TPWKY	This is Exactly Right.
Tori	So my name is Tori and I'm from Utah. I had always been a healthy girl with no serious ailments or illnesses. I spent most of my high school cycling, swimming, running, exercise was my whole life and I was always very healthy. At age 19 I created a plan to serve a religious mission and then come home and spend the rest of my life doing Ironmans and one day making it to the Kona Ironman Championship. However those plans would quickly change. In March of 2014 I left on a religious mission to Arizona for 18 months doing service outdoors and teaching. I ran nearly everyday of this mission and did quite a lot of bike riding as well.
	Initially going out to Arizona we were warned about Valley fever, we were told always to stay inside if there was a dust storm or if it was extra dusty outside because Valley fever was in the spores that swirl in the dust. Though we tried to stay inside from the dust storms, being outside was inevitable and being around the dust was inevitable. Hello, it's Arizona and we spent so much time outside. Fast forward, it was August 29th, 2015. I was 17 days away from going home and seeing my family again and finishing this service and that day my life would change forever. I woke up with a bit of chest tightness but shrugged it off. I still went on our morning run but could barely make it more than a quarter mile when the chest pain became so intense. I ended up going to an urgent care and sitting in the waiting room for three hours, gasping for breath, because their computer was down.
	I was in so much pain I could barely breathe. When the computers finally came up, I was able to get an X-ray by the urgent care doctor. After analyzing the X-ray, nothing of concern showed up so the doctor presumed that the only explanation was something similar to shingles because I didn't have a fever, I didn't have a cough, I didn't have a rash or anything else. I was given steroid shots and pain medications and then sent on my way. After a few days, I began to have a low-grade fever and some body aches. Progressively the fevers got worse and the aches more extreme to which point I felt unable to move my joints. Exactly one week from my initial trip to the urgent care, I was back again with fevers, nausea, a developing cough, consistent chest pain with absolutely no relief and convinced this was more than shingles. I wanted to die with the pain I was experiencing. Luckily the computers didn't have issues and I was able to get right into the doctor and he immediately ordered an additional chest X-ray again just to see.
	I will never forget that X-ray as his assistants helped me stand up because I screamed in agony trying to expand my joints and my chest, all of which were screaming back at me tenfold what I was screaming out loud. The X-ray came up on the screen starting from the bottom up. As I watched it, I saw spiderweb clouds covering my entire right lung. Even I knew something was wrong. In a week's time, my chest X-ray had dramatically changed. The doctor spent what seemed like years just looking at the X-ray and deemed it appropriate for me to go to the ER and get a stat CT scan and be admitted. When I got there my O2 sats were in the 80s at best and the CT scan that they quickly did showed fluid around my entire right lung and beginning around my lower left lobe. It was clear whatever I was experiencing was spreading quickly. I was quickly treated by teams of infectious disease doctors, pulmonologists, and respiratory therapists. Blood samples were taken and sent off to labs. In the meantime I was treated for anything and everything.

	One of the first things they tested for was Valley fever. The blood antigen test that they did ended up coming back negative for Valley fever oddly enough, but they wanted to test part of my lung tissue to be sure. I was then presumed to maybe have tuberculosis and/or a staph infection. I was primarily treated for that along with antifungals for the possible Valley fever. In the coming days I got sicker and weaker, my cough persisted and became more violent. So much water was in my lungs that each time I coughed I felt like I was drowning because so much water came up. Every bone hurt and my fever couldn't get under control. I remember multiple mornings being visited by the infectious disease doctor and her sitting by the side of my bed, holding my hand and telling me she didn't sleep, worried I wouldn't make it through the night.
	On September 12th, three days before I was supposed to return home to Utah, the concoction of medication that they had me on seemed to be stabilizing me and my resting air O2 sats looked as if they could be stable for a short flight home. By this day, the atrophy and emaciation of my once very strong, healthy body was shocking. I could no longer even sit up in my hospital bed without being winded or gasping for air. Standing up was a special task of its own that I could no longer fathom doing on my own. I was wheeled in a wheelchair through the airport to greet my family. The active, vibrant athlete they once knew returned home bruised and beaten by an unknown cause. We later received a call from Arizona that the tissue biopsy did end up growing Valley fever and that Valley fever was indeed the culprit.
	The year following this infection would be very trying to say the least. I continued to be sick, returning to the hospital a few additional times, I lived on the couch barely even able to get myself up for months, still coughing up water continuously, taking quick, shallow, frightening breaths and too weak to do much of anything on my own. Everything caused me to be out of breath. Very different from what I grew up knowing. As it stands today, I still get a CT scan about once a year, sometimes every six months depending on what my infectious disease doctor says. My lower two lobes of my right lung are dead as well as the lower lobe of my left lung. I have the equivalent of one lung in my body. The remaining tissue eventually took up the task of providing my body with enough oxygen to live a normal life.
	When I was able to start moving again after many years, exercise became a daunting feat. Getting my heart rate up was very difficult and typically resulted in a coughing attack. It took years for me to work up the stamina to ride a bike. To this day I cannot run and am a mediocre athlete at best. I can enjoy movement for the most part and do what my lungs will allow. Walking up hills and stairs tend to be most difficult. I'm on forever antifungals because for whatever reason, my body being an anomaly doesn't like to fight Valley fever. However today I'm grateful for a body that did fight, though my goals and ambitions changed drastically, I survived and walk today with the equivalent of one lung.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Allmann Updyke	Thank you so much, Tori, for sharing your story with us.
Erin Welsh	Yeah, wow. Thank you, thank you. Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	And today we're talking about coccidioidomycosis.
Erin Welsh	Ooh, well done.

Erin Allmann Updyke	Thank you.
Erin Welsh	We think that's how we're supposed to say it.
Erin Allmann Updyke	We've been practicing a lot.
Erin Welsh	Yeah. If that's the wrong way to pronounce it and it's really bothering you, it's gonna be a long episode for you guys.
Erin Allmann Updyke	It's gonna be terrible. It's gonna be worse than giardia. (laughs)
Erin Welsh	But listen, I went to YouTube and I found like an actual clinical lecture on coccidioidomycosis.
Erin Allmann Updyke	Nailed it.
Erin Welsh	Hopefully. And this is how the person pronounced it! And so we got our pronunciations from a clinical lecture from like a school of public health, so.
Erin Allmann Updyke	We're trying our best as always, aka in case you have no heard of this, the other name for it is Valley fever.
Erin Welsh	Yes. This is gonna be a cool one because it's our first human fungal pathogen.
Erin Allmann Updyke	Which is just... I can't believe it's taken us this long.
Erin Welsh	We've done chytrid.
Erin Allmann Updyke	We did chytrid. And actually someone asked us recently if we've ever done Cordyceps, which we haven't done on this podcast but we did talk a lot about Cordyceps on an episode of The Biology of Superheroes podcast.
Erin Welsh	Yes.
Erin Allmann Updyke	So definitely check that one out if you haven't listened to that already.
Erin Welsh	Oh yeah. But we're not talking about Cordyceps today, we're talking about coccidioidomycosis. But before we begin-
Erin Allmann Updyke	Mm-hmm, it's quarantini time!
Erin Welsh	It is quarantini time, my favorite time. What are we drinking this week?
Erin Allmann Updyke	We're drinking the Dust Devil.
Erin Welsh	This is a fantastic name and it's so fantastic that we cannot take credit for it. I actually found it, it was the title of a paper. Some of the papers I read for this episode have the greatest titles. This one is 'Dust Devil: The Life and Times of the Fungus That Causes Valley Fever.'

