TPWKY - Ep 210 - Histoplasmosis

[00:00:00]

Macy: My name is Macy, and I'm a 25-year-old from Southern Indiana. During my senior year of college, I started feeling pretty tired and chilly just a couple of days after I returned to campus after Thanksgiving break. I had a lot of final projects and studying to do, but I was feeling really exhausted, so I decided to give myself a break and lie down for a short nap.

Not long after that, I realized that I might be running a fever. I took my temperature to find that it was just over 100 degrees. It was 2022, so I took a quick at-home COVID test, but it was negative. I figured I would keep an eye on it and see how things progressed over the next few days. But over the next week, my temperature steadily increased to just over 101 degrees.

I wasn't experiencing a runny nose, cough, body aches, or anything else you would expect with a cold. I had been feeling more tired and had started taking a nap each day after class, but I was still able to function almost like any other college student. By day 12, my fever was reaching over 103 at times, and I was much more fatigued and sleeping even more.

But now I was starting to notice some shortness of breath just walking from my apartment door to the elevators in my building. It was also getting a little uncomfortable to breathe deeply. At that point, I decided I should go to the doctor, but with as busy as urgent cares are in a big college town during flu season, I wasn't able to get in anywhere for a few days.

I went into my urgent care appointment on day 16 of this fever, expecting to be tested for a few infections, get an answer and be sent home with some antibiotics. Instead, when the nurse practitioner came in to tell me about my results, she said that everything had come back negative. I do have a history of immunosuppression though, so she chose to send me to the emergency department for further workup just to be sure that she wasn't missing anything big.

In the ED the doctors told me that my chest x-ray and CT showed some sort of pneumonia covering both lungs top to bottom. I was admitted, and over the next few days I was treated with empiric antibiotics while they tried to figure out what was causing this. In the meantime, I continued to run a fever and got more and more fatigued. Around day four in the hospital, they started treating me

with oral antifungals, as they began to suspect that it was more likely to be a fungal infection. On day seven, I was told definitively that I had pulmonary histoplasmosis. My doctors were somewhat stumped as we could not pinpoint any likely exposure event. They chalked it up to me being immunocompromised and living in the Ohio River Valley.

That evening I was given amphotericin B. They were planning to put in a PICC line for continued infusions on discharge if I tolerated it well. But during that infusion, I experienced severe nausea, headache, and I spiked a fever for the first time that day. On my eighth morning in the hospital, they chose to go ahead and give me a second amphotericin B infusion before switching me to oral itraconazole and sending me home.

I was kept on Intraconazole for a full year after that. I followed up with pulmonology for about three months and had to follow up with infectious disease for a couple of years. It has now been over three years since I was diagnosed with histoplasmosis, and I'm fully recovered. I just have a few small pulmonary calcifications on my chest x-ray to show for it.

EW: Macy, thank you so much for sharing your story with us. We, we really appreciate it.

EAU: Yeah, I mean, it really does mean a lot. Thank you.

EW: Yeah. Thank you. Hi, I'm Erin Welsh

EAU: I'm Erin Allmann Updyke,

EW: this is, This Podcast Will Kill You

EAU: welcome to Histoplasmosis.

EW: Histoplasmosis. It's taken us a while to do this, despite getting requests for it and also this being one of the more abundant, prevalent.

EAU: Much more common than other fungal pathogens that we've covered on the podcast, which I didn't really realize honestly.

EW: I didn't either. I mean, I, I think when I saw, the first time I read about how people in the Ohio River Valley, like 90% have been exposed, I'm like, oh, I, I've lived there. That's where I grew up. I have been exposed to histo. It never occurred to me.

EAU: Yeah,

EW: Uh, yeah.

EAU: same.

EW: Yeah. I'm excited to learn more about the biology. 'Cause I'm like, when does somebody find out? Anyway, there, there's so much to cover. There's, I'm so excited for this episode. So, uh, but, so we gotta get to through some things first. Like

EAU: as always. It's quarantini time.

EW: Yeah. What are we drinking this week?

EAU: drinking the fungus among us, which we're pretty sure was the title of our Blastomycosis episode. But it's a great, it's a great title,

EW: this is truly the fungus that is among

EAU: way more so than blasto.

EW: At least for, you know, the eastern half of the United States, but also other places. And it's also more broadly spread. I know, I know.

EAU: It's everywhere.

EW: everywhere. Uh, okay. In, yeah,

EAU: among us, Erin.

EW: It is. Um, it's going, we modeled it to look like, maybe I shouldn't say that. I'll say the ingredients first.

EAU: Okay.

EW: It has coconut cream, pineapple juice, uh, lime juice. It's really good. And we did, we used coconut cream because, uh, of the way that a lot of exposures to histoplasmosis occur, which is through bat guano and bird excrements. So we wanted it to look a little bit poopy, [00:05:00] like bird poopy.

EAU: a little bit. Bird and bat poopy.

EW: In the spirit of histo.

EAU: you can find the full recipe for that delicious quarantinis on our website. This podcast will kill you.com and all of our social medias. Are you following us on the socials? Because we're there,

EW: We are there. Make sure you follow review, subscribe, rate, et cetera. And our website, things that you can discover on there, include transcripts, links to our bookshop.org affiliate page, our Goodreads list, music by Blood Mobile. Um, a firsthand account form, a contact us form, and uh, links to merch, Patreon. Wow. I think that's it.

EAU: so much.

EW: Yeah. Check it out. Sources. 'cause I have a lot of more sources than I anticipated for this and some really great ones that I am encouraging people to read.

EAU: I am so excited.

EW: Ah.

EAU: Also, apologies because my cat is being very loud in the other room right now.

EW: Is he hungry or is it the day It can't be. It can't be.

EAU: he's always hungry and he's always been fed, so I

EW: yeah, he's just, he's just making himself known.

EAU: Yep.

EW: Yeah.

EAU: Uh, well, Erin, should we, should we get into this?

EW: Let's do it. Let's take a quick break and get started.

EAU: Histoplasmosis is the name for a disease caused by a fungus called Histoplasma capsulatum.

EW: Mm-hmm.

EAU: And it turns out that there's actually quite a lot of genetic diversity in this particular fungal species. There's probably, I don't know, they might even be split into multiple species at some point.

EW: I don't know how fungal species differentiation works.

EAU: Me neither. So I'm not,

EW: but

EAU: get deep into it. Today we're just gonna kind of focus on the Histoplasma capsulatum group. Okay. And we have covered a relatively similar fungus, at least in the kind of pathophysiology of how it works in our bodies earlier. And that is blastomycosis caused by Blastomyces. Um. But don't worry if you didn't listen to that episode or if you don't remember anything from it because neither did I. So

EW: Although it's a good episode. I remember

EAU: a really good episode. 'Cause there's deep time and dinosaurs and yeah, it's a really good episode. Um, but unlike Blastomyces, the fungus that is the focus of today's episode, histoplasma is extremely abundant in the environment. It turns out.

EW: Extraordinarily so.

EAU: You mentioned Erin, that classically in the US we associate Histoplasmosis with the Mississippi and Ohio River Valleys. That's like what we learned in med school. And I did look this up this time because I like kind of knew exactly where those were geographically. But let's be real. Not everybody does. So the Mississippi River runs north south from like Minnesota all the way down and exits in the Gulf of Mexico. The Ohio River is one of its many tributaries that runs sort of east west ish from Pennsylvania to where it lets out in the Mississippi River. And so classically, this is where most cases of Histoplasmosis were seen. And so that is the kind of association in a lot of people's minds. And it's true that today, the vast majority of cases in the US are

centered in these regions. But it is not only these regions where this fungus can be found. This fungus exists in the soil as a mold

EW: Mm-hmm.

