Libby	On a Saturday in the late summer of 2018, I went to visit two of my best friends to have dinner and play with their little ones who were about two and four years old at the time. My friend is a teacher and had recently gone back to school in preparation for the coming fall semester, so her kids had just started going back to daycare after a summer home with mom. My friends told me that there had been an outbreak of hand, foot, and mouth disease at their day care and both of the little ones had gotten sick. They said it was super contagious for kids but not to worry is it doesn't really affect adults. I saw a couple of little red bumps near their ankles but thought nothing of playing with the tots or kissing them goodnight as usual.
	The following Wednesday around 2am, I sat straight up in bed shaking with violent chills and experiencing what might have been the worst sore throat of my life. I checked my tempt and had a fever around a 102. So I loaded myself with NyQuil and stayed home sick from work for the next two days. By that Friday, I was starting to feel a little better and I returned to work. But that day the blisters started. They were mostly painless, just empty bubbles of skin on my hands and feet that would rise to the surface and then tear off in chunks. At that point I was pretty sure that I had a case of hand, foot, and mouth. Remembering that the disease was very contagious for kids, I did my best to be conscientious and avoid my coworkers with children at home at the team meeting that morning. As the days went by, my sore throat eased and I was feeling like my normal self but the bubbly blisters on the palms of my hands and soles of my feet kept coming.
	A little after a month after initially feeling sick, I shared a kombucha with my mom, really thinking nothing of it as I had felt fine for weeks at that point. Three days later however she was hit with a terrible sore throat and fever and then blisters. I had given her hand, foot, and mouth five whole weeks after I first got sick, I was shocked. So I did a quick google and discovered that once infected a person can be contagious for up to 11 weeks. That's almost three months, a fiscal quarter. I was floored.
	And after that I got serious about making sure I didn't get anyone else sick. I remember putting a reminder in my phone for a date in late October that would have been around 11 weeks after my initial infection. And in the meantime I was not going to be swapping spit with anyone. I went to the lake with my girlfriends around then and I vividly remember that I had taken a piece of duct tape and covered the label of a jar of salsa and scrawled the word INFECTED on it in sharpie so that I could double dip safely.
	One of my girlfriends remarked that she felt like if she didn't catch hand, foot, and mouth from me then we must not be that good of friends. But thankfully I didn't get anyone else sick. The blisters did stop around that 11 week mark and the course of disease was pretty similar for my mom. I think most people, especially parents, are at least vaguely aware of the disease but I hope that more people come to realize that adults can get sick too. And I also hope that more people become aware of just how long an infected person remains contagious.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	That sounds awful.
Erin Welsh	I know about hand, foot, and mouth because I have a lot of friends who have had it or their kids have had it. But I guess I just didn't really, it never really registered how long it can last and how long you're infectious.
Erin Allmann Updyke	Yeah. Yeah.

Erin Welsh	Also how awful it is to just have your skin sloughing off.
Erin Allmann Updyke	It doesn't sound fun, let's say that.
Erin Welsh	That is the understatement of the century for sure.
Erin Allmann Updyke	Thank you so much, Libby, for being willing to share that story with us.
Erin Welsh	Yes. Yeah. Sorry you had to relive it on the podcast but we all appreciate it. 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 hand, foot, and mouth.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	And we've gotten so many requests for this one.
Erin Allmann Updyke	I mean it is so common.
Erin Welsh	It is. And I don't think I even realized how common it was. Do you know if you had it as a kid?
Erin Allmann Updyke	I was thinking about asking my mom because I have no recollection of it.
Erin Welsh	Yeah. I'm the same. No idea.
Erin Allmann Updyke	Mom?
Erin Welsh	Mom.
Erin Allmann Updyke	Can you text me? Let me know.
Erin Welsh	Text us. Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	But it seems like it's everywhere and maybe it's just like because that's the age that we're at where you just hear about...
Erin Allmann Updyke	Everyone's toddlers bringing it home from daycare.
Erin Welsh	Exactly.