Erin Allmann Updyke	Ooh, I love it!
Erin Welsh	Isn't that great? And that's by Lewis, Bowers and Barker. Another one of my favorite paper titles for this episode was 'Coccidioidomycosis: What a Long, Strange Trip It's Been' or something to that effect. (laughs)
Erin Allmann Updyke	(laughs) Aw, you're so adorable.
Erin Welsh	It's great. Anyway, what is in the Dust Devil?
Erin Allmann Updyke	It's a tequila-based pear cider situation.
Erin Welsh	Yeah. It's tasty, it's got tequila of course, it's got pear juice, it's got a spiced simple syrup and we threw in some orange liqueur. Anyway, we'll post the full recipe for this quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com as well as on all of our social media channels, so make sure you follow us there.
Erin Allmann Updyke	Definitely. What other business do we have to attend to, Erin?
Erin Welsh	We got some of the most incredible responses from our sweating sickness episode or after our sweating sickness episode.
Erin Allmann Updyke	Yeah, we did.
Erin Welsh	Oh my gosh, so many people wrote to us or commented with their different hypotheses as to like what caused this super bizarre disease and I wanted to shout out on in particular from someone who wrote us this incredibly detailed email about how they went down into this deep rabbit hole looking into possible causes and came up with a walnut mold, penitrem A, as their hypothesis.
Erin Allmann Updyke	I just love it. I love that there are people out there as nerdy as us doing these deep, deep dives on things like what caused sweating sickness. It's so beautiful.
Erin Welsh	Yeah! And came up with a walnut mold. And like honestly I kind of buy it. It seems quite plausible, like the symptoms lineup, a foodborne toxin could very well move along trade routes like we talked about. And I just wanted to say thank you for everyone's responses and this email in particular because I got such a kick out of it.
Erin Allmann Updyke	I love it. (laughs)
Erin Welsh	Do we have more business?
Erin Allmann Updyke	I did want to say, I finally checked our P.O. Box that I'm really bad about checking and I wanted to say thank you to Sabrina for your thank you note.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	So adorable, she sent us a thank you card just to say thanks for making the podcast and that she really likes it. And I really like you.
Erin Welsh	It's was the sweetest thing.

Erin Allmann Updyke	Anyways, that's all. Okay.
Erin Welsh	Okay, let's talk fungus, please. Please.
Erin Allmann Updyke	(laughs) We'll take a quick break and then dive into the biology of coccidioidomycosis.
Erin Welsh	(laughs)
Erin Allmann Updyke	Did I say it right that time?
Erin Welsh	I think so.
Erin Allmann Updyke	I think I did. Okay.
TPWKY	(transition theme)
Erin Allmann Updyke	Coccidioidomycosis, aka Valley fever, aka our first human fungal pathogen. It's actually two different species of fungi, Coccidioides immitis and Coccidioides posadasii which are both endemic to desert areas in mostly the southwestern U.S. So Coccidioides immitis tends to be more prevalent in California and Coccidioides posadasii mostly in Arizona. But these fungi are also found throughout New Mexico, Utah, into Texas, we'll talk a little bit later about how maybe it's all the way up in Washington, as well as down into parts of Mexico and Central and South America.
	So let's get into the disease that's actually caused by this fungus. This is a pathogen that is not contagious, so it has not been shown to be spread from person to person or from animal to person, because this is also a fungus that can infect other animals aside from humans, especially dogs. But I am not really gonna talk any more about infection in animals like at all. But this is a fungus that's called dimorphic, so it has two entirely different forms that it exists in and I have to confess that I know so little about fungus that I still have so many questions about how the heck this is possible. Like it's so fascinating. Okay, let's get into it. In the environment this fungus exists as a mold, it's called a mycelium. So if you were to grow a whole bunch of it, like very concentrated in a jar or something and pick it up, it would look kind of like a little cotton puff, like a little ball of white little wispies.
Erin Welsh	Mm, like cotton candy.
Erin Allmann Updyke	Yum! Microscopically, if you look at these little wispies in more detail, they're called branching septate hyphae, what does that mean? They're kind of like... This is the way I'm gonna describe it, Erin. It's like a tree made out of toilet paper. So it's like long, stringy bits that have branches like a tree would but then they're separated at certain points like the way that toilet paper is so it has the septations.
Erin Welsh	Oh! Okay.
Erin Allmann Updyke	And so what happens is that during times of drought or low precipitation, those toilet paper squares which in the fungus are called arthroconidia or arthrospores, they dry out and then they break off super easily, like if your house got toilet papered and then the wind picked up and broke off a bunch of little squares of toilet paper and then toilet paper flew all around your neighborhood.

Erin Welsh	Yeah.
Erin Allmann Updyke	And then what happens is that you as a human breathe those spores in. So that is kind of the life cycle in the environment. So you have these mycelia, these long branchy stringy bits that break off when they dry out and then can become borne on the wind, in the soil.
Erin Welsh	Excellent.
Erin Allmann Updyke	Now you breathe them in. And now we have to talk about what happens in us because it's totally completely different than what happens in the environment. So when you breathe in a spore, literally potentially just one, it only has to be one spore could potentially infect you. What happens is you breathe it in and it goes down into the bottom of your respiratory tract and then lodges in your terminal alveoli, you're terminal bronchioles like right where gas exchange is supposed to be happening. And once it gets there it begins to enlarge and it forms what's called a spherule, like a big sphere.
Erin Welsh	Okay.
Erin Allmann Updyke	I don't know why it's called that.
Erin Welsh	Like a beach ball in your alveoli.
Erin Allmann Updyke	In your lung. And in this spherule it begins to replicate and forms thousands of endospores.
Erin Welsh	Oof. Within this spherule.
Erin Allmann Updyke	Within the spherule.
Erin Welsh	Okay.
Erin Allmann Updyke	And then eventually that spherule will rupture and release those thousands of endospores that can go on to travel, form new spherules which make more endospores, etc, etc.
Erin Welsh	That's cool, so it brings it's own little like reproductive machinery.
Erin Allmann Updyke	Yeah, it just does it all on its own, it's asexually reproducing, just boop-boop-boop-boop making a bunch of little endospores. But that's completely different than how it lives and replicates in the environment, in the soil. And it gets even weirder because if for example you take a sample of someone's sputum, like gunk that they coughed up when they were infected with Coccidioides, and that's a whole bunch of endospores inside a spherule, if you left that on the counter it would grow mycelium. It would grow into the environmental form, which by the way would be highly infectious if it dried out.
Erin Welsh	So there's some kind of cues that it's using.
Erin Allmann Updyke	Yes. Some kind of cues to know that it's in a host vs in the external environment.
Erin Welsh	I wonder what those cues are.

Erin Allmann Updyke	Me too, Erin. Me too. (laughs) But we're gonna focus on what happens when it's inside of your body. If somebody is a fungus researcher, it would be awesome to know more details about that fungus because hoo boy. But in general, once this happens inside of our lungs, our body reacts to this fungus. It's going to induce an immune response, it's going to recruit a lot of inflammatory cells and that's going to kind of result in the symptoms that we see. So let's talk about those.
Erin Welsh	Yeah.
Erin Allmann Updyke	If you have any symptoms at all which about 40% of people who get infected with Coccidioides will, 60% of people won't have any symptoms at all. If you have these symptoms, most commonly it presents as an acute pneumonia. And I think we've talked very peripherally about pneumonia in the past, I'm actually gonna talk kind of a lot about pneumonia in this episode which is exciting.
Erin Welsh	Ooh, yeah.
Erin Allmann Updyke	But pneumonia is basically just the way that we say there's an infectious cause of inflammation and fluid filling up the air sacs of the lungs.
Erin Welsh	Okay.
Erin Allmann Updyke	So it's inflammation of the lungs but pneumonia is used specifically to mean an infectious cause of that inflammation. So with coccidioidomycosis - did I get that right?
Erin Welsh	I think so. Honestly it's like we've said it and I've thought it so many times it's starting to sound weird.
Erin Allmann Updyke	I know. 1-3 weeks after inhalation of the spores you have basically pretty typical pneumonia symptoms: fever, a cough that's quite productive of like gunk, very profound fatigue, like just feeling very exhausted, and probably chest pain especially when you take really deep breaths. With Coccidioides infection it's also really common to have a headache and the chest pain tends to be very severe. And with this type of pneumonia, the fatigue can last for months and months. So even as the pneumonia resolves, that fatigue can persist.
Erin Welsh	Okay.
Erin Allmann Updyke	If you were to take a chest X-ray or a chest CT scan which would be very likely to happen if you went to the ER or the doctor's office, it would look like pretty much most other causes of pneumonia, which means it would look like there's fluid in some portion of your lung, either in just one lobe or maybe in like the middle region which is called the hilar region around the trachea, like where the trachea divides. You might have some swollen lymph nodes along that region, that's a little bit more common with a Coccidioides pneumonia rather than other types of pneumonia. One other thing you might have that's not as common with other forms of pneumonia is you might have some skin changes, like some red, painful, swollen bumps along your shins that are called erythema nodosum or another red, splotchy rash that can occur kind of across your body that's called erythema multiforme.
Erin Welsh	Question.
Erin Allmann Updyke	Okay.