EAU: and it can be found on every continent except Antarctica.

EW: Yep.

EAU: It loves humid nitrogen and phosphorus rich soils, which means that it tends to grow very well where there's a lot of poop. Bird poop and bat poop specifically.

EW: Yeah. Oh, I was trying to get deep into like, what, what makes a bird poop different, uh, different amounts of nitrogen and phosphorus. I, I, I mean, I don't know the answer,

EAU: I love

that.

EW: I was there, there was a period of time, there was like a few hours where I was like, bird poop composition. Yeah.

EAU: different birds different. I'm, I'm sure the composition's quite different.

EW: Right, right. And which one does histoplasma like, you know, I, we do know some of that.

EAU: Exactly. I was gonna say, there are some papers with that and it, it also seems like bats are a particularly important component of the histoplasmosis cycle. Um, especially because the fungus itself can also be found in the bats. And so then bat poop not only is good fodder in the soil for this mold to grow, but can actually contain the histoplasma so they can spread it as they poop around the world. Hmm.

EW: Right. Yeah. Bas can ba, although I did also hear, so birds can't be [00:10:00] infected, it seems, but their feathers might be able to carry it because they're all poopy.

EAU: Yes. 'cause they're covered in spores and things that just so lovely. But okay, if this fungus was just a mold living in the soil, then we wouldn't be talking about it on this podcast would kill you.

EW: well, we might at some point,

EAU: Maybe, but realistically. We probably

EW: pathogen, so what makes it pathogenic? Yeah.

EAU: What makes a pathogenic is that this fungus like blastos that we've covered before is what's called thermally dimorphic, which means it can exist in two different forms depending on the temperature largely of the environment in which it exists in.

EW: hmm.

EAU: So in the environment, in the soil, which is gonna be a cooler temperature, like let's say ideally 25 to 30 Celsius, which is like seventies to eighties, that's their sweet spot. That's when we see this fungus existing as a fungus as a mold in this filamentous branchy form. But it can also exist as a yeast, which is a single celled fungus when it is exposed to higher temperatures around 37 degrees Celsius, AKA human body temperature, 98.6 Fahrenheit.

EW: Okay, so tell me, how does that work? Like if you are exposed to the mold, can you, could, will that turn into a yeast? Yeah. Tell me about

EAU: I would love to tell you about it. The answer is yes. So this is an example of an environmentally transmitted pathogen. So this is not something that's transmitted person to person. If I have histoplasmosis, I cannot give it to you, Erin, especially not over the internet. Um, and there aren't any like vectors directly involved. Yes, a human gets exposed via exposure to the mold form of this fungus that thrives in the soil. So little bits of these hyphy, this filamentous branching mold, can break off in the soil. And the way that this form of the mold reproduces is it forms these spores called conidia. And those are what get dispersed into the environment so that this mold can continue to, you know, grow and, and move around the environment. So those spores, as well as little bits of the filaments themselves get mixed up in the soil and they can end up blown by the wind directly into our noses or many mammals, noses where we're gonna breathe them in. And once they are inside our warm human body. They're actually gobbled up almost immediately by our immune cells. They're gobbled up by cells like macrophages, which are kind of like one of the bouncers of our

immune system that gobble things up that don't belong. And Histoplasma is like well adapted to this process once it is engulfed by a macrophage in this warm environment. It switches

EW: That is, oh my gosh.

EAU: They completely transform. They rearrange the entirety of their cell walls and how they exist and how they reproduce and turn into this yeast form. Now, yeasts, which are single celled fungi,

EW: Mm-hmm.

EAU: they don't reproduce by making spores. They reproduce by a process of budding, which basically just is like if you have one yeast cell, they kind of bloop pinch off, and now there's two of them and so on and so forth. Histoplasma does this inside of our macrophages.

EW: so it's like a virus.

EAU: body. Yes. It's an intracellular pathogen.

EW: Okay. I did not know it was an intracellular pathogen. That is so, okay. So then it, it re it, um, it buds and buds and buds inside this macrophage. And then to the point where the macrophage bursts. Like does it wait for the macrophage to burst or does it go anywhere? Where does it go in your body?

EAU: Eventually it will kill this macrophage, right? Eventually it will, it will reproduce so much and so many times that these macrophages burst open, and then now these yeasts are free to be gobbled up by other macrophages and continue this process.

EW: so it's all macrophages is the intracellular part of

EAU: there's other cells too, but macrophages are one of like the main ones

EW: Okay. Yeah.

EAU: Where this is happening is primarily in our lungs because we are exposed. Yeah. By breathing it in. And so these tiny little spores that we've been exposed to get down into our lungs, and that's where they're transforming into this yeast form. As our macrophages are gobbling them up, they're trying mount

a typical immune response, and that means that they are flagging and telling other immune cells like our T cells to come in and get rid of this pathogen. And for the vast majority of us, that is the end of the story.

EW: Okay. Okay, so you exposure, we have [00:15:00] not gotten to infection yet. This is still like what an exposure would look like that could potentially lead to infection. You're breathing in these spores. They turn into yeast, they start to replicate, and then at some point throughout this process, as more and more macrophages are infected, your T cells are like, we're shutting this down

EAU: Absolutely.

EW: unless it progresses.

EAU: Can't. Exactly. So for the vast majority of us, we will have exposure, some kind of immune response, and it's, you know, it's our whole entire immune system that's involved. And then goodbye fungus. The end. We do a really good job of clearing this fungus classically. However, also classically, fungi are really good at flying under the radar and can find ways to avoid being completely eradicated. So for some people, whether because they're immunocompromised or just because they were exposed to a really high dose, right? Like they inhaled a whole face full of these spores, they could end up with a symptomatic infection. So let's talk about what that looks like, shall we?

EW: Yeah. Mm-hmm.

EAU: If someone is going to have symptoms from exposure to histoplasma, the most common thing they're going to have is a pneumonia, which is unsurprising 'cause again, this is all happening in our lungs. Usually this is only happening if you're exposed to a really high concentration of spores and it's gonna take some time because these yeast aren't like really fast at reproducing, you know, take some time. So after an incubation period of usually a couple of weeks or so, but anywhere from like three to 21 days, some of the papers I read said, um, you'll start to have kind of non-specific flu-like symptoms, fever, headache, cough, maybe some chills, muscle aches. Um, it'll look like a pneumonia.

EW: Okay.

EAU: Many people might go to the doctor, be treated for bacterial pneumonia. And then they might get better all on their own. And the antibiotics absolutely were not the thing that made them get better, but most people who have even an

acute pneumonia from histoplasmosis are gonna recover all on their own and get over this infection.

EW: Okay.

EAU: For others that maybe had a really even higher exposure or just are susceptible for one reason or another, they might have a more severe course. They might have increased inflammation, they might end up having like difficulty breathing, shortness of breath. Or if you actually checked, you know, their oxygen concentration, it might actually be low. Um, and so in those cases, people might actually get the diagnosis of histoplasmosis and then they might actually need treatment with antifungals. But that's not necessarily like a majority of people who are even having symptomatic acute pulmonary histoplasmosis. But

EW: But

EAU: that is not the end of the story for some people.

EW: okay. Real quick though.

EAU: Give it to me.

EW: How long on average does this last, if it is a self, self, uh, what do you call

EAU: A self-limiting

EW: Self-limiting infection.

EAU: a good question. I don't have like a perfect timeline. I would expect it to be like within the, within what would be a typical course of pneumonia for a lot of people. So maybe a couple of weeks max or so. But it all is just gonna depend on what your immune response to it is, whether or not you get severely sick, um, and things like that. So it's, it's very person dependent.

