorrhagic fever, this is really, really broad. But thinking of more of the bunyaviruses or the arenaviruses which seem more likely candidates than the flaviviruses and the filoviruses in this case.

Erin Welsh

Right.

Erin Allmann Updyke

I think that the time course fits a little bit better, not to mention the mortality rate. I mean again, we would likely be looking at something that is causing a disproportionately high mortality rate because of the population that it's affecting or because it was a particularly virulent strain or serovar or subserovar. But it still just seems to me to fit better in terms of the time course, in terms of how rapid the disease was, in terms of how it seems to have spread. But we don't know, we don't have that granular of data.

Erin Welsh

You know Erin, I think I could be convinced of anything. Like I feel like I don't... I know so much more and I'm just like yep, I still have no idea.

Erin Allmann Updyke: Yeah, I feel like I just want for it to be a viral hemorrhagic fever. And I don't know why, I can feel it being a bias for me right now.

Erin Welsh: And I feel slightly similarly about typhoid. I think only because of my Google Scholaring of nosebleed and the fact that it was mentioned in many papers as being a cardinal sign of early disease.

Erin Allmann Updyke: Yeah.

Erin Welsh: I don't understand that for typhoid.

Erin Allmann Updyke: I don't either. Especially because I definitely don't remember reading it at all.

Erin Welsh: And so it's like again, there is so many grains of salt. This is like my salt shaker that it's-

Erin Allmann Updyke: Shaken everywhere.

Erin Welsh: Right. And I do love a salty dish so it's always full. But we have to consider the sources for these accounts.

Erin Allmann Updyke: Yeah.

Erin Welsh: Who's writing these symptoms, what emphasis are they placing on them? How accurate are these symptoms? How is the translation? How accurate is everything? How much evolutionary gap there is between what pathogens existed then and what they look like today, how much is our care of these pathogens today influenced by the hospital systems? By being able to give someone IV, antibiotics, whatever for these conditions that we're treating. We're going to do the best we can at putting ourselves in that time period but we are super limited by both that time period as well as our own biases.

Erin Allmann Updyke: Also the nodules behind the ears that were full of pus.

Erin Welsh: Back to Google Scholar we go.

Erin Allmann Updyke: I mean that doesn't sound like a virus at all. I'm about to talk myself out of a viral hemorrhagic fever because that symptom doesn't make sense. I wonder how many people that physician examined to say that that was the symptom that was seen in all of them.

Erin Welsh: That's a good question. No idea.

Erin Allmann Updyke: So many of our episodes where we actually deep dive on an individual pathogen, we still have so much like sometimes the symptoms are this or sometimes it's that, sometimes the incubation period is two days, sometimes it's three weeks. And that usually comes from a lack of clear data, right. And so in this case I think it really just highlights how difficult it is to try and make these retrospective diagnoses when there's such limited data and such difficulty in interpreting that data. What it makes me feel like is it's amazing that we've been able to identify the causative agent of any outbreaks ever.

Erin Welsh: It's true.

Erin Allmann Updyke: You know?

Erin Welsh: It's true, yeah.

Erin Allmann Updyke: But it also I think does because we have for a lot of things, it makes these kinds of ones that much more interesting. Because it's like what is it about these outbreaks that have made them so difficult to pinpoint to a particular pathogen?

Erin Welsh: Well we don't know it turns out.

Erin Allmann Updyke: But I had so much fun. I just want to read. Can you tell me where I can read more?

Erin Welsh: I absolutely can. There is a whole lot here. So there are several papers by Acuña-Soto et al that really go into a lot of these and do some great analysis of drought and putting forth different hypotheses. And then there is the Nature Ecology & Evolution paper from 2018 titled 'Salmonella enterica genomes from victims of a major sixteenth-century epidemic in Mexico', really fascinating. But I want to give a special shout out to the supplemental information. It was the best supplemental information I've ever read. Do not sleep on it, I absolutely really appreciate the amount of work that people put into that.

Erin Allmann Updyke: Ooh.

Erin Welsh: And then finally, if you want to get a little bit more background on the history of the Aztec empire and Mesoamerica, there's a great book called 'Fifth Sun' by Camilla Townsend that I really enjoyed.

Erin Allmann Updyke: I actually didn't have that many papers for this episode because I mostly just read over my notes from all of our old episodes. How fun. But I do have a few additional sources on Salmonella Paratyphi. I now want to read the supplemental material for that one paper because I did not read it. And I also have a couple of really great papers on the pathogenesis and the molecular pathogenesis of all of the different viral hemorrhagic fevers. So if you want to read more about all of those and then a bonus one on Parvovirus, just as a teaser for a future episode. But you can find the list of our sources from this episode and all 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 so much to Tom Breyfogle for the incredible audio mixing.

Erin Welsh: And thank you to you, listeners. We hope that you enjoyed this and learned something new.

Erin Allmann Updyke: I know that I did so I'm hoping that everyone else did and isn't just like WTF did we even talk about in this episode?

Erin Welsh: Right. Write in your thoughts, please.

Erin Allmann Updyke: Please.

Erin Welsh: Yeah.

Erin Allmann Updyke: Do you want more of these? Because I bet there's more.

Erin Welsh

Yes, I do.

Erin Allmann Updyke

And a special thank you as always to our patrons. Thank you so much for your support.

Erin Welsh

Yes, it really means the world to us. Well until next time, wash your hands.

Erin Allmann Updyke

You filthy animals.