Erin Allmann Updyke	Yeah.
Erin Welsh	But there's a lot to unpack about this episode. I'm excited to dive in.
Erin Allmann Updyke	Me too.
Erin Welsh	But first-
Erin Allmann Updyke	It's quarantini time.
Erin Welsh	It is. What are we drinking this week?
Erin Allmann Updyke	We're drinking Out of the Mouths of Babes. Get it?
Erin Welsh	I do get it.
Erin Allmann Updyke	Yeah, you get it. If you don't listeners, it's because it can be transmitted by respiratory droplets and it's mostly little kids. Okay? Erin, what is in Out of the Mouths of Babes?
Erin Welsh	I didn't expect this one to crack me up as much as it did, like we were talking about it all day. Why is it so funny now?
Erin Allmann Updyke	You know, because it's the moment.
Erin Welsh	It is. It's a pretty delicious drink. It is gin and cherry juice and some lime juice and some tonic water.
Erin Allmann Updyke	So refreshing.
Erin Welsh	Yeah.
Erin Allmann Updyke	We'll post the full recipe for that quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com and our social media. Do you follow us there? You should follow us there.
Erin Welsh	You should follow us there. On our website thispodcastwillkillyou.com... Must I go through the spiel? There's lots of good stuff. There's transcripts and there's bookshop.org and our Goodreads list and merch and music by Bloodmobile and resources or the citations for all of our episodes. What do I normally say? References? You know, there's lots of stuff there. Check it out. It's a great time.
Erin Allmann Updyke	It is. It is. Well with that, shall we get into the biology of this disease?
Erin Welsh	Let's do it. Short and sweet intro, I'm loving it. Let's dive in right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	Hand, foot, and mouth disease, not to be confused with hoof and mouth or foot and mouth, which is something different that affects animals.

Erin Welsh	The naming is confusing.
Erin Allmann Updyke	Yeah. I don't know, I didn't do it. But anyways, hand, foot, and mouth disease is an extremely common viral infection of humans. It's caused by any one of a number of different viruses in the group enterovirus, which I think the only other enterovirus that we've covered so far is poliovirus, if I'm remembering correctly.
Erin Welsh	I think that's right.
Erin Allmann Updyke	Yeah. So as usual viruses are going to get a little confusing in this episode but we'll do our best. So enteroviruses are a group of single stranded non enveloped RNA viruses that are all in the family Picornaviridae. And this includes a lot of different serotypes and subtypes of enteroviruses. And by a lot, I mean over 90 or over 100. And a lot of these are viruses that people have probably heard of because they cause disease in humans. These include coxsackieviruses, polioviruses, enteroviruses, echoviruses. And enteroviruses actually also include rhinoviruses, like the cause of common colds.
Erin Welsh	I learned about that. But also what's an echovirus? Because I kept seeing that and I was like this must be of public health importance in some regard but I just don't know what.
Erin Allmann Updyke	Echoviruses cause other viral illnesses. That's all I've got.
Erin Welsh	Causes illnesses.
Erin Allmann Updyke	Yeah. There's like a whole bunch of different types of illnesses that all of these enteroviruses can cause, including echovirus and one's called parechoviruses as well. There's a whole bunch.
Erin Welsh	Too much.
Erin Allmann Updyke	It's too much. And the organization and like subtyping system has changed in recent years. So now all of the human enteroviruses in the genus Enterovirus are four major species, A through D. Within each of these A through D, there are a bunch of different stereotypes that used to be always called say Coxsackievirus A1, 2, 3, 4, 5, blah, blah, blah, blah, blah. And Coxsackievirus B, blah, blah, blah. They used to have a bunch of different names and now they've all been grouped within these A through D species.
Erin Welsh	Yeah, that was interesting.
Erin Allmann Updyke	Yeah.
Erin Welsh	Because when I was looking at old papers and then new papers and I was just trying to reconcile like what are they talking about?
Erin Allmann Updyke	I know.
Erin Welsh	How are these things related? You know, it's hard.
Erin Allmann Updyke	Well the good news is that we don't have to talk about every single enterovirus in the world today.
Erin Welsh	Wonderful. Wonderful.