EW: And so most of these people are diagnosed based on symptoms, and it is, and they're diagnosed as as having bacterial pneumonia.

EAU: Yeah, it's very like we probably drastically underestimate the actual incidents of acute pulmonary histoplasmosis because so many cases are either never seen by a healthcare professional because they think it's just some other

cold or flu. Um, or yes, they're misdiagnosed as community acquired pneumonia treated with antibiotics and they get better, but not because of the antibiotics and it was actually histoplasmosis.

EW: I have two questions. The first is, at what point does exposure become infection? Like in order for an infection to count as infection, do there have to be symptoms? Yes.

EAU: don't know. It's a

EW: Okay. Okay.

EAU: I'm nodding because it's such a good question, but I don't have an answer for you.

EW: Okay. Um, and then the other question is, at what point does, you know, you said these diagnoses are often bacterial. At what point does, does Histoplasma become the horse and not the zebra? I guess

EAU: Yeah.

EW: like at what point do people start to say this is, it's not resolving with antibiotics or like it's still Yeah.

EAU: That's a really great question, Erin. I don't have an answer for that either, Sorry. it's gonna so depend right [00:20:00] on like what hospital you end up in, who you are, how sick you are, like how much people are looking into this. Are you getting worse and worse and worse, or are you getting kind of better? Like do you have access to diagnostics, do you not? Like there's so much that's gonna play into

EW: risk factors that would suggest this is an opportunistic?

EAU: Yeah, like I will say, I mean, ha having worked in hospitals like, but not in a region that is common for histoplasmosis. I mean, in med school I was, but I don't remember thinking that much about Histoplasmosis in med school. But like whenever there was someone who's not getting better, then one of the things at least that we would do would be to talk to the infectious disease folks. And this is often one of the first things that they would think of. And that's why it's so valuable to have access to infectious disease experts because they're gonna think of things that other physicians might not remember as often or might not be top of mind when the symptoms are hard to, to kind of pinpoint.

EW: Or if you're not in the geographic region, where this is classically a histo, histo zone. Yeah.

EAU: But as we know, as we'll talk about it happens outside of

EW: It's growing. Yeah.

EAU: So those are great questions though. And I like how, when is it considered an infection versus not? Is such an interesting question because we don't know, most of the literature says that like less than 1% of people will have symptoms, but like that other 99%, do we consider them having been infected? I mean, if they mounted immune response, then yes, you do consider that, right? Even if you were totally asymptomatic. So I think a lot of people had been, have been infected, but just really very few of them end up actually having symptoms.

EW: And you can become re-exposed and reinfected. Okay.

EAU: Yeah. Yeah. And. Along those lines, Erin, this acute like limited infection is not the end of the story for a lot of people because this fungus can continue to grow even as we are mounting an immune response to it. And if that happens, there's kind of like two main ways that it can go in the long term, or not even the long term, but there's two kind of ways that it can grow. One is that this yeast can continue to replicate, but our immune system can be kind of fighting back at the same time. And so it can do this thing that we do with a lot of infections that are really hard to eradicate, where our immune system kind of decides, look, we can't really get rid of this thing entirely, so let's wall it off.

EW: Ah,

EAU: And so that results in the formation of these things called granulomas, and that's these like inflammatory little pockets of fungus and immune cells that kind of can just like sit there. This,

EW: is, we've, we've, we've encountered this before. 'cause I feel like I made some bad cask of amontillado Edgar Allen Poe joke about walling off

EAU: probably. That sounds

EW: Okay.

EAU: Yeah. No idea what episode that was. I mean, it could have been

EW: Could it have been blast out?

EAU: Could have been tb. Um, but that was so long ago. I don't know. But these, you can see things like this in, in tuberculosis. Absolutely. And histoplasmosis is easy to conflate with tuberculosis in a lot of cases. Um, and what's interesting is that this can happen. This process of this granuloma formation can happen even without any clinically apparent disease. So even without having had any known symptoms, you can end up with these granulomas in your lungs that you might find on, say, a CT scan decades later.

EW: Decades later.

EAU: actually quite a common cause of pulmonary nodules, like asymptomatic pulmonary nodules. What?

EW: And so that would just be like a, a random finding, or would you be going in for something

EAU: No, they're re It's really common that we have just incidental pulmonary nodules. They're

EW: like, whoa, check out. Check this out. Yeah. Okay. Okay.

EAU: So these, these granulomas can do two sorts of things. One is they can just sit there and be an incidental nodule that never causes a problem, or they could result in a chronic sort of disease that may or may not have symptoms and that may or may not be able to reactivate. We see this chronic pulmonary histoplasmosis much more commonly in people that have preexisting lung conditions like COPD, and it can really mimic tuberculosis because it tends to be in the upper lobes of the lungs where we see these granulomas and they can really progress with time to where eventually they kind of really cause significant damage throughout the lungs. But it's usually only in lungs that already have underlying structural damage.

EW: Gotcha.

EAU: So that's one way that this disease or that this fungus can kind of proliferate in our lungs, sort of low level. But the second way is that this fungus, this [00:25:00] yeast could continue to grow unchecked and can invade our lymphatic system or our bloodstream, and then end up causing a disseminated infection where it can spread. Because it's inside of our blood cells, inside of our white blood cells, to literally any organ in our body, our eyes, our spleen, our

liver, our bones, our skin, our nervous system, almost any organ, really any organ. Our colon is actually a really big one, and this disseminated histoplasmosis is what we tend to see in people with immunocompromised like uncontrolled HIV or like a solid organ transplant who's on immunosuppressive medications or a congenital immune deficiency, or especially today, people who are on medications like TNF Alpha inhibitors, which are a class of medications that's used to treat a really wide variety of autoimmune conditions like rheumatoid arthritis or ulcerative colitis and things like that.

EW: So, uh, there can be these, these nodules, and there can be disseminated disease. How long does it take for disseminated disease to develop and can it kind of bypass these other stages and just sort of be disseminated?

EAU: Yes. That's, those are really great questions. So, to answer the first question, I don't have an exact timeline, um, because we don't really have, um, at least from what I read, and so if I missed it, someone please let me know. But there's not like really great like, oh, here's an exposure versus here's disseminated disease, like ti timelines out there, if that makes sense. So it's gonna really depend on who the person is and how sick they were or how compromised their immune system was to begin with. But then, yes, they absolutely could have disseminated disease without having like a pneumonia type infection first, if that makes sense.

EW: And then what are the symptoms of disseminated

EAU: Yeah, great question. They can be really non-specific, which can make them really hard to identify. Um, what you end up seeing are these same kind of granulomatous lesions, wherever this yeast has disseminated to the lungs, the liver, the brain, the colon. Um, and so it really depends on how far this has progressed and what organs it has invaded to know what the symptoms are going to be. But often what we see are fevers, um, and especially fevers that don't respond to antibiotics, right, or that we can't find a source of a bacterial infection. Um, we can find weight loss. Because this tends to be like a really progressive disease. When you look at people's blood, like when you know they're in the hospital 'cause they're sick and you're checking their blood, we see that all of their blood counts. So like white blood cells, red blood cells, platelets tend to go down, down and down. And that's what we call pancytopenia. That's a pretty bad prognosis in histoplasmosis. I don't know the exact mechanism of it.

EW: Okay.