Erin Welsh	What else causes those two things?
Erin Allmann Updyke	So a number of different, these are not specific to Coccidioides infection. These are both caused by an immune response to this infection, not form like a disseminated fungus. So there's actually a number of different infections that can cause similar findings, like different viruses and bacteria.
Erin Welsh	Okay but I mean like what's the mechanism? Like why does that happen in these different infections?
Erin Allmann Updyke	That's a really good question that I don't know the specifics of it aside from the fact that whatever specific immune response is being generated, that's what then causes this.
Erin Welsh	Okay. And this is only like an occasional sign of disease.
Erin Allmann Updyke	Mm-hmm, it's not always.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	Yeah. So it's also kind of person-specific, like some people might be more likely to have this immune response than others. Yeah. But most of these people with this presentation will recover and be pretty much fine with or without any treatment. And keep that in mind, ding-ding-ding, with or without treatment because it'll become really important later on.
Erin Welsh	Okay.
Erin Allmann Updyke	But some people won't. So there's a few other forms that this disease can take. Some people will go on to have a chronic form of pneumonia that's called chronic progressive pneumonia. And I had a hard time finding the exact percentage of people that go on to have a chronic pneumonia which basically would be like all the same things that you have with this pneumonia, so cough, potentially coughing up blood because you have so much inflammation and infection, you'd go on to have weight loss because you've essentially been sick for so long that you're just not eating, you feel really, really bad, the fatigue is extreme, and on X-rays you still see those same pneumonia changes. But based on everything that I read, it seems like it's likely less than 5% of the time, but I didn't get a hard number on chronic pneumonia.
Erin Welsh	Okay.
Erin Allmann Updyke	But even if the pneumonia resolves or is treated and goes away, sometimes all of the fluid and gunk that's left behind from the infection can kind of persist and what it does is contract into like a cavity that our body kind of walls off and it just stays there. And this can happen like 5-10% of the time, so you'd still see like a nodule or a cavity if you looked at an X-ray of a person with this.
Erin Welsh	This is in their lung?
Erin Allmann Updyke	In their lung. Now most of the time that's all and nothing ever happens beyond that, but in 30-60% of people with these nodules they actually still have an active infection, it's just not spreading or doing anything. So if you tested them for Coccidioides you would find it. And so this could potentially reactivate or have like waxing and waning symptoms.
Erin Welsh	Wait a second, so the fungus is still there in that nodule?

Erin Allmann Updyke	Mm-hmm.
Erin Welsh	But it's been walled off.
Erin Allmann Updyke	It's been walled off.
Erin Welsh	So it's like that Edgar Allen Poe story, The Cask of Amontillado?
Erin Allmann Updyke	(laughs)
Erin Welsh	Do you know what I'm talking about?
Erin Allmann Updyke	I probably have read it but I don't specifically remember it.
Erin Welsh	It's the one where they wall the guy up inside.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	They wall him up and like leave him.
Erin Allmann Updyke	Yeah, I was gonna say it's kind of like TB.
Erin Welsh	Oh. (laughs)
Erin Allmann Updyke	But yeah, also that.
Erin Welsh	I feel like that says a lot about our personalities.
Erin Allmann Updyke	(laughs) Yeah this is not uncommon in other fungal infections as well. Fungal infections are very difficult to kind of treat and deal with and our immune system doesn't always do a great job of responding to them. Now, there's something else that can happen that gets a lot worse. So in somewhere between 1-5% of cases the infection can spread beyond the lungs and result in what's called disseminated disease. So overall if you look at everyone who gets infected with Coccidioides, the percentages are like somewhere between 1-5%. But if you look just at people who are in some way immunocompromised, whether that's from HIV infection that has a low CD4 count or some kind of congenital immunodeficiency, someone who's on immunosuppressants because of an organ transplant or whatever, in this group it's like 30-50% of people could go on to develop disseminated disease.
Erin Welsh	Okay, so it's like...
Erin Allmann Updyke	So it's disproportionate who is likely to get a disseminated infection.
Erin Welsh	Right, right, right.
Erin Allmann Updyke	But even in people who are otherwise immunocompetent, somewhere between like 1-3% of people will go on to develop this systemic infection.
Erin Welsh	Okay.

Erin Allmann Updyke	So once this fungus spreads from beyond your lungs< so it like makes its way from your alveoli out into your bloodstream, it can go literally anywhere and infect in theory any organ or any system. But there are a few places that it goes most commonly. The skin is one of them and this results in a kind of ulcerations or nodules or big kind of like blisters that burst open that you see on the skin. It can go to the lymph nodes which would cause a lot of lymph swelling, it can go to the joints which would cause a lot of joint pain. But the most severe and terrifying manifestation is if it goes to the meninges, which is the lining of our central nervous system. So this means it's managed to cross the blood-brain barrier and result in meningitis which is untreated is fatal over 90% of the time.
Erin Welsh	Yeah.
Erin Allmann Updyke	And this also tends to happen months or even years after an initial respiratory pneumonia-type infection.
Erin Welsh	Months or years.
Erin Allmann Updyke	Yeah so it's a long process of this fungus making its way through our body and wreaking havoc.
Erin Welsh	So is it possible that somebody becomes infected and then doesn't know for years and years that this is what they have?
Erin Allmann Updyke	I don't think for years and years but potentially yes because for example if they form like a nodule and they're otherwise immunocompetent, then their immune system can keep that at bay. If they then become immunosuppressed for some reason later on, this could be reactivated.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	Gotcha.
Erin Allmann Updyke	Yeah. So yeah, so that's kind of like the general overall biology of coccidioidomycosis.
Erin Welsh	Well said.
Erin Allmann Updyke	Thank you. It is treatable with antifungals but the thing is, and I'll talk a little bit more about this in the current events section, it's a very underdiagnosed cause of pneumonia even in regions where it's endemic, like where we know that it's definitely circulating. So a lot of people who present with pneumonia just get antibiotics and then they're sent on their way home. So that's why a lot of people just recover without ever actually getting the proper treatment because they just got antibiotics and then they felt crappy for like three months and then they got better, maybe that was the fungus. But there are guidelines for when you should treat vs when you don't necessarily need to treat if you think someone's gonna clear it. But they're not clear, there's not a good consensus, we don't have good evidence-based guidelines on exactly how to treat coccidioidomycosis.
Erin Welsh	It seems interesting considering... Well, I'll talk about the history a bit but like-