Erin Allmann Updyke	Hand, foot, and mouth is most commonly caused by a few of these human enteroviruses, specifically ones in enterovirus group A. These ones have names, coxsackievirus A16 and human enterovirus 71. Although there are a few others as well, including coxsackievirus A6, which we'll talk about, and A10, A8, and a few others. All of these that cause hand, foot, and mouth tend to be in this enterovirus group A species.
Erin Welsh	But there are B group species that cause, or coxsackie group B that cause hand, foot, and mouth occasionally? Saw some papers.
Erin Allmann Updyke	Probably, yes.
Erin Welsh	Okay. soft.
Erin Allmann Updyke	Not to an extent that I'm going to talk about them in any great detail. But as we'll see, what hand, foot, and mouth disease really is kind of a presentation of a generalized viral illness. And so that's why you can have a variety of different virus subtypes, call them subspecies, call them stereotypes, what have you, that are all slightly different. Some of them are more virulent than others, so they might have a tendency to cause more severe disease. Some of them might be less virulent than others, so cause a less severe disease. But overall there is a group of these viruses that cause very similar signs and symptoms and that group of signs and symptoms is what we call hand, foot, and mouth disease. Does that makes sense?
Erin Welsh	Yeah, it's interesting because I think that a lot of the time we think about one disease, one pathogen, but we've also covered many that don't follow that rule.
Erin Allmann Updyke	Right.
Erin Welsh	And for some reason I feel like this hand, foot, and mouth in particular, because there's such variation in those signs and symptoms associated with different viruses, that I was like why are we calling this all the same thing?
Erin Allmann Updyke	I think that that's a really valid point honestly. Like how we define these different viruses to begin with and then how we define the clinical syndrome that we call a disease. It's really interesting to think about which came first.
Erin Welsh	Yeah.
Erin Allmann Updyke	And maybe you'll tell us, Erin.
Erin Welsh	Will I?
Erin Allmann Updyke	And also how we make those distinctions. I think it's really valid. Today I'm going to focus on coxsackievirus A16, enterovirus 71, and a little bit about coxsackievirus A6 because those are the three that I found the most information about, as we'll see. But first, let's keep it a little bit more general, shall we?
Erin Welsh	Love that.

Erin Allmann Updyke	Enteroviruses as a group are transmitted in a number of different ways. Think back to our poliovirus episode. Poliovirus by the way is enterovirus group COVID, so not very closely related to all these A group enteroviruses but kind of closely related. So enteroviruses are transmitted by direct contact with things containing the virus, like secretions. The blisters that we'll get to talking about with hand, foot, and mouth disease are full of virus, so direct contact with these blisters or that fluid can transmit the disease. Respiratory droplets are a huge source of transmission for a lot of different enteroviruses, including those that cause hand, foot, and mouth. And importantly fecal-oral, as with poliovirus. And this is especially an important way of transmission for kids and between family groups. And because enteroviruses are really hardy little viruses, environmentally stable, they can also be transmitted via fomites, so infected surfaces as well.
Erin Welsh	I mean they're hardy little beasts, you have to admire them. But you can also be horrified by them too.
Erin Allmann Updyke	Yeah, of course.
Erin Welsh	How long are we talking?
Erin Allmann Updyke	I knew you were going to ask that I have like star, star, star, how long? I don't know as usual but I can tell you these are very environmentally stable viruses. They can be recovered from water sources including ocean water. Hi, did my masters on some of that. They're resistant to freezing, they're resistant to most alcohol-based hand sanitizers that we use, they're resistant to a lot of cleansers. Yep.
Erin Welsh	They are the 0.1%?
Erin Allmann Updyke	Exactly.
Erin Welsh	No!
Erin Allmann Updyke	Because they're non enveloped viruses.
Erin Welsh	Yeah.
Erin Allmann Updyke	They have evolved to withstand the acidity of our stomach and be transmitted fecal-oral. So they are very hardy. Yeah, it's great. The incubation period, so the time between when you get exposed to when symptoms develop for most enteroviruses, including the ones that cause hand, foot, and mouth disease, is generally between 3-5 days. And as we'll see and as you heard in our firsthand account, the whole course of hand, foot, and mouth disease usually lasts between a week and 10 days. But you can continue shedding virus, especially in your stool but also even in your like throat secretions, so in your saliva, for weeks at a time. It's gnarly. And these are incredibly contagious viruses. So if we look at studies that have tried to estimate the R0 which listeners likely remember is the reproductive number, the average number of new cases that become infected by a single index case, like how many people get sick from one sick person. The estimates range between two and five which varies by virus subtype but anything over one means you have like exponential growth and outbreak potential.
Erin Welsh	And these studies, did they look like within different populations? Because I would imagine daycares would be on the higher end of that.