EAU: And yeah. Beyond that, the symptoms can be just really non-specific. If someone has a lot of lung involvement, they might have symptoms that look like pneumonia, but again, they're not getting better. With antibiotics, we can often see, and this is when it gets really extreme, um, like colon perforations and things, which of course is like a surgical emergency, and that's if the colon is very involved. Um, if it's in the brain, then you might have symptoms similar to meningitis. If it's in the eye, then you might have damage to the eye, including vision loss. Um, so it really just, it's so, so varied and it really just depends on where it has disseminated to.

EW: Yeah, that makes sense. Um, is there, okay, two, uh, sorry, I, I feel like I'm like just preempting you,

EAU: I love it. I love it. Keep going.

EW: What is the breakdown of, let's say, you know, a hundred people. Are, are, become infected with Histoplasma every year. What proportion of those are self, like, uh, asymptomatic? What proportion are symptomatic and self resolved? What are the ones that are nodules? What are the ones that are disseminated?

EAU: Yeah. This is such a great question. I don't have, I wanted to find like exact stats on that, but the best that I got is that a lot of the papers say that 1% of people, so 1%, one out of that 100 would have a symptomatic infection. So we're gonna have to go bigger. We'll go like a thousand, you know? Um, and then 60% of people who have a symptomatic infection will have, uh, respiratory symptoms. So that's more that like acute, um, pulmonary infection of the rest of the 40%. I don't know what that breakdown is. How much of that 40% is like a chronic pulmonary histoplasmosis versus a disseminated someone with immunocompromised having a disseminated infection.

EW: Okay.

EAU: Don't have it. I don't have a breakdown on that other 40%. Of the 1%.

EW: Of the 1%,

EAU: the 1%.

EW: uh, okay. And treatment.

EAU: So before I [00:30:00] talk about treatment, I wanna just mention that one of the big problems, and we kind of have alluded to this, but one of the big issues with Histoplasmosis is being able to diagnose it to begin with. Um, because if it's an acute infection, then it looks a lot like a bacterial pneumonia, right? Um, maybe an x-ray would look a little bit different or a little bit more patchy rather than like, you know, a low bar that we would see with a bacterial, um, infection. But really it's not super different in those early stages for acute infections. And so in those cases it can be hard to diagnose because you're not thinking about it. Like you said, horses not zebras. But when it becomes chronic, it can just be so non-specific that it's hard to think of. And then even when you think of it, the gold standard for diagnosis is always culture, but it can take six weeks to culture this fungus, at which point you needed to do something already. Right? So there is a lot of work being done and there are a lot of other tests out there to look at things like antigen detection, um, including in like urine, which is really great because that makes it cheap and easy. It's like very easy obviously to collect urine compared to like cerebral spinal fluid from people. Um, and then there's also PCR based methods, but those are not available everywhere. So especially in places where histoplasmosis historically has been thought to be less common, um, there's a lot of issues with even having the tools in place to be able to detect this pathogen, which is a huge problem because if you can't diagnose it, then you can't treat it.

EW: Yeah.

EAU: Now when it comes to treatment, not everyone ends up needing treatment, right? If this resolves on its own, then people don't need to be treated. And in fact, the like guidelines from the Infectious Disease Society of America, which I think are under revision 'cause they haven't been updated since 2007, um, really emphasize like trying to not treat it unless you really have to. So unless somebody is really getting sick, and that's because fungal pathogens are really difficult to treat. And the antifungal medications that we use tend to be pretty hard on our bodies and cause quite a lot of side effects. Um, so the two main medicines that are used are amphotericin B, which like pokes holes in the fungus and then. Kills them. Um, but also pokes holes in our own cell membranes because it binds to cholesterol in our cells and so it can cause pretty severe kidney and liver damage, um, in some cases. Um, and then the other medicine that's uses Itraconazole, which is a, another antifungal medication that also can have a lot of damage to the liver because of the way that it's metabolized. And in either case, people often need at least six to 12 weeks of therapy and sometimes six to 12 months of therapy.

EW: Okay. That's, that's a long time to be with those side effects.

EAU: Exactly. So it requires quite a lot of close monitoring and everything. When it comes to the like, big, big picture, um, of mortality from histoplasmosis, the mortality rates are actually quite high. Um, they're five to 8%, and that's in the us like that's based on US statistics. And even those statistics are really generalized across the board, like that's from the symptomatic infections that we know of. Um, but in certain subpopulations or in certain geographical regions, um, this mortality rate can be substantially higher. So for example, in people with HIV who end up with disseminated histoplasmosis, the US mortality rate is closer to 10% is what I saw. But in some places, like in some areas of Brazil, it's up to 40%.

EW: Oh my God.

EAU: And a lot of that is due to delays in diagnosis and treatment and access and things like that. So. It is not a minor disease when it becomes disseminated

EW: Yeah, yeah.

EAU: And that is histoplasmosis. Erin,

EW: Ooh. It's a, I mean, fungal infections in general are. A just harder,

EAU: they're so much

EW: they, our body doesn't do as well recognizing them, often we have a harder time treating them, and then once they kind of establish a foothold, it seems really difficult to

EAU: they're really good at just sort of like resisting our clearance, you know? So tell me, Erin,

EW: Mm-hmm.

EAU: how did we get to here? Where did this fungus among us come from?

EW: Great. Great questions.

Our picture of histoplasmosis has taken shape over the past century and change, in fact, 2026 Marks 120 [00:35:00] years since it was first described.

EAU: Oh, wow. Okay.

EW: And over that time it has transformed from a rare disease to one of abundance, not just in terms of the number of annual exposures, which is numbering in the hundreds of thousands, millions potentially, but also in terms of where it thrives. It loves nutrient rich soils like those that have been enriched by, uh, bat guano or bird excrement. I won't say contaminated. This theme of abundance is something that I'm gonna come back to later on. But for now, let me take you through the history of this fungus, which oddly enough started out not as a fungus, but as a protozoan, according to the guy who first observed it.

EAU: Oh, what, okay. Tell

EW: So in December 1905, Samuel Taylor Darling had freshly arrived in Panama, uh, in the canal zone, where he acted as a pathologist in the hospital where he was working. On December 5th, uh, 1905, a 27-year-old man, a carpenter, checked himself into the hospital with when his illness, which had started a few months earlier as fever and vomiting, uh, it took a turn for the worse. He was described as quote, uh, "mildly delirious and incoherent" with an enlarged spleen, but his lungs were clear and his blood did not contain any malaria parasites. Over the next 24 hours, he steadily declined and he died on the evening of the 6th of December. A preliminary diagnosis of milliary tuberculosis was given, which is when the tuberculosis bacteria have spread throughout the body, forming nodules and leading to these, uh, systemic symptoms. And initially the autopsy seemed to confirm this diagnosis. Quote, "the odor on opening thorax was suggestive of pulmonary tuberculosis." End quote.

EAU: Interesting.

EW: I don't know, but he, I mean, the, the way he wrote about that is just sort of like, everyone knows what this,

EAU: knows what this

EW: what this smells like. Yeah,

EAU: I mean, I guess that makes sense in that if you do something very often and you are exposed to I, I am, I am not surprised that the formation of a bunch of case eating granules has a specific smell to it.

EW: totally. Totally.

EAU: interesting though.

EW: Yeah. I just have never encountered that. Like, yeah, I'm never that like c diff has a particular smell, but like, I didn't Anyway, so, but also quote " the lungs on section were found studded with pale gray miliary, tubercle tubercle from two to three millimeters in diameter." But as Darling continued with the autopsy, he noticed several findings that contradicted the initial tuberculosis diagnosis. Things like "the tubercle were not as closely packed or so numerous as is often found in milliary tuberculosis, and the general color of the lungs was quite red" end quote.

EAU: Interesting.

EW: Yeah.