Erin Allmann Updyke	I can't wait to hear about the history, Erin can you please tell me all about it? Because I read like a tiny bit by accident and I was like what!
Erin Welsh	Wait, are you ready now?
Erin Allmann Updyke	Yes, I'm ready now. (laughs)
Erin Welsh	Oh. (laughs) Okay. I'm not, so let's take a quick break first.
Erin Allmann Updyke	Okay.
TPWKY	(transition theme)
Erin Welsh	Prominently displayed at the Institute of Parasitology in Buenos Aires is a head.
Erin Allmann Updyke	Oh.
Erin Welsh	A human head stored in formalin and labeled as Exhibit 1.
Erin Allmann Updyke	Oh gosh.
Erin Welsh	Mm-hmm. When this preserved head was discovered in 1948, there was no identifying card to describe who the head once belonged to, when it was removed for storage, and why it was preserved.
Erin Allmann Updyke	I'm sorry, someone just came across a head?
Erin Welsh	Like in a jar in formalin, yeah.
Erin Allmann Updyke	Okay.
Erin Welsh	Uh huh.
Erin Allmann Updyke	Not creepy at all.
Erin Welsh	Well and the guy who came across this head, Dr. Flavio Niño, didn't need any sort of card to tell him who it was. He recognized it immediately as being the head of Domingo Escurra, removed and preserved after Escurra's death 50 years prior.
Erin Allmann Updyke	What? Erin.
Erin Welsh	Yeah. Okay so we've got the who and the when, but the why remains. Why was this head removed and placed in formalin in 1898?
Erin Allmann Updyke	Yeah.
Erin Welsh	And as far as I know still on display in 2021.
Erin Allmann Updyke	What?

Erin Welsh	Because it turns out that this head's original owner, Domingo Escurra, was the first described case of coccidioidomycosis.
Erin Allmann Updyke	So someone preserved his head.
Erin Welsh	So someone preserved his head.
Erin Allmann Updyke	Okay.
Erin Welsh	Yeah. In January 1888, Domingo, who was then a 32 year old member of the cavalry in northern Argentina, he woke up from a nap and noticed what he thought was a spider bite on his right cheek. Spoiler alert: it's never a spider bite.
Erin Allmann Updyke	It's never a spider bite.
Erin Welsh	Unless you're in Australia, that might be a different story. But like it's never a spider bite.
Erin Allmann Updyke	It's never a spider bite. That's our title. (laughs)
Erin Welsh	(laughs) He tried various treatments to heal the lesion but nothing seemed to work. The original lesion grew larger and rougher, his lymph nodes swelled, and new lesions appeared all over his face and neck. Eventually he sought help at the military hospital where they promptly diagnosed him with lupus vulgaris and discharged him with a prescription for nitric acid. But of course the nitric acid didn't do anything.
Erin Allmann Updyke	No.
Erin Welsh	So when the lesions continued to get worse, he was sent to a hospital in Buenos Aires. This time he was diagnosed with mycosis fungoides. Erin, what is that just like briefly? I googled it and I can't remember now.
Erin Allmann Updyke	It's a type of T cell lymphoma. So it's a type of cancer of the skin that manifests with a lot of skin issues.
Erin Welsh	Okay. It's interesting because it has 'myco' in the-
Erin Allmann Updyke	Yes, mycosis.
Erin Welsh	And so it makes you think that it's fungus-related but it's... Also, mycosis fungoides.
Erin Allmann Updyke	I know, it's very confusing. But yes, it's a type of T cell lymphoma.
Erin Welsh	Not infectious, not contagious, not whatever.
Erin Allmann Updyke	No, no.
Erin Welsh	Okay. And so these treatments once again failed and then he was put under the care of Alejandro Posadas who was a 21 year old intern with a mustache that makes Salvador Dali's look tame.
Erin Allmann Updyke	(laughs)

Erin Welsh	It is an incredible... It might be the most incredible mustache I've ever seen.
Erin Allmann Updyke	Whoa.
Erin Welsh	Yeah. At this point when Posadas first met Domingo, Domingo had a large purple fungal-like mass covering his right cheek and vegetations on his nose, his arm, his trunk, and his extremities. He must have been in incredible discomfort. And Posadas, trying to find out what exactly was going on, put some of Domingo's lesions under the scope and noticed that it was riddled with multinucleated giant cells and then some smaller cells with granular contents. He put two and two together and figured that these cells were a type of protozoan.
Erin Allmann Updyke	Okay.
Erin Welsh	They weren't. (laughs)
Erin Allmann Updyke	(laughs) He tried though.
Erin Welsh	He tried. But that they were probably the ones responsible for Domingo's condition.
Erin Allmann Updyke	Mm-hmm, okay.
Erin Welsh	And he published his findings in 1892.
Erin Allmann Updyke	Wow.
Erin Welsh	So this is like the first time that what would later turn into coccidioidomycosis was described.
Erin Allmann Updyke	Yeah.
Erin Welsh	This unique but kind of lonely case in that it was singular, right, could have gone unnoticed for years. But - and this is just what really gets me - it didn't. Like I feel like so many times we've come across, 'Oh and then finally someone had to look back hundreds of years and link together all of these cases'.
Erin Allmann Updyke	Right. Yeah like it was lost for decades or whatever and then they found the same thing and then saw it in some record somewhere.
Erin Welsh	Yeah!
Erin Allmann Updyke	Yeah.
Erin Welsh	But yeah, this case wasn't lost to time or whatever because a couple of years before Domingo Escurra noticed his spider bit that wasn't actually a spider bite, another guy by the name of Joas Furtado-Silveira had immigrated from the Azores to San Francisco where he began working as a farm laborer. And soon after his arrival, he noticed a sore on his neck that just wouldn't go away. He ended up seeking medical help, nothing made it better, and he eventually deteriorated until he died much more quickly actually than Domingo Escurra. He had to endure much more horrifying treatments like carbolic acid, cauterization, bromine plus cocaine.
Erin Allmann Updyke	Oh.

Erin Welsh	Yeah. And seemed to suffer much more before his death in 1895. And before he died, a couple of doctors popped a bit of tissue from his neck lesion under a scope and once again they saw giant cells and granulated cells of various sizes which they realized were just like the ones that Posados had written about. They were like, 'Hey that reminds me of this.'
Erin Allmann Updyke	I am very impressed.
Erin Welsh	I know! I know. And they did though, they did disagree with the diagnosis of mycosis fungoides but they did notice the connection between the two conditions and once again said these cells were likely responsible. They also believed that they were a new species of protozoan, which they weren't, it's fine, and thought that they looked similar to coccidia and so they named it Coccidioides. Coccidia-like.
Erin Allmann Updyke	Oh, that makes sense, okay.
Erin Welsh	Yeah. And these two researchers who were doing this study, Rixford And Gilchrist, presented all these findings at a meeting of the California Academy of Medicine in 1894.
Erin Allmann Updyke	Okay.
Erin Welsh	And so begins the modern history of coccidioidomycosis. But before I keep going on that path, you know that I have to ask 'But what about the not so modern history?' So these two, Domingo and Joas, were not the first two people to get infected with this little fungus, right.
Erin Allmann Updyke	Of course not. If we've learned nothing from this podcast, we've learned that is absolutely not the case.
Erin Welsh	Absolutely not the case. Okay, so we have to go back. Like way, way back. So you mentioned that coccidioidomycosis is caused by these two species of fungus, Coccidioides immitis and Coccidioides posadasii. And even though it was relatively recently that Coccidioides posadasii was recognized to be separate species, it was like 2002 I think.
Erin Allmann Updyke	Oh, okay.
Erin Welsh	It turns out that this species is actually much older than Coccidioides immitis and it's likely that immitis evolved from posadasii. And there seems to be still a little bit of debate about the geographic origins of Coccidioides posadasii but most papers I read seem to agree that it is thought to have originated somewhere in southern Arizona or northern Mexico, maybe around like 800,000 years ago. And then more recently, well not recently to us but like more recently, 365,000 years ago Coccidioides immitis, which is found most commonly and has the most diversity in the Central Valley of California, that's thought to have diverged from posadasii when like the glaciers and the inland sea of that area of California retreated, so it kind of like trapped it there in this little like, you know-
Erin Allmann Updyke	Little valley home.
Erin Welsh	Exactly.
Erin Allmann Updyke	Little allopatric speciation.