Erin Allmann Updyke	Exactly. So these vary based on population, they vary based on virus subtypes. So for enterovirus 71 it's estimated usually closer to 5. And then for coxsackievirus A16, it's like an average of 2.5 or so. So yes. And then also if you look specifically in like household transmission, in some studies household transmission is like 52% of households are going to get infected and other studies as high as 85%, especially for kids under 6. So it's incredibly infectious, really easy to spread around. But what actually are the symptoms? Like what is hand, foot and mouth disease? For the most part, hand, foot, and mouth disease is considered a relatively benign self limited disease. As we heard in our firsthand account, that doesn't mean it's not miserable to have but it does tend to be self limited and not very severe. However I am going to get into some of what the potential complications are because it's always important to talk about these complications because they're real and they do exist, even when they're incredibly rare. And because it's also fascinating from a virology perspective how something can cause such a mild illness and such a severe illness with the same virus.
Erin Welsh	Yeah.
Erin Allmann Updyke	So I don't want to fearmonger too much in this episode because the whole group of enteroviruses, we're talking about over 90 different viruses, a lot of them have the potential to cause severe disease but the vast majority of cases of what we call hand, foot, and mouth are relatively low virulence pathogens or for whatever reason are causing self limited disease in the vast majority of people that they infect. In fact many people who become infected are asymptomatic entirely and are just happily shedding virus to everyone else without getting sick at all.
Erin Welsh	Do we know what proportion of those are asymptomatic?
Erin Allmann Updyke	It's a great question. It does depend a lot on the virus and also what age group we're talking about, much more common in adults to be asymptomatic compared to kids. Estimates range between 10%-70% of people become symptomatic, which is like a huge range. But for example with poliovirus, about 75% of people are asymptomatic and only 25% of people show symptoms of polio. So it's likely on the low end of people who show any symptoms whatsoever after exposure.
Erin Welsh	Okay. I have a couple of like immunity questions and infectiousness questions. Should I hold those til the end?
Erin Allmann Updyke	You can ask them now if you like, before we get into the symptoms.
Erin Welsh	Okay. About the infectiousness, you said that you can shed virus for weeks and weeks after first showing symptoms. Are you infectious only once you start showing symptoms?
Erin Allmann Updyke	Great question. I believe like with many enteroviruses, you can potentially shed virus before you realize that you're symptomatic, say before your fever starts, spoilers.
Erin Welsh	And then I think this actually is really sort of jumping ahead.
Erin Allmann Updyke	Okay.
Erin Welsh	But in terms of reinfection or immunity, is there any sort of cross serotype or cross species immunity? And I guess maybe not enough because there's no vaccine, spoilers. I don't know.

Erin Allmann Updyke	A few spoilers, jumping ahead just a little. But in general because we are talking about a whole bunch of different viruses, you can certainly get infected and have hand, foot, and mouth disease multiple times in your life. Yay, woohoo. But it's very likely that there is some degree of cross protection among different say coxsackievirus strains and numbered enterovirus strains. Because adults are much less likely to have symptomatic hand, foot, and mouth disease and it's thought that that's very likely due to previous exposure, the most susceptible people for hand, foot, and mouth disease, both severe disease and just symptomatic disease in general, are little kids especially under age 5, especially under age 2 really. So yeah.
Erin Welsh	Okay.
Erin Allmann Updyke	But so there's likely some degree but certainly not enough that we have the potential for one vaccine for all of it.
Erin Welsh	Right. And also like the fact that these are RNA viruses that-
Erin Allmann Updyke	Right, mutate.
Erin Welsh	Yeah. They're just mutation happy and yeah.
Erin Allmann Updyke	Yeah, it's fun.
Erin Welsh	Good stuff.
Erin Allmann Updyke	Okay, so let's talk about what this looks like, shall we?
Erin Welsh	Yeah. Finally there.
Erin Allmann Updyke	So most cases of hand, foot, and mouth happen in little kids, that's the stereotype for a reason. Mostly kids under age 5. And so this illness starts as many childhood illnesses do and that is with a fever. Likely this goes hand in hand with some general malaise. The kid is probably feeling pretty crappy and they probably have a sore throat. They're probably eating or drinking a lot less than usual because of that sore throat. And because we're talking about little kids, a lot of these kids are pre-verbal, they might not be able to tell you that something is wrong. So that eating and drinking a little bit less and maybe being crankier than usual might be the first signs that something is wrong, since they can't tell you my throat hurts. Then it'll start with the rash. And this rash happens in three major places, the hands, the feet, and the butt.
Erin Welsh	I knew you were gonna say that actually.
Erin Allmann Updyke	Yeah. A lot of people call this hand, foot, mouth, and butt disease.
Erin Welsh	Can we like shorten the disease name somehow please? I think we need to keep adding body parts to it. and fingernail disease because it's part of the hand. But yeah.
Erin Allmann Updyke	But those are the main places where we tend to see this rash. It can be across the whole arms and legs, it can go on to the genitals as well. One thing that's interesting and kind of specific about hand, foot, and mouth is that on the hands and feet, this rash is often found on the palms and soles specifically. This is a place that not a lot of other viruses or pathogens cause a rash. And I know you're gonna ask because you've asked in previous episodes and no, I still don't know why.