And his suspicions were confirmed when he took a look at some blood smears under the microscope and found no tuberculosis bacteria, but instead " enormous numbers of small bodies generally oval or round. Most of them were intracellular in alveolar epithelial cells while others appeared to be free in the plasma of the spleen and rib marrow." End quote.

EAU: I love that description, Erin.

EW: And to darling's eye, which admittedly was limited by crude microscope equipment. These round bodies resembled protozoan parasites, like those that cause leishmaniasis.

EAU: Right? Yeah.

EW: And so he concluded that this was a new species of, uh, pathogenic species of protozoan distinct enough to warrant a new name: Histoplasma capsulatum.

EAU: Huh. That's how it got its name.

EW: That's how it got its name.

EAU: How interesting. Gar.

EW: Yeah. Yeah. And this incorrect categorization as a protozoan, it didn't last all that long. It was just like five years later in 1912, uh, after he published this paper, or after he foresaw it, rather, another famous pathologist, uh, Henrique de Rocha Lima published a report where he was like, um. Are you sure it's a protosome? Because I just compared with what Histoplasma looks like next to

leishmania and yeast, and it looks a lot more like yeast than a protozoan parasite. So like, it was corrected pretty shortly after. Confirmed a number, you know, years later. But, but like,

EAU: Erin. I just love that your description of that made it sound like he was so polite about it.

EW: I, I mean, I'm sure

EAU: so sorry dude, but like I just, I wanted you to know

EW: make sure like, can we just double check this again?

EAU: really cute.

EW: That's how I'm imagining

EAU: I

EW: very gentlemanly about the whole thing.

EAU: Oh, I don't, that's making me cry.

EW: Wow. Your, your bar for jokes

EAU: I, I know it's, I don't know what's going on with me.[00:40:00]

EW: Ah, um, this, this correction was ultimately of course, necessary. Like it was, it had to happen, but it was kind of, kind of inevitable. Like someone was going to come to this conclusion sooner or later, and it didn't exactly like shake the mycology world to core, right? Histoplasma was not widely known at all, and those who had heard of it thought it, thought of it as a rare tropical disease. So, of, of limited interest, I would say, uh, more of like a medical curiosity than something of like major, major importance. Yeah. The first inkling that it might be more than that though, came in 1932, and this is when Dr. Catherine Dodd asked another physician at her university, Dr. Edna Tompkins, to take a look at a blood smear that she had just taken from a child with an unusual form of anemia

EAU: Hmm.

EW: A few years earlier. Dr. Tompkins. So the one that she had asked to look at the slide had just so happened to attend a demonstration on histoplasmosis given by a researcher who had visited Dr. Samuel Darling to learn about the fungus. And so he came to this hospital and was like, here's this presentation. Here's how you look at it. Or Here's, here's what it looks like. And so when she saw the blood smear, she was like, I've seen this before. Right? Like, this looks familiar. And so she reached out to this researcher who had presented this, this demonstration to confirm her suspicions. Yes, it was histoplasmosis. And so why this was a landmark moment in Histoplasmosis history is because this was the first time that someone had been diagnosed while they were still alive.

EAU: Oh wow.

EW: Case prior to this, which was not very many cases had been diagnosed at autopsy. So this gave researchers an opportunity to better culture and characterize the organism, and also just to describe like symptoms while someone was still alive. And the work that was done on just this one case tied up many loose ends, at least in terms of the fungus itself. It fulfilled Cox postulates. It identified the best medium for growth, led to the development of a test, and hinted at a more widespread distribution of this organism in nature, like in the environment, something that would be confirmed in the following decades. Up until the 1940s, those who had heard of Histoplasmosis considered it a rare, almost uniformly fatal disease. Very different than the pathogen you described Erin, where it was, you know, 1% actually as symptomatic. Yeah. So what did it take to change that perception? Tuberculosis.

EAU: Everything

EW: Everything is tuberculosis. It's still happening.

EAU: yeah. Okay.

EW: And so what was going on is that increasingly doctors were finding that some patients that seemed like they had to tuberculosis had a negative TB skin test.

EAU: Mm.

EW: Health exams during World War II laid the groundwork for this. X-rays had become part of the screening process to see whether someone could enlist and physicians began to notice these calcified regions, these nodules in the lungs on x-ray without an accompanying, uh, positive TB test. Mapping out

where this happened showed Kentucky, Tennessee, Ohio, North Carolina, West Virginia, Mississippi, Missouri, Indiana, and Illinois as the hotspots for this phenomenon.

EAU: Oh my gosh.

EW: And this is where just, I think I mentioned it earlier, but up to 90% of residents are estimated to be exposed during their lifetime.

EAU: Yeah, yeah, yeah. And like have evidence of prior, like antibody response, meaning that they had an

EW: They've been been infected.

EAU: most likely.

EW: Yep. And so a few years after this of World War ii, once, once these, uh, these draft screenings were over a few years later, uh, by which point a histoplasmosis test was available, the same phenomenon was observed in into tuberculosis, sanatoriums, and it pointed not towards an unusual form of tuberculosis, but a separate disease entirely.

EAU: Wow. Okay.

EW: Yeah. A paper from 1962 looked at 81 sanatoriums across the us, Canada, and Cuba, and found that seven and a half percent of the 45,000 patients screened were positive for histoplasmosis.

EAU: So like they were in there being treated for tuberculosis, but they actually had histoplasmosis. Fascinating. Erin.

EW: Yep. At least one quarter of those had active histoplasmosis. And few were also positive for tuberculosis. So how many people in Sanatoriums actually had histo and not tuberculosis or, and then developed TB during their [00:45:00] time there?

EAU: of course.

EW: No, I, right. No idea. But more than zero, especially in the areas that we tend to think of as the classic histoplasmosis region. So for instance, it more in on that paper from 1962, the percentage of people who were positive for

histoplasmosis in Indiana, Kentucky, and Tennessee respectively was 15%, 14% in 13%.

EAU: Oh, so like much higher than just the baseline. Oh,

EW: Yeah. Much higher than the 7.5%. So this definitely pointed towards a tip of the iceberg situation. Far from being a rare tropical disease, histoplasma probably led to millions of exposures every year and thousands of active cases in certain regions of the United States. But how were they getting it? A number of outbreaks throughout the 1950s and the 1960s helped to shed light on that question, and a pattern gradually emerged. Exposure to disturbed soil, like through construction or tornadoes. I saw a paper that was like tornadoes as the, as a spreader of histoplasmosis. Totally makes sense. 100%. And that is tornadoes zone. Like It's not quite all of tornado alley, but like a, there are tornadoes that absolutely happen there. Yeah. But even just like walking around right. Can disturb soil. And it's not just any soil soils enriched by bat guano or bird excrement seemed particularly prone to harboring the fungus. Research demonstrated that, like we talked about, many bats can be, or while, while many bats can become infected, birds cannot, but the poop of both animals is just stupendous for histo growth. And birds might be able to carry it in their feathers. Outbreak investigation often led to like a chicken coop or a roof where, uh, pigeons, roosted, or a cave where bats lived. So for instance, the 1970 Earth Day outbreak, where nearly, yeah. Ironically, where nearly 300 students in faculty at a junior high school in Delaware, which was 40% of the entire staff and students there that were symptomatic after cleaning up Blackbird and pigeon roosting sites

EAU: they all were

EW: cleaning up for Earth Day

EAU: and then they all got histo. It's not funny,

EW: It's not funny, but it is just like, of course, like

EAU: course you

EW: to do one thing. Yeah. Ugh. But yeah, histoplasma caps. Adam was later isolated from the soil where they were doing the cleanup. A paper from 2016 by Benedict and Modi examined Histoplasmosis outbreaks in the United States and Puerto Rico since 1938, and found that in the 105 outbreaks that they examined, 77% were associated with bird or bat poop.