Erin Welsh	There we go.
Erin Allmann Updyke	Wow.
Erin Welsh	Keeping isolated by the Sierra Nevadas.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. And the next big moment in the evolutionary history of this little fungus is the arrival of humans in North America. And there's a cool paper from 2001, so it might be a little bit out of date but current papers still do reference it, and it traced the genomic diversity of different isolates of Coccidioides posadasii, so the older one, all throughout the regions that it's been found in North America and South America and found that based on the types of and the levels of diversity in the South American isolates, it seems that during the Pleistocene, ancient humans who migrated down from North America to South America also brought the fungus with them along those migration routes.
Erin Allmann Updyke	Okay, okay.
Erin Welsh	Yeah. But their estimate of when Coccidioides posadasii arrived in South America is a little bit broad, so like anywhere between 9000 and 140,000 years ago.
Erin Allmann Updyke	No big deal.
Erin Welsh	No big deal. That's a pretty big range. So they also say, okay yeah, it could've been a species of rodent or it could have been before, but that does seem to be the direction how it happened.
Erin Allmann Updyke	Okay.
Erin Welsh	Okay. And I will say that a lot of this genomic analyses of the evolutionary history and stuff are kind of plagued by these problems of sampling bias.
Erin Allmann Updyke	Yeah.
Erin Welsh	So like because Arizona has been so extensively sampled, is it just that we think it originated there because we see the most diversity? If we sampled more in Guatemala, for instance, might that point to a Guatemalan origin?
Erin Allmann Updyke	Totally. That totally makes sense.
Erin Welsh	Yeah. So in any case, ancient humans in North and South America were no stranger to this fungus. And to further show this, there's a skeleton from Arizona from around 1000-1400 CE that has signs of destructive lesions and also microscopic examination show that there were spherules and endospores that resembled Coccidioides immitis or posadasii, it's an older paper so everything was called immitis.
Erin Allmann Updyke	Stop it. What?
Erin Welsh	Yeah.
Erin Allmann Updyke	That's so cool! We haven't had bones in a while, Erin.

Erin Welsh	I know. And they were like, this may not necessarily cause actual lesions on the skeleton necessarily but they were pretty confident it wasn't just contamination from the soil, cause that you could imagine would be a big problem.
Erin Allmann Updyke	Yeah, of course. Yeah.
Erin Welsh	And then in prehistoric middens, so like old trash heaps essentially, in California Coccidioides immitis was found at higher rates than in surrounding soil which could suggest that the people who used the middens had the disease. That ones a little bit more hand-wavey to me.
Erin Allmann Updyke	Yeah, definitely.
Erin Welsh	All right so coccidioidomycosis has probably been around and infecting people and animals for hundreds of thousands of years before it was first described. And Domingo and Joas just happen to be the first two people whose unfortunate encounter with this fungus was documented. But they definitely weren't the last and these two reports, instead of being lost and forgotten, somehow ended up kicking off this era of coccidioidomycosis research that picked up steam significantly throughout the 20th century. And part of it is because after those first two cases happened, more seemed to kind of steadily trickle in and the geographic patterns of this disease, like how they kept popping up in the same areas, that helped physicians kind of make the link between them all.
Erin Allmann Updyke	Got it.
Erin Welsh	In 1900, so just a few years after Rixford and Gilchrist named their new microbe, a physician also working in San Francisco named William Ophuls, who by the way had a scar on his cheek from a duel back in Germany-
Erin Allmann Updyke	Love it.
Erin Welsh	He later became the Dean of the Stanford School of Medicine.
Erin Allmann Updyke	Wow.
Erin Welsh	With a dueling scar on his cheek.
Erin Allmann Updyke	With a dueling scar.
Erin Welsh	So cool.
Erin Allmann Updyke	In 1900, okay.
Erin Welsh	In 1900. And so Ophuls was like, 'Wait a sec, this is not a protozoan, it's definitely a fungus, you guys. What's going on?'
Erin Allmann Updyke	(laughs)
Erin Welsh	And so he did a bunch more research on it, describing its life cycle, its various morphologies, its route of transmission, and proposing a name for the disease which he called coccidioidal granuloma. But this disease, coccidioidal granuloma, was often the more severe of the ones that you described, right?

Erin Allmann Updyke	Right.
Erin Welsh	So it was super painful, disfiguring, debilitating, sometimes fatal. And that makes sense that that would be the one described first.
Erin Allmann Updyke	Right and so that's a disseminated infection, so that's an infection that has gone to the skin and presumably also to other organs which would be why it would be fatal.
Erin Welsh	Right, exactly. But that's not the only form of disease that coccidioides causes.
Erin Allmann Updyke	No. And it certainly not the most common.
Erin Welsh	Right.
Erin Allmann Updyke	So? (laughs)
Erin Welsh	East of San Francisco, residents of the San Joaquin Valley were plagued by a mild illness which usually consisted of respiratory symptoms, a high white blood cell count, and sometimes those painful lumps or those red lumps, erythema nodosum.
Erin Allmann Updyke	Mm-hmm.
Erin Welsh	People called it San Joaquin Valley fever and no one could figure out what was causing it. A physician named Myrnie Ade Gifford had been working on the problem as part of her job as the Chief Assistant Health Officer of Kern County in California and she spent months trying to link it to Ascaris roundworms. But then she finally found Coccidioides from a guinea pig that had been experimentally infected from someone's sputum.
Erin Allmann Updyke	Gross.
Erin Welsh	Poor guinea pig.
Erin Allmann Updyke	I know.
Erin Welsh	And she knew that Coccidioides was the pathogen responsible for coccidioidal granuloma but the people she was seeing, like her patients were nowhere near that sick, like at all. So could there still be a connection or was this just contamination? She showed her research to her former teacher/mentor, Ernest Dickson, and asked him whether he thought the two diseases could be caused by the same thing. And then she added that several of the patients she had treated had also presented with erythema nodosum. And for Dickson, this was the clincher. A few years back, Dixon had a young med student working in his lab named Harold Chope who on day one of the job, poor guy, opened an old petri dish full of an old Coccidioides culture and then breathed in a bunch of the old spores.
Erin Allmann Updyke	Oh no!
Erin Welsh	So he brought it up to look at it closely, breathed on it, and all the spored went airborne right into his-
Erin Allmann Updyke	Of course. He poofed it and breathed it.

Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	Oh poor guy.
Erin Welsh	Oh yeah. Within 9 days, Chope was in the hospital with severe chest pain, a bad cough, yellowish sputum streaked with blood, and there didn't seem to be much of a chance that he would recover. And like a bunch of newspapers picked up the story and he was presented as this heroic young researcher martyred for the cause of disease, I don't know. But he hung in there.
Erin Allmann Updyke	Okay good.
Erin Welsh	Eventually he would be discharged from the hospital and sent somewhat ironically to Arizona to recuperate.
Erin Allmann Updyke	Oh gosh. (laughs)
Erin Welsh	(laughs) But before that happened, he developed erythema nodosum which si the same symptom that Gifford had observed in some of her patients with San Joaquin Valley fever. And to Dickson this was strong evidence that the two diseases, so San Joaquin Valley fever and coccidioidal granuloma were caused by the same pathogen and that the Valley fever was just a mild form, yeah.
Erin Allmann Updyke	Right, I mean it's almost like all of the times that we've had people who were reckless enough to intentionally infect themselves with whatever thing that they were studying to try and prove, but this poor kid just did it.
Erin Welsh	(laughs) Right. I mean in some ways, you know how in our Rocky Mountain spotted fever episode we talked about how everyone got Rocky Mountain spotted fever or one of the other tick-borne pathogens?
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	It's kind of the same thing. A bunch of people got infected who were researchers who worked on this, it was sort of like a rite of passage.
Erin Allmann Updyke	(laughs) I mean, it is very infectious, like one single spore and you can get infected. So it's not that surprising.
Erin Welsh	Yeah. It's not that surprising. And so Dickson was like, 'I've solved the puzzle.' And he presented this hypothesis at a meeting of the California Medical Association and he never once acknowledged that it was actually Gifford who had come up with the idea.
Erin Allmann Updyke	Ugh.
Erin Welsh	Yeah, which is really frustrating.
Erin Allmann Updyke	That is infuriating.
Erin Welsh	Eventually in the 1950s her contribution would be recognized but like still really annoying.