Erin Welsh	What are the other ones? I was hoping you weren't going to quiz me because I don't know.
Erin Allmann Updyke	Syphilis can.
Erin Welsh	Okay.
Erin Allmann Updyke	I think that's probably one of the main ones that we've covered on this podcast. Rickettsia or Rocky Mountain Spotted Fever.
Erin Welsh	Right, yeah.
Erin Allmann Updyke	Rat-bite fever can, we haven't done that. There's a number of other pathogens but it's kind of a relatively short list.
Erin Welsh	Okay.
Erin Allmann Updyke	So it makes people who are trying to figure out what's going on clue in that oh this might be hand, foot, and mouth disease. The rash itself usually starts as little red spots, flat, little red spots that progress into blisters that are filled with fluid. And again, this fluid is full of virus. The ones on the hands and feet and butt usually don't itch, they usually don't hurt that bad, but the ones that are in the mouth can be quite sore and like I said can make it so that you don't want to eat or drink a lot. Or little kids might have a lot of drooling just because of how uncomfortable they are.
Erin Welsh	Why is it that the ones in the mouth, why does your throat hurt?
Erin Allmann Updyke	So because you're not just having like sores in that area, you're also having a lot of generalized inflammation.
Erin Welsh	Okay.
Erin Allmann Updyke	Because that infection is there in your throat essentially.
Erin Welsh	Right. Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. So adults and older kids certainly can get hand, foot, and mouth, like you heard in our firsthand account. But it's more common in little kids likely because of both exposure, the list of things that small children will not lick is much shorter than the list of things that they will put in their mouth. And like I mentioned because of cross protection that you get from prior exposure as we grow up. So by the time you're a grown up, you've been exposed. Now most of the time that is how this infection goes, it'll run its course, kids and adults need symptomatic treatment. Popsicles, rest, hydration, that sort of thing. And then people tend to recover over a pretty long course of 7-10 days. But that's not where we're going to end.

That uncomplicated form of hand, foot, and mouth can be caused by any of the pathogens that I mentioned that cause hand, foot, and mouth disease, coxsackievirus A16 is probably one of the most common causes of uncomplicated hand, foot, and mouth. Enterovirus 71 is the other most common cause of hand, foot, and mouth. But enterovirus 71 can also cause a much more severe infection. All of these can but enterovirus is more likely to cause a more severe infection. And one of the main ways that does this is by invading the central nervous system. Many viruses including our friend polio, which again is related to these viruses, can invade our central nervous system and cause a number of different severe neurologic manifestations.

In the case of enterovirus 71, it's often a viral meningitis or encephalitis. So infection and inflammation of the brain or meninges, the lining of the central nervous system. So this, instead of just looking like a fever and sore throat and feeling sick, would look like a fever, stiff neck, headache, potentially loss of consciousness or behavioral change. These are very typical viral meningitis symptoms and they're very serious. In the case of enterovirus 71, if it invades the nervous system, it tends to cause a brain stem encephalitis specifically. So our brain stem is the bottom part of our brain that controls a lot of our basic functions like breathing and our heart being able to function properly. So when you have inflammation of this part of our brain, what we can see is then issues in the way that our heart and lungs are able to actually function. So this can lead to a lot of edema or swelling and fluid in the lungs because they're not working the way that they're supposed to neurologically. And that actually can lead to death in severe neurologic enterovirus 71 infections.

This virus can also affect the spinal cord and cause an acute flaccid paralysis, which really looks a lot like poliomyelitis. So this is an infection and inflammation of the sheath around our nerves that then cause our nerves to our muscles to not be able to function and a flaccid paralysis. I want to stress that these are not common manifestations of enterovirus 71, of hand, foot, and mouth disease, but they are really important because these are potentially deadly infections and in some cases can result in lifelong complications from a severe neurologic infection. To put some numbers into perspective though, in some of the larger enterovirus outbreaks that we've seen, for example in Malaysia in the late 90s, there was over 2600 cases of hand, foot, and mouth disease that were reported and 34 deaths. So a very small number comparatively but still a number.