EAU: Yep.

EW: And while earlier outbreaks tended to be rural and more limited, later outbreaks grew to be more urban and occasionally enormous. So for instance, a couple of outbreaks in Indianapolis in the late 1970s and early 1980s resulted in an estimated 200,000 people becoming infected a hundred K in each outbreak, roughly. Yeah. Yeah. That's what the estimates are.

EAU: But that's not all symptomatic. That's

EW: No, no,

EAU: total because

EW: We're again, because it. This question of, yeah, exposure versus infection, and the epidemics, both of these were associated with construction. So like there was the tearing down of an old amusement park, a a along with construction of a new tennis stadium, and then the construction of like a swimming gym, swimming pool, gym thing on a university campus. So you got all that soil being disturbed and then winds carrying it throughout the city where, which is densely populated and boom, like everyone is just breathing in histo.

EAU: Histo.

EW: Yep. And then the 1980s and the AIDS pandemic ushered in the next era of Histoplasmosis. Histo plasmosis is a disease that you mentioned. Erin disproportionately affects people with me, with weakened immune systems. And over the course of the next few decades, it proved to be devastating, like truly devastating for so many people infected with HIV, who, especially those living in endemic regions with case fatality rates up to 60% in some situations. And effective treatments for histo back then were few and far between, and still relatively little was known about it. And so this period led to a big push for more research to better understand this infection and just growing awareness of the disease overall. As you might expect, these years of research led to histo turning out to be much more prevalent and widespread than expected. Not just restricted to the [00:50:00] Mississippi, Ohio River Valleys, but elsewhere in North America, south America, parts of Africa and Eastern Asia. And its range is shifting currently, just as it once did. Histoplasma likely originated in South America and began its spread to these other regions about 13 million to three and a half million years ago, something like that.

EAU: Just a casual

EW: Just,

EAU: million year range

EW: mean, that's how it goes. But that is when the global c, the global climate was warmer and it experienced a pause and kind of range contraction during the Pleistocene about like a hundred and, or sorry, about 1.8 million years ago when the climate cooled. And then as it warmed again, it reestablished itself, flourishing in warmer and wetter areas.

EAU: Erin. Warmer and wetter,

EW: and wetter as always, well wetter in some places. Yeah. As always, we can look towards the past to better predict our future. Ongoing human induced climate change is altering where this fungus can live and how we interact with it. As temperatures have risen, histoplasma has expanded northwards in North America and to other temperate regions where it historically has not really occurred or has not been that prevalent, such as Northern Italy, parts of Argentina and Turkey. This global warming might not only impact the range of this pathogen, but also how deadly it is. It might be selecting for more virulent and heat tolerant strains, meaning it could better infect us. It might be more infectious in humans, or also animals like our pets or bats enabling greater spread. Or in the case of bats, more harm on top of another fungal pathogen that they're currently dealing with the white nose syndrome. So what will the impact be? We don't know.

EAU: Time will tell.

EW: Time will tell. Will increasing construction and land use change affect exposure to this pathogen? Seems pretty likely.

EAU: I'm gonna go, yes. That's my, that's where my money is.

EW: Yep. What we do know is that Histoplasma will continue to change in the coming years due to human intervention. And I wanna wrap up today by talking about this change, not in terms of a hypothetical future, but as a hypothetical past. What might Histoplasmosis have looked like 150 or 200 years ago, particularly in the region that we think of as classic histo country, the Ohio and Mississippi River Valleys.

Why would it have been any different than today? My answer, the passenger pigeon,

EAU: Stop it.

EW: known as Ectopistes migratorius

EAU: Okay.

EW: Erin, do you know about the passenger pigeon?

EAU: I mean, I know that they were a thing that people used to send messages and things.

EW: Different, different pigeon.

EAU: Oh, that's a different pigeon.

EW: Mm-hmm. I think that's the carrier pigeon.

EAU: Okay so what the heck is the passenger pigeon

EW: Okay. Uh, the passenger pigeon, this might be my first tattoo ever.

EAU: Okay.

EW: The passenger pigeon was once the most numerous bird in North America with an estimated population of five to 10 billion, with a b was before European invasion, three to 5 billion after. Which means that at one point there were more passenger pigeons than humans on the planet.

EAU: Wow.

EW: Wow. Over the 18th and 19th centuries, the passenger pigeons steadily declined until the sole remaining member of the species, Martha, died in the Cincinnati Zoo on September 1st, 1914. She was 29 years old.

EAU: Oh wow.

EW: Her passing marked the end of an era. Never again would flocks of these birds, tens of millions strong blot out the sun as they flew in search of food. This extinction served as a wake up call and inspiration for the modern conservation movement. And while researching for this episode, I saw a passing reference to the passenger pigeon in a textbook called One Health and

Mycology, where the author just kind of almost in a throwaway line, suggests that this bird drastically impacted Histoplasmosis distribution across the United States. And I was like, uh, what? So, okay. So since most histo outbreaks are associated with exposure to bird or bat excrement, the presence of billions of birds and the untold amounts of their poop could have driven the spread of histoplasmosis across the landscape, or at least provided the nutrients necessary for their growth. Yeah, I've always had a soft spot for the passenger pigeon. Uh, growing up in northern Kentucky, we would often go to the Cincinnati Zoo where there's a statue of Martha and an exhibit on the passenger pigeon, and it always like struck me as horribly sad. And also somehow, like another era, like it is another [00:55:00] era and it, yeah, I, I've always had a, a soft spot I guess. So when I saw that mention in that book, I had to pull on that thread and I was like, okay, where, where do we go from here? So just to, just to prepare you, I did not find any conclusive evidence linking the passenger pigeon to histoplasmosis, but I did find plenty that is suggestive of a connection. And so if it's all right with you, I thought I'd spend the last bit of time just going through some of these observations and really just like, this is my time to pay tribute to this amazing species. Yes, me too. I'm so glad. We'll get tattoos together.

EAU: We've been, I've been trying to get you to do that for a long

EW: I know. I know. That first one won't be T-P-W-K-Y. It'll be the passenger

EAU: I don't know if mine's gonna be the passenger pigeon, but maybe you're, you're gonna convince me right

EW: Your favorite species driven to extinction by humans.

EAU: Give me, Erin.

EW: Yeah. Okay. Okay. The passenger pigeon could be found throughout the eastern half of North America, basically east of the Mississippi River, halfway north into Canada and halfway or so, halfway into Canada on the northern side and halfway down Florida. But its breeding range was primarily across the Ohio River Valley and Great Lakes region, Indiana, Ohio, Michigan, Wisconsin, Kentucky. If you look at a map of histoplasmosis outbreaks and passenger pigeon distribution, it is almost spot on. Like the Venn diagram is a circle kind of a thing. Correlation is not causation, and there could be many reasons for that overlap. Just like, Hey, the both things, like the same environment

EAU: exactly. Other

EW: warm and and humid. Yeah. But it is compelling nonetheless, especially when you consider the poop. John James Audubon described what he saw in the 1820s and 1830s quote. "The dung lays several inches deep, covering the whole extent of the roosting place like a bed of snow. Many trees, two feet in diameter I observed were broken off at no great distance from the ground, and the branches of many of the largest and tallest had given way as if the forest had been swept by a tornado" end quote.

EAU: Because of how many birds are sitting on there. Oh my gosh.