Erin Allmann Updyke	Yeah.
Erin Welsh	So now that researchers had a better picture of the disease caused by Coccidioides, they could start digging into questions like where does this happen? What animals does this happen to? How often does it happen? And so on. And these massive questions would almost all be taken up by another Dickson's students, so Gifford was one of Dickson's students, a guy named Charles Smith.
Erin Allmann Updyke	Okay.
Erin Welsh	Also Harold Chope's frat brother. This just perfectly illustrates how-
Erin Allmann Updyke	Incestuous?
Erin Welsh	You could say incestuous or how connected the world is. It's a small world if you have a very specific study organism, everyone knows everyone. And Smith spent the late 1930s wandering all over Kern and Tulare counties in a truck named The Flying Chlamydospore.
Erin Allmann Updyke	Nope.
Erin Welsh	Yep.
Erin Allmann Updyke	Don't call it that.
Erin Welsh	(laughs) A chlamydospore is a thick-walled, hyphal cell that functions as a spore. That's what I have in parentheses. I love it. And he was just looking for people who had developed erythema nodosum.
Erin Allmann Updyke	Okay.
Erin Welsh	He was like, 'Okay, I wanna know.' And he found what he was looking for because over 18 months he saw over 400 people who reacted to a skin test with coccidioidin. And this is in two counties in California, like I feel like that's kind of substantial.
Erin Allmann Updyke	Erin, I can't wait to tell you about the current events.
Erin Welsh	Oh I have a little bit of a taste of it, it's horrifying, yep. He found that a good chunk of the people who seemed to have been infected at one point were just asymptomatically infected and that the disease was much more prevalent than previously thought. And that people who were new to the area or, and I saw this in a lot of the early studies, weren't white, seemed to be more likely to develop severe disease. And I know that these studies were back from the early 1900s and so I don't know what their reasons were, but that's a very common thing that you see even in literature from today.
Erin Allmann Updyke	Yeah all of the literature from today still says the same thing and I agree, I don't know exactly what they're basing that on.
Erin Welsh	Right, right. So Charles Smith was also infamous for hating to wash glassware, like in the lab. He hated doing it. And so that is how through a series of serendipitous accidents, I don't know, involving dirty Wasserman tubes, he developed a complement fixation test for the disease.
Erin Allmann Updyke	(laughs) Like accidentally figured out.

Erin Welsh	Accidentally. He like left 'em on the counter, he was like, 'I'll wash 'em later, I'll wash 'em later.' And then they formed these little like buttons that he was like, oh that can be... Anyway, this was a huge step forward though, this complement fixation test, because it became the standardized way to test for exposure to the disease and it allowed for these large scale prevalence studies without the need for growing the fungus in lab animals. Why was so much focus place don coccidioidomycosis? Cause it kind of seems like it was. I mean yes, it could absolutely be deadly and debilitating but there were also so many other diseases that were in constant circulation, like this is still pre-antibiotic and pre most vaccines.
Erin Allmann Updyke	Right.
Erin Welsh	But coccidioidomycosis did pose a big threat to California's rapidly growing population. Why was it growing? The Dust Bowl.
Erin Allmann Updyke	The Dust Bowl.
Erin Welsh	Throughout the 19302, tens of thousands of families picked up from their eroded and parched farms in the prairies and headed to California. And this enormous influx of people meant a whole new bunch of susceptibles for Coccidioides. And so the disease became much more visible.
Erin Allmann Updyke	Mm-hmm, that makes sense.
Erin Welsh	And so Erin, sidenote, I still really wanna do an episode on the Dust Bowl.
Erin Allmann Updyke	I know. (laughs)
Erin Welsh	Can we do it? And if you, listeners, can't wait until that episode comes out, go read 'The Worst Hard Time' because that's an amazing book. Okay so if the Dust Bowl was indirectly responsible for coccidioidomycosis becoming more visible and fueling more research in the 1930s than in the 1940s, that role would go to WWII. As the U.S. got ready to enter the war, a bunch of airfields were established for training purposes and what better place than the southwestern U. S.? Smith, so like Charles Smith from before, took this opportunity to set up a prospective epidemiological study where he began skin testing all of the newly arrived personnel to these airfields.
Erin Allmann Updyke	Uh oh.
Erin Welsh	He made notes of how living conditions impacted disease risk, like tents. And even though on Smith's recommendation the airfields implemented dust control strategies, there was still plenty of coccidioidomycosis cases for Smith to make a detailed study on all the ways the disease could manifest, the incubation period, the timeline of disease, and so on. And what this and other research conducted during this time ended up showing was that this disease was essentially endemic in a good chunk of the southwestern United States. And the other thing that the 1940s would do was to firmly establish Coccidioides as a pathogen of incarcerated populations.
Erin Allmann Updyke	Oh yeah.

Erin Welsh	Oh yeah. During WWII, specifically between the years of 1942 and 1945, the United States set up concentration camps previously known as internment camps in the western states and other places as well for the forceful relocation and incarceration of around 120,000 people of Japanese ancestry. 62% od whom were U.S. citizens, actually. At least one of these camps which had a population of 13,000 was located on the Gila River in southern Arizona, which was a hotspot for coccidioidomycosis. And the high prevalence of this disease was known before the camp was established, of course, and so no one was too surprised when cases began popping up at the camp or nearby at the prisoner of war camp where German prisoners were being held. And I didn't see any solid numbers for infection rates or like total number of cases at these concentration camps, but I did see that at the prisoner of war camp where Charles Smith visited I think at least once, he estimated that between 2/3 to 3/4 of new arrivals would become infected within one year of arriving.
Erin Allmann Updyke	Oh my god.
Erin Welsh	Based on living conditions and just the super high endemicity of the pathogen. And there do seem to have been some deaths at that camp.
Erin Allmann Updyke	Mm-hmm.
Erin Welsh	And Erin, I'm sure you're gonna talk a whole lot more about how coccidioidomycosis is still super prevalent at prisons and maybe about some of the ethics of intentionally building or maintaining prison facilities where infection is a certainty.
Erin Allmann Updyke	Oh, there's so much there, Erin.
Erin Welsh	Oh boy. But yeah. But at the time that these concentration camps and other prisons were first being built, there weren't any effective treatments for the disease and no vaccines. And I know that treatment is still more art than science even today. But the big increase in cases during WWII in endemic areas allowed Smith and other researchers to notice that infection with the fungus did seem to protect you from getting it again, which then spurred on some vaccine work. And alongside this vaccine research which ultimately did seem to produce a vaccine - I read a paper that was like, 'Oh and then they all injected themselves with this vaccine and it seemed to work.'
Erin Allmann Updyke	Oh.
Erin Welsh	I don't know. 1950s and then it was sort of dropped.
Erin Allmann Updyke	1950s. (laughs)
Erin Welsh	But it seems like this vaccine research was being done at the same time that the U.S. was looking into this as a potential bioweapon. Not to weaponize it but to see how feasible it was for other people to weaponize. And also like how worried should we be about this? Should we make a vaccine just in case? Etc. And then finally treatment emerged in the 1960s in the form of amphotericin B, like we talked about in our organ transplant episode, and since that one can be a bit toxic, later development of antifungal azoles was kind of a relief. And I say 'kind of' because yeah, all the problems you talked about. And then the next time we really saw like a huge increase in interest in coccidioidomycosis was of course during the AIDS pandemic in the 1980s where that seemed to be suddenly this fungus that was like oh generally it causes mild infection, became like an absolute killer disease.
Erin Allmann Updyke	Yep.