Erin Welsh

Wow.

Erin Allmann Updyke

In Taiwan in the late 90s, an estimated 1.5 million people were infected with hand, foot, and mouth disease. 405 admitted to the hospital with some type of neurologic complications and 78 children died in that big outbreak.

Erin Welsh

Jeez.

Erin Allmann Updyke

Yeah. And then in 2008 in mainland China, just under 500,000 cases and 126 deaths in children were reported due to hand, foot, and mouth disease. And the vast majority of those cases were likely or confirmed to be enterovirus 71 which is really common in Asia but is present around the world.

Erin Welsh

For a typical outbreak or like a suspected outbreak of hand, foot, and mouth, how often is virus testing done to know which strain it is?

Erin Allmann Updyke

Yeah. It's a really good question. It's going to vary so much by place that I don't have a great answer to that.

Erin Welsh

Okay.

Erin Allmann Updyke	Yeah. Here in the US, the vast majority of people who get hand, foot, and mouth disease probably never even go to a doctor, so we might not even know that they had it. If they do go to a doctor, it's probably not the emergency room. So they probably don't even have the capacity to do that viral testing. Maybe they do, maybe they don't. But if they're not that sick, then they're likely to not get testing anyways. So it's really very likely that it's only the severe cases, the ones who are very sick, who have these maybe neurologic signs or signs of just a more severe infection that end up in emergency rooms, that end up getting testing. And that testing would probably need like multiple rounds of testing to be able to determine exactly which strain of an enterovirus or which species of an enterovirus we're dealing with.
Erin Welsh	Right, yeah. And so it's possible, is it possible, I'll rephrase that, to have multiple circulating viruses that are the cause or contributing to the outbreak at the same time?
Erin Allmann Updyke	For sure, yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. Because these all pretty much exist across the globe. There's of course geographic variation in what's most common but all of these enteroviruses that can cause hand, foot, and mouth are pretty widespread and becoming more so because of globalization.
Erin Welsh	So how likely is it that if you repeatedly get hand, foot, and mouth, or you get hand, foot, and mouth multiple times, how likely is it that those are coxsackievirus A16 and then A6 or just a mutated version of A16?
Erin Allmann Updyke	I think that's an impossible question to answer. It's a fun one though. I'm not even done though because there's one more specific virus that I want to shout out. And when I'm shouting out these specific ones, do know that any and all of these viruses that cause the disease or the clinical syndrome that we call hand, foot, and mouth disease, any of them can cause severe infection or can cause mild infection. It's just that some of them have been shown so far to be more likely to cause a severe infection than others. So enterovirus 71 is more likely to cause neurologic manifestations if there are going to be neurologic manifestations. Coxsackievirus A16 is more likely to just cause uncomplicated, regular run of the mill hand, foot, and mouth. And then there is coxsackie A6, this is yet another strain of coxsackievirus which really recently has been found to cause hand, foot, and mouth disease, like 2008 was the first big outbreak. Correct me historically if I'm wrong.
Erin Welsh	I thought... Hold on, I'm looking at my notes but I swear I have a paper from 1960.
Erin Allmann Updyke	I thought that's enterovirus 71.
Erin Welsh	85!
Erin Allmann Updyke	Oh. I don't even talk about 85.
Erin Welsh	I mean I mentioned it briefly but that's it.
Erin Allmann Updyke	It must have come and gone. It had its time.
Erin Welsh	Or not. Who knows, I guess?