EW: Yeah. It's like hard to fathom until you listen to some of these descriptions. 'cause there's another one. This is also from Audubon quote. "The air was literally filled with pigeons. The light of noonday was obscured as by an eclipse. The dung fell in spots, not unlike melting flakes of snow." To have the sun obscured. Yeah, these flocks were millions strong. That's not a small amount of dung, which also could have provided excellent substrate for histoplasmosis to grow. Histoplasmosis that could have been misdiagnosed as tuberculosis, especially since the diagnostic technology for TB X-rays and tuberculin and skin tests was only developed in the last years of the bird's existence.

EAU: Erin.

EW: Perhaps it's a coincidence that high tuberculosis mortality in the late 1800s was observed in the histoplasmosis corridor, which was also the passenger pigeon breeding grounds. Perhaps not. I wish, I wish I knew. I really wish I knew, and maybe if I had like another few weeks slash do a PhD on this, then I could. But I, yeah, I, I, I really do wish that the information was out there somewhere. So, but I did find, again, going back to just a few compelling statistics. So during World War I, so 1914, 1918, 23% of draftee in Kentucky were rejected due to tuberculosis. And that was compared to the national average of 9%,

EAU: Oh,

EW: which is kind of interesting. Could be for many different things. Many different things. Could be, you know,

EAU: but could be histo.

EW: Could be histo, maybe. Alexander Wilson, the founder of American Ornithology, described a breeding site in Kentucky that was several miles wide

and nearly 40 miles long by his estimate. Quote, "in this tract, almost every tree was furnished with Nest, wherever the branches could accommodate them. Several people informed me that the noise in the woods was so great as to terrify their horses, and that it was difficult for one person to hear another speak without bawling in his ear. It was dangerous to walk under these flying and fluttering millions from the frequent fall of large branches broken down by the weight of the multitudes above, and which in their descent often destroyed numbers of the birds themselves. While the clothes of those engaged in traversing the woods were completely covered with the excrements of the pigeons." End quote.

EAU: You're Wow.

EW: Yeah,

EAU: I cannot imagine

EW: I know. Doesn't it [01:00:00] seem like fantastical?

EAU: Yes,

EW: But it was real. I mean, like, ma, some of this was exaggerated, no doubt, but like, you can't, not all of it. 'cause this is also many, many, many, many, many different accounts of how many birds there were.

EAU: there were

EW: Yeah. Interestingly, in August, 1980, just I was like, oh, this sounds like similar settings to what happened in this 1980 Histoplasmosis outbreak when a group of people were traveling through, it was a cross country wagon train. And in 1980 it was for like a troubled youth camp thing. Yeah. And they were traveling through Eastern Kentucky, uh, and 81% of the 85 people on the train developed histoplasmosis after stopping on the site of a former Blackbird roost. Uh, it is interesting. And it wasn't even that like they were doing a lot of digging. It was simply just like setting tents up.

EAU: Oh wow.

EW: Yeah. Can you imagine traveling through a passenger pigeon roosting site, tens of miles long,

EAU: No.

EW: Or even just standing beneath a flock as it passed overhead? I've got one last quote, uh, from from Wilson, also in Kentucky, quote, "happening to go ashore. One charming afternoon to purchase some milk at a house that stood near the river. And while talking with the people with indoors, I was suddenly struck with astonishment. At a loud rushing roar succeeded by instant darkness, which on the first moment I took for a tornado about to overwhelm the house and everything around in destruction. The people observing my surprise, coolly said, it is only the pigeons. And on running out, I beheld a flock, 30 or 40 yards in width. These continued passing for more than a quarter of an hour" end quote.

EAU: 15 minutes of so many birds that they blocked out the sun

EW: They, yeah,

EAU: and you thought it was a tornado.

EW: Right. Birds. Numerous enough to be mistaken for a tornado whose excrement was inches deep in roosting sites, where roosting sites left their mark on the forest. For years, passenger pigeons were a force on this continent, and their decline and ultimate extinction was a shock, although it really shouldn't have been. Since Europeans landed in North America and began to cut down enormous forests to make way for pasture land, the birds began to drop in abundance. By the early 1800s, they still numbered in the billions, but population growth and deforestation over that century contributed to their annihilation, along with the introduction of species that competed for resources like pigs. And the free for all hunting in which quote, "wagon loads of the young birds could be easily obtained." End quote, tens of thousands, even over a hundred thousand killed at once just for sport like there were, they just would, many of them would just rot, 'cause people could only, a lot of people ate them for food. But this type of a thing was just like a free for all, just complete waste. Yeah. And it's possible that also as they declined and their strength in numbers could no longer protect them from predators, including humans, they just couldn't recover year after year. Conservation as a concept was still in its infancy, and no one thought to create a captive breeding program, which could have preserved the species, but without adequate continuous forest, it's doubtful that they could have ever recovered to their billion strong numbers. And there is some talk from the resurrection company with all the dire wolf like overhype. But again, I feel like those resources could be better spent on actual conservation efforts rather than implying that like, oh, it's fine. If it goes extinct, we can always bring it back. And guess what? This, this technology is proprietary. So good luck. Um, yeah,

EAU: Uh, no, jeff Goldblum said it best. Okay.

EW: I, I, yeah, I, that's a whole, I could, that's, that's a soapbox that I should probably just

EAU: know exactly.

EW: at this point

EAU: That's exactly how I feel.

EW: Uh, but when, when passenger pigeons were made extinct, north America lost a major ecosystem engineer. These birds preferentially fell on mast from Red oaks and the forest where they roosted were filled with broken branches and twigs and trees leading to more intense and frequent forest fires. Part of the natural, you know, like cycle of forest fires, these two things, uh, favored white oaks, which are more fire resistant. And when the passenger pigeon went extinct, the forest of Eastern North America shifted from white oak to red oak, which is just kind of an interesting component of this.

EAU: I love this. Makes me just love ecology so much. Like I used to, you know, like, it's like the story of the otters and the sea urchins and the kelp and the like. It's the same, [01:05:00] uh, keystone species.

EW: keystone species. Everything is connected. It's,

EAU: is connected.

EW: It is, it is just amazing also how little people have heard, like it's also

EAU: heard of this at all.

EW: Yeah, and it was just over a hundred years ago that the, that Martha died. Um, but all also of interest, forests lost a major seed distributor and tree mast consumer as well. So like acorns, like all of the stuff, the seeds and stuff that trees, these trees produced. And that opened up a niche for competitors like deer and rodents leading to an explosion in their populations, which may have contributed to the rise of Lyme disease. Passenger pigeon extinction, man.

EAU: It's all connected.

EW: Did the extinction of the passenger pigeon also reduce histoplasmosis across the landscape? I, it's possible. I don't know. I mean, all of this is the, the links between histo and the passenger pigeon is speculation on my part. I'm just trying to connect to the dots across these historical accounts of a lost bird and our modern understanding of this fungal disease. The discovery of Histoplasma capsulatum occurred just eight years before Martha's death and nine years after the last passenger pigeon in the wild was killed. Histoplasmosis is a disease of abundance, and it's possible that some of this abundance can be attributed to this once abundant bird. I'm not sure we'll ever know the relationship between the two, but we can't afford to ignore the role that we humans play in the rise and fall of species. So with that, Erin, I'll turn it over to you to tell me where we are with Histo today. Oh, and also I wanted to mention, I wore this, this sweater that has birds on it. Can you see this bird over here

EAU: I can.

EW: My little guy? Yeah. In, in honor of the passenger pigeon.

EAU: Erin, I don't even wanna say anything. I just wanna end it there, but I will. Only because I already wrote it down. So listen,

EW: don't let good work go to waste. Yeah.

EAU: We'll wrap this up real quick here.