Erin Welsh	So it's been about 130 years since this pathogen and the disease that it causes was first described and we've learned quite a lot since that time about its ecology, its epidemiology, disease course treatments, etc etc. But there's still quite a bit that we're trying to figure out and it's becoming more and more of a pressing issue with the steadily growing number of cases, climate change, expansion into new areas, disproportionately high rates in incarcerated populations. So Erin.
Erin Allmann Updyke	Oh, here we go!
Erin Welsh	Tell me where do we stand with coccidioidomycosis today and what are we doing about it?
Erin Allmann Updyke	Ooh, I can't wait to tell you about it. Let's take a quick break first.
Erin Welsh	Excellent.
TPWKY	(transition theme)
Erin Allmann Updyke	All right. I should say really quick in case I didn't say it clearly in the biology section, since you mentioned how we still don't really have perfect treatment, it's especially true for people who don't have a lot of risk factors for a disseminated or severe disease. People who we know are high risk who have certain chronic diseases etc are definitely gonna need to be on treatment possibly for their entire rest of their life. And that we do know.
Erin Welsh	Yeah.
Erin Allmann Updyke	But it's the kind of lower risk people that it's a little bit tricky. So I'm really excited to get into some of these details, Erin. Unsurprisingly and as always on this podcast, the number of reported cases greatly underestimates the actual number of cases. But let's talk at least briefly about what those reported cases are and then I wanna do something that I haven't done in a long time, which is math. (laughs)
Erin Welsh	Ooh! (laughs)
Erin Allmann Updyke	To kind of just emphasize why it is that we know how underreported this disease is. Okay.
Erin Welsh	Sounds great, I'm excited.
Erin Allmann Updyke	Me too, it was really fun and it took me way too long to do this math. (laughs)
Erin Welsh	(laughs)
Erin Allmann Updyke	So like you said, the number of cases has been steadily increasing and while there's a thought that maybe this is just better recognition, the data actually doesn't support that. So this is definitely increases in cases, not just increasing in reporting. So in 2011 was actually the greatest number of reported cases in the U.S. and I'll just say up front, I really only have data for the U.S., that's where this is like more well reported and where cases seem to be the highest in the world. So in 2011 there were 22,641 cases reported. The vast majority of those are in California and Arizona but several other states as well. And then in 2018, so the most recent year that I could find data for, there were 15,611 cases reported.

Erin Welsh	That's a lot of cases.
Erin Allmann Updyke	That's a lot but your like, 15,000 is not. The real number is probably 150,000 or more.
Erin Welsh	So it's like literally an order of magnitude.
Erin Allmann Updyke	An order of magnitude. And let's talk about why, cause it gets fun.
Erin Welsh	Ooh.
Erin Allmann Updyke	There have been a number of studies that have tried to estimate how much of the share of community-acquired pneumonia is accounted for by coccidioidomycosis. And they've done this in a number of different ways and what they have found is that in endemic areas, especially in Arizona and parts of the Central Valley of California, coccidioidomycosis accounts for up to 30% of all community-acquired pneumonia.
Erin Welsh	30%?
Erin Allmann Updyke	Okay, so sidebar, pneumonia is very, very common.
Erin Welsh	Yeah.
Erin Allmann Updyke	There's a lot of different types of pneumonia and we often differentiate them by saying is this a community-acquired pneumonia, like did you get this in your normal, everyday life in the quote "community"? Or is this a hospital-acquired pneumonia, like you were in a healthcare facility and that's how you got it? The reason that we do that is partly because hospitals don't like it when you get sick inside of them, but also because it tends to be different organisms that are more likely to cause a community-acquired vs a hospital-acquired pneumonia. So it can help clinicians to decide how to treat this pneumonia.
Erin Welsh	Uh huh, uh huh.
Erin Allmann Updyke	But there are a lot of different potential causes. There's viral pneumonias that don't need any antibiotics, there are bacterial pneumonias, a lot of different types of bacteria, and then there are these fungal pneumonias. I'm getting excited. But overall, pneumonia as a blanket diagnosis is one of the leading infectious causes of hospitalization and death for adults in the United States.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	It's the second-leading cause of hospitalizations, period, among adults in the U.S. And there are like 4.5 million doctors visits annually for community-acquired pneumonia.
Erin Welsh	This is what's so interesting because coccidioidomycosis is not contagious.
Erin Allmann Updyke	Right.
Erin Welsh	And so these are all individual exposures, not like someone standing next to someone on a bus and then coughing and whatever.

Erin Allmann Updyke	Yeah. Right, exactly.
Erin Welsh	Wow. And 30%. That's wild.
Erin Allmann Updyke	30%. And community-acquired pneumonia is estimated to cause between like 23-27, so let's split the difference and call it 25 cases per 10,000 adults every year that require hospitalization. So that's just the ones that are bad enough that someone ends up in the hospital.
Erin Welsh	Yeah. That's a lot.
Erin Allmann Updyke	That's a lot. So if we backup to knowing that coccidioidomycosis, 30% of all of these community-acquired pneumonia cases are going to be caused potentially by coccidioidomycosis. And estimates range across its geographic range from like 17-30%, so if we again split the difference, we can do some math here.
Erin Welsh	(laughs)
Erin Allmann Updyke	And we can say, okay, if there's 25 cases per 10,000 adults per year that require hospitalization and there's 39 million people in California, not all of them may be in super endemic regions but whatever, it's Erin's math. And let's say only 20% of those cases are actually caused by coccidioidomycosis, that's almost 100,000 cases of pneumonia requiring hospitalization every year in California caused by coccidioidomycosis.
Erin Welsh	That's requiring hospitalization, that's a lot.
Erin Allmann Updyke	Right. That's a lot!
Erin Welsh	Yeah.
Erin Allmann Updyke	So that is how we can get to these estimates of what is the true burden likely. And so now the question is if we know that 30% of these cases, or you know, 17-30% of these cases are caused by Coccidioides, but only 15,000 are reported, why do we still have such a big discrepancy? And it turns out because in the cases where they've looked into this, we find that oftentimes anywhere from 15-30%, often less than 15% of the time do we actually test someone with a community-acquired pneumonia for the pathogen.
Erin Welsh	Is that just because like in general if you're looking at the U.S., it's most likely to be these other pathogens and so you just either give someone some sort of antibiotics or be like, oh it's viral or whatever. And it's just like faster? Like does it cost a lot of money to test? Is it a lot of resources? What's the argument against testing I guess is what I'm trying to figure out.
Erin Allmann Updyke	So you're asking a lot of good questions and the answer is it's all of those things and then some. So part of it is certainly if you live in New York State, are you gonna test everyone with pneumonia for coccidioidomycosis? No, that would be completely not indicated.
Erin Welsh	Right.