Erin Allmann Updyke	Well in any case, this particular virus seems to be more likely to cause both severe disease in the form of severe skin manifestations and more likely to cause symptoms and severe disease in adults. So remember most of the time adults don't end up getting symptoms even if they become infected and are shedding these various viruses. But coxsackievirus A6 seems to be an exception. This virus has been making its way across the globe and is now present pretty much worldwide. And cases associated with this particular virus have caused extensive cutaneous or skin variants, some of which were not previously seen in coxsackievirus infections.
	So these include things like very, very large blisters, like deep blistering eruptions. They include much more extensive involvement of the skin, so not just hands, feet, butt but across the entire arms, especially in areas that you tend to get eczema, so like in your elbow folds and things like that. This is called eczema coxsackium. It has also been shown to cause these lesions that look like very, very thick blisters, kind of crustier looking than a normal blister, not quite a fluid filled situation but a really widespread very itchy rash, which normally a hand, foot, and mouth disease rash is not itchy. It also can cause what's called a delayed onychomadesis, if I'm saying that correctly, aka your nails fall off.
Erin Welsh	It sounds like a much lovelier way of saying and then your fingernails fall off.
Erin Allmann Updyke	Your fingernails fall off.
Erin Welsh	And toenails?
Erin Allmann Updyke	And toenails potentially too. This happens from arrest of the nail matrix growth plate. So it stops your nails growing for a little while. And then a few weeks or months after you get infected, that nail just falls off. It'll grow back. And this one is a really horrible image, palmoplantar desquamation, aka the skin of your hands and feet just slough off.
Erin Welsh	Yeah.
Erin Allmann Updyke	The same way that we might see in a fungal infection or in like a maceration, if a foot has been in like a wet boot for too many days. Sorry, your face.
Erin Welsh	Ugh yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	I mean just the word slough alone is enough to just... Ugh.
Erin Allmann Updyke	I know. It's bad.
Erin Welsh	Yeah.
Erin Allmann Updyke	And this is not only in adults. Coxsackievirus A6 has been found to cause these more severe skin manifestations in both kids and adults. Why? Great question, me. I don't know. Presumably it's something about the difference in these virulence factors but we don't know the specific ones. And the same is true for enterovirus 71. With all of these, it's also very likely that host factors are playing a role as well, whether that's differences in the way that we respond, for example in our T cell response to these various viruses, that certain individuals might be more likely to have a severe case than other individuals. But again, we don't know what those host factors are either.

Erin Welsh	Right.
Erin Allmann Updyke	But in general, all of the variety of viruses that can cause hand, foot, and mouth disease, while they vary here and there, some being more virulent, some less so, in general these are all human specific viruses that have a pretty wide tropism, that is they can infect a pretty wide range of cell types. And that is how they can end up causing disease across this wide spectrum. Our skin as well as our nervous system giving us fevers, etc, no matter how we get exposed, whether it's fecal-oral or respiratory. So yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Anymore questions?
Erin Welsh	I mean treatment I assume is supportive if necessary. Like you said, hydrate chill.
Erin Allmann Updyke	Hydrate, chill. Yeah, we don't have any specific antivirals at this point. But especially in the case of severe infections or neurologic manifestations, hospitalization with just supportive care is kind of the only thing that's available.
Erin Welsh	Right.
Erin Allmann Updyke	But that is hand, foot and mouth.
Erin Welsh	You know it's funny because I thought I would be feeling very strongly about needing there to be multiple names but it seems pretty consistent. I mean there's like degrees.
Erin Allmann Updyke	Yes, there's degrees. I think that that's a good way of looking at it, there's degrees and then there's complications, right.
Erin Welsh	Yeah.
Erin Allmann Updyke	But they all share this sort of clinical picture of fever, feeling crappy, this rash that's pretty specific, usually there's throat involvement, lesions in the mouth, and then there's complications therein. There's this can invade further and cause what a lot of viruses can cause in terms of neurologic manifestations or it can cause really bad skin rashes that might look a little bit different and make it harder to diagnose. But at the end of the day, are still hand, foot, and mouth disease. I do think that, and again I am not a virus genetics expert by any means, but the fact that they're all named different viruses I think makes them seem like they are more distant from each other than in actuality.
Erin Welsh	Right. It's like more like along the lines of like a salmonella-
Erin Allmann Updyke	Exactly.
Erin Welsh	Serotype, the numbered serotype or whatever.
Erin Allmann Updyke	Precisely. So now you can think of these all as variants of human enterovirus group A.
Erin Welsh	Right, right.

Erin Allmann Updyke	And then you think oh okay, that kind of makes sense. But we also don't fully understand why this one and not that one.
Erin Welsh	Right. And there are more viruses that cause it which just adds a little bit more flavor to the whole thing.
Erin Allmann Updyke	Sure does.
Erin Welsh	And like what's coxsackie group B doing in there?
Erin Allmann Updyke	Well that's just enterovirus group B. So they're not far off.
Erin Welsh	Yeah. But how is it different? Why is there A, why is there B?
Erin Allmann Updyke	So yeah. But Erin, where did these things come from? Why do they do this to us? Or maybe not that part.
Erin Welsh	It's a philosophical question. I don't know, it could be. Yeah, let's figure out how we got from there to here right after this break.
TPWKY	(transition theme)
Erin Welsh	Hand, foot, and mouth disease. What have we gotten ourselves into? And I say this because just like we talked about, the biology of this disease is a teeny tiny bit more complicated than this one microbe, one disease model that we're used to hearing about, that we're used to learning about. And because of this the way this disease can manifest is sometimes like it depends. It depends like you said on the host, it depends on the the type of virus, it depends on the age of the individual, like it depends on lots of different things. And as we'll likely learn about in the current event section, the nature of some hand, foot, and mouth disease outbreaks has been changing in kind of major ways with some epidemics, like you talked about Erin, involving never before seen case numbers or these new symptoms, fingernails, or mortality rates.
	And it's interesting to see if in the future, as we gain more resolution on the role that these different viruses play in disease manifestation, like maybe we will get some sort of like separating out of names kind of in the way that the naming or classification of coxsackieviruses has been revised confusingly. But it's not all nonstop complications. And well yes but also no. We're going to get a little mid episode break here because the history of hand, foot, and mouth disease is fortunately like pretty darn straightforward. So much so in fact that it's not even going to take up this whole history section.
Erin Allmann Updyke	Ooh.
Erin Welsh	Yeah. So this gives me a chance to explore something that I've been wanting to on this podcast for a very long time.
Erin Allmann Updyke	Oh my gosh, I'm so excited. I have no idea what it is.
Erin Welsh	I'm going to keep you in suspense on what exactly that something is and first we're going to talk about the history of hand, foot, and mouth disease.

Erin Allmann Updyke	Okay.
Erin Welsh	In 1957, 1958, and 1959, outbreaks of a highly infectious disease seemingly never before described were reported in New Zealand, Canada, and England respectively. The disease seemed to affect primarily children and was very mild, with many parents not even feeling like they needed to call a doctor. So a lot of the cases in some of these outbreaks were only, like the case numbers only went up after the fact, after the outbreak was over when they started to like survey the community and parents were like oh yeah, my kid was fine.
Erin Allmann Updyke	Popsicles.
Erin Welsh	Popsicles. Delicious. Infections involved lesions in the mouth and on the hands and the feet and sometimes rashes on other parts of the body. Sometimes there was a fever but in general recovery was rapid and complete. While only 8 children were involved in the earliest New Zealand outbreak or at least discussed in this paper, a total of 60 cases occurred in the Toronto one and 83 in the Birmingham, England outbreak, again including all or predominantly children. If we had to give medals out for each of these outbreaks and what they contributed, it would go like this. 1957 New Zealand, the first recognized outbreak of hand, foot, and mouth, though only in retrospect was it recognized as hand, foot, and mouth because they didn't test for the virus at the time. 1958 Toronto, first time that coxsackievirus A16 was found in samples from people who were infected, showing that this was a viral infection caused by an enterovirus. And 1959 Birmingham, the first time the name hand, foot, and mouth was used to describe this disease.
Erin Allmann Updyke	Okay.
Erin Welsh	So kind of like boom, boom, boom, here we go, done.
Erin Allmann Updyke	You got it.
Erin Welsh	It's the mid 20th century, virology is like just cruising. Well really getting started but...
Erin Allmann Updyke	They got it. Yeah.
Erin Welsh	Pretty cool stuff. But even at the time that these early outbreaks were reported, none of the researchers involved thought that this must be the first time that humans have been infected with this disease. They just figured that previous cases or outbreaks had probably been chalked up to foot and mouth disease or some other viral infection. The timing of the discovery of hand, foot, and mouth disease seems likely to be a combination of this is a very mild illness that has flown under the radar, this looks like something that has already been described and so didn't really encourage a closer look, and we only just now have the molecular tools to be able to identify and classify viruses.
Erin Allmann Updyke	Yeah. Ding ding. Makes sense.

Erin Welsh	Makes sense, yeah. But as it always happens, once hand, foot, and mouth disease was a known entity, a reported entity, it began popping up all over the world, like seriously global. The same year of that Birmingham outbreak in 1959, there was an outbreak of coxsackie A16 described in California and in the years that followed, Hawaii, Arizona, Japan, China, Vietnam, Malaysia, Australia, Thailand, Spain