Oh gosh, that was so much. I'm like still reeling. So histoplasmosis has been described as the most common endemic mycosis in the Americas. And the fungus itself has been reported, like you mentioned, Erin, across the United States, especially in the eastern half, especially in the Mississippi, Ohio River Valleys, but also throughout a large portion of Latin America, including Central and South America. It has been found in central and Western Africa. Though there, and this is what I said at the very beginning, there's like different sort of subspecies or like variants and so there's a little confusion over there. Um, and it's been found across a lot of Asia as well. Truly, this is a global pathogen. The more that we look for it, the more that we find it

EW: Mm-hmm.

EAU: In the us, which is where we have probably the most data on, like incidence and prevalence. The estimated incidence overall is between one to two cases per 100,000 people.

EW: Okay.

EAU: I don't know if that is the incidence of symptomatic infection, but I anticipate that it is. So that's how many symptomatic cases we expect because like we've said numerous times now, it's estimated that anywhere from 60 to 90% of people who live in areas of high histoplasma in the soil. They show evidence of prior infection.

EW: Yeah.

EAU: And in the US this disease is only reportable in like 14 states in those areas that we know histoplasmosis is more common. So our data isn't great across the rest of the country. And that one to two cases per 100,000 is averaged across the whole country. So it is higher incidence in places like Kentucky, Ohio, et cetera, where this is more common. Right.

EW: Yeah. Yeah.

EAU: And so then how do we, like how many cases are there in the US across like each year? We don't, we really don't have good numbers. There was a paper I found that looked at like Medicare data, um, over a nine year period from 2007 to 2016. That said there were 79 or so thousand cases that were reported. These are all gonna be symptomatic cases, of course. And those are just the ones that are reported

EW: Wow. Because it's not, it's not reportable only in 14 states across, so,

EAU: this was looking at like Medicare data, like hospital data and things like that. So where there was like a histoplasmosis, you know, case documented, but another paper suggested that there [01:10:00] could be upwards of 500,000 new infections each year in the US

EW: saw that because I mean, and it, that makes sense. If you think about,

EAU: about the asymptomatic infections.

EW: the people who recover be, even though they're in, they're diagnosed with bacterial pneumonia. Yeah.

EAU: A hundred percent. So that's, that's including all of that, like, you know, self-limited disease or asymptomatic disease. Um, so it's suggested that like

over 40 million people in the US at least have been infected. And that's probably an underestimate.

EW: That is

EAU: It's like so common. It's so, so, so common. And like I said, the more places that we look for it, the more places that we find it. In Central and South America, there are cases reported year after year. We're seeing more and more case reports across Asia, especially in the Yangtze River Valley in China.

EW: River Valley's man. Mm-hmm.

EAU: Pronunciation there. Yeah, river Valleys. But there's also been case reports in Thailand, in South Korea, in India. In Africa, it's been reported in Uganda, Tanzania, and South Africa. Um, and one of the things that we talked about is the impact of this disease on people who are immunocompromised, especially in people living with HIV,

Especially in areas that lack access to either diagnosis and or treatment For HIV, especially in places where there's a lot of stigma associated with HIV still. So there are a number of papers out there that are looking at Histoplasmosis, specifically in people living with HIV, and one of the places that they're doing a lot of research on this is in Brazil. And in some cases, not only is the case fatality rate of histoplasmosis so high in people living with HIV, but there's estimates that the mortality rates. People living with HIV with histoplasmosis are equivalent to, if not exceeding the mortality due to tuberculosis.

EW: That's, oh my God,

EAU: I know. So this is a hugely impactful disease. Like it is way more widespread and it is a, it is a much bigger concern, certainly than I realized. Um, and with more and more people. Being put on medications like these TNF alpha inhibitors, and that's just one example, but there's a lot of like strong association between those types of drugs and fungal infections like histoplasmosis specifically. Um, but those among other drugs that cause immunocompromise and immune suppression. Our understanding of histoplasmosis is like more important than ever, right? That we're able to diagnose it, that we have access to better treatments, which we don't right now. Like our treatments are ancient and not great.

EW: great. Yeah.

EAU: And like you mentioned, we might not have a current day passenger pigeon situation. But given how much land use change is happening, how rapid land use change is happening in places, the effects of climate change on fungal pathogens broadly including histoplasmosis, like this is very likely to only continue to increase histoplasmosis.

EW: Absolutely.

EAU: So. That's what I got.

EW: We should be talking

EAU: We should be talking more about it. We should be talking more about

EW: And about the passenger pigeon. But that's my personal, my, my, my personal like, uh, obsession.

EAU: I love it. Now I need to look up like images of the passenger

EW: There. They're really, I mean, it's, it's certainly pigeon like, but it's, it's, I think it's quite beautiful. And there was a strong amount of sexual dimorphism, which not all pigeons have anyway, so, yeah.

EAU: I, I love, that's my favorite thing I've learned. So

EW: Uh, I'm glad.

EAU: you wanna learn more, we'll tell you.

EW: We have, I have, like I said, I really because of the, the rabbit hole pigeonhole. Um, ha ha. Again, you're showing how low your bar for jokes is, Erin.

EAU: I'm in a good mood, I guess.

EW: Um, but the, I have so many sources because I was like, and what about this and what about this? So anyway, lemme take you through a couple on histo. There's a paper from 1957 by Schwartz and Baum called The History of Histoplasmosis, 1906 to 1956. It was a great sort of primer on like what people have discovered and where are we from here, uh, then from 2022 by Taylor, et al considerations about the geographic distribution of histoplasma species. Yep.

EAU: Mm-hmm. Saw

EW: And then if you would like to read about the passenger pigeon, I read a book called A Message from Martha by Mark Avery. Uh, but there's like a few, there's like a number of passenger pigeon books out there, and I have a couple papers about the genome. Anyway, it's, um, it's, it's, and, and did I find one about its diet? I did find one about its diet. Yeah. Anyway, go ahead, Erin.

EAU: Uh, so I had a number of papers as well. Uh, just a few that I'm [01:15:00] gonna shout out here that were really good overviews of histoplasmosis itself. One was by Linder and Kaufman from 2019 in current fungal infection reports called histoplasmosis: Epidemiology, diagnosis and Clinical Manifestations. Um, another from 2024 by gandhi, et all that was called Histoplasmosis around the world, a global perspective on the presentation, virulence factors and treatment of Histoplasmosis on, there's too many and they're all just like really long titles. Uh, there's a whole bunch there. Okay, I have an interesting one that was comparing Histoplasmosis to Blasto Mycosis. Um, so if you want more details on those, the the similarities and differences, we got 'em all on our website. This podcast will kill you.com. Right under the episodes tab, you can find the list of sources from this and every single one of our many episodes.

EW: episodes. Yeah. Uh, thank you again so much Macy, for sharing your story with us. We really appreciate it.

EAU: We do. Thank you. Thank you.

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

EAU: Thank you to Lianna and Tom and Pete and Mark and everyone at Exactly right. For everything that you do.

EW: Thank you. Thank you. And thank you to you listeners. Uh, if you find more info about the passenger pigeon and histo or refuting the link or things you want to know more about or whatever, let us know what you think. We always like to know.

EAU: if you already have a tattoo of a passenger pigeon, can you send it so that Erin can get some

info? Please, It's gonna be that and the Tasmanian tiger

Oh, I love it. That's so cute. Um, and as always, a special shout out to our patrons. Thank you so much for your support. It really does mean, it really does mean a lot to us.

EW: It, it, it really does. It means so much to us. Thank you. Until next time, wash your hands. I.

EAU: You filthy animals.