Erin Allmann Updyke	But even in places, like they've done studies in California and Arizona where this is highly endemic and they found that less than 15% of all community-acquired pneumonia cases have an identified pathogen detected. Part of it is that it is very difficult to be able to get the proper samples that you need to be able to do this test isn't always easy. But also if someone is coming in and isn't all that sick, you take a look at their X-ray and you know they're not going to be hospitalized, they're just going to be treated kind of as an outpatient, then a lot of times you won't do a ton of testing because you'll say, 'This is most likely what it is, if you don't get better, then come back.'
Erin Welsh	Right, right, that makes sense.
Erin Allmann Updyke	It's a lot. And that why we do distinguish at least between is this hospital-acquired or community-acquired, like we're trying to narrow down what is the most likely pathogen that's causing this and how are we going to treat it.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	Yeah so it's very interesting when you think about that and then you think of how many people might've had this infection, went to the doctor, got antibiotics, took them, got better. The antibiotics didn't make them better but most of these cases resolve on their own without any treatment. So that's kind of how we get to those numbers. But like you already touched on Erin and since this is TPWKY, you'll also be unsurprised, listeners, to know just how huge the disparities are in who gets infected probably and who gets diagnosed and who gets treated.
	So we've already mentioned a number of different groups that are at risk, like people who are immunocompromised in some way or another, people who are pregnant have a much higher risk of having disseminated disease, and like you mentioned, Erin, it's been shown and a lot of the literature states that African- Americans and people of Filipino descent tend to be more at risk for disseminated disease, so that severe manifestation of disease. But a lot of the studies that showed this that are cited in more recent literature were done in like the 1940s. And I'm not sure what the kind of explanation would be. If we think about people during the Dust Bowl time coming in, because one thing that we have seen in places like Arizona today, where Arizona has a large elderly population of people who came from somewhere else in the country and moved to Arizona when they were older so they never had any exposures.
Erin Welsh	Yeah.
Erin Allmann Updyke	Those people seem to be at higher risk for infection. So is that what was driving these studies early on? I really don't know but I do think that we really need to ask ourselves as a community of people researching and writing papers about coccidioidomycosis is how much of this disparity is true today and how much of it is due to differences in healthcare access among vulnerable or marginalized populations or among healthcare providers and adequate diagnosis and treatment and all of that. So I don't know the full answer to that. So definitely exposure and certainly people who work in certain situations that put them in close contact with soil are at much higher risk of contracting disease like agricultural workers, construction workers, people who work in the soil or have contact with the soil. But the other place this is a massive issue Erin, that you mentioned, is for incarcerated individuals. California's Central Valley which is Coccidioides territory, is home to a lot of prisons.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	The incarcerated population of California from 1980-2000 increased eightfold. And so what you're saying, Erin, is like we already knew this was a problem back in the 1940s.

Erin Welsh	I mean we've known that for decades. For almost 100 years.
Erin Allmann Updyke	Right. But then they were like, 'Let's build a bunch of prisons right on top of all this.' 89% of people who are incarcerated in these prisons in the Central Valley are brought from non-endemic areas of California.
Erin Welsh	Yeah.
Erin Allmann Updyke	Which means that they have not previously been exposed, potentially.
Erin Welsh	Ugh, yeah.
Erin Allmann Updyke	So in the last several decades there have been quite a number of outbreaks in prisons that have resulted in a large number of deaths and in fact continue to result in deaths annually. And there's a few papers that say, 'We've tried this type of medical restriction where if you have these certain diseases then you can't be put in prisons in this particular area.' But it turns out there've also been studies from the CDC that show that that really doesn't actually work to reduce exposure or cases. So there's another program to try and risk stratify people using skin testing where if they've never been exposed to Coccidioides and don't have a positive skin test, then they can't go to certain prisons. But that was a small study and I'm not sure that any of that has actually been implemented yet today.
Erin Welsh	It's an interesting approach because it seems like another solution would be to not have prisons there... I mean the whole prison system, that's a whole other aspect but like-
Erin Allmann Updyke	I was gonna say the problems with the prison system are not something we're gonna get into right now. (laughs)
Erin Welsh	(laughs) It's like scales and scales and scales of different levels of this.
Erin Allmann Updyke	Exactly. Honestly Erin, that's still a thing, so.
Erin Welsh	It's doesn't... Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	Yep. And so we've kind of covered a lot of sort of frontiers on things we need to do a better job of, right, diagnosing, deciding who and when and how to treat the problem of all of the prisons in the Central Valley. But also let us not forget that this is an environmental pathogen so what about climate change?
Erin Welsh	It's not good.
Erin Allmann Updyke	It's not great. There have been a number of recent studies that have modeled what the environmental risk factors are fro infection which is awesome, and unsurprisingly it seems very related to rainfalls. So larger rainfalls, heavier rainfalls in the winter followed by drier summers results in what they called in these papers "a grow and blow phenomenon".

Erin Welsh	Okay.
Erin Allmann Updyke	Where a lot of the fungi can grow and exist in the environment during that wet winter and then they get dried out in the dry summer and then you get increases in infection because of the dry soil blowing in the air.
Erin Welsh	You're basically recreating Harold Chope's old dried out petri dish.
Erin Allmann Updyke	(laughs) Yeah. Exactly. And so this sort of climate modeling has been shown to be in line with retrospective data on where we see cases, and so these match up really well both in Arizona and in California. So now the kind of question going forward will be can we use this knowledge to try and predict out to the future when we might have like a bad year for Coccidioides infection, something like that.
Erin Welsh	Yeah.
Erin Allmann Updyke	But that still doesn't answer the question of climate change specifically. And so one thing that I wanted to mention that I think is really important in thinking about this is that we've seen in the last decade or so a number of cases pop up in areas that aren't generally considered endemic like Washington state which has had also a steady increase in the number of confirmed endemic cases of coccidioidomycosis.
Erin Welsh	Where in Washington state?
Erin Allmann Updyke	Oh good question, I don't actually know what county it was in Washington state. But even in 2017, it was still only 12 cases. But they have identified that those cases were endemic, they weren't from travel. So we don't have a truly great handle on what the distribution of this fungus is worldwide to begin with but we know that climate change is very likely to have some effect. But since we don't exactly know where it is, it's hard to say exactly what that's going to do, if that makes sense.
Erin Welsh	Yeah, totally.
Erin Allmann Updyke	But yeah so there's a lot of room for research here.
Erin Welsh	Oh yes. It's an open petri dish.
Erin Allmann Updyke	(laughs) Just don't breathe it in.
Erin Welsh	Just don't breathe it in. (laughs)
Erin Allmann Updyke	So yeah, that's coccidioidomycosis. Sources?
Erin Welsh	Sources. Okay I wanna shout out a paper by Deresinski and Mirels, 'Coccidioidomycosis: What a long strange trip it’s been', definitely wins my favorite title I think. That was a very useful paper, as was a book from 1980 by David Stevens called 'Coccidioidomycosis: A Text.' And I have a bunch more that I will put on the website.
Erin Allmann Updyke	I also have quite a number of papers, many of which are just titled 'Coccidioidomycosis' which I found hilarious.

Erin Welsh	(laughs) Straight to the point.
Erin Allmann Updyke	Straight to the point, no messing around. You can find our list of sources from this episode and every single one of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab.
Erin Welsh	Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	And thank you to the Exactly Right network of whom we're very proud to be a part.
Erin Welsh	And thanks again Tori so much for sharing your story with us, we really appreciate it.
Erin Allmann Updyke	Yeah. And thank you to you listeners for listening to this podcast. We hope you enjoyed this one, I feel like maybe some people might not have ever heard of it so hopefully this was a fun new one for people.
Erin Welsh	Yeah it's kind of niche but then it's like also really interesting.
Erin Allmann Updyke	Yeah.
Erin Welsh	I don't know, I had a lot more fun than I thought I was gonna have in the research to be honest.
Erin Allmann Updyke	(laughs) Me too. I feel like we put this one off for a while and I'm glad that we did it.
Erin Welsh	Yeah! It was a good one. Okay well, until next time, wash your hands.
Erin Allmann Updyke	You filthy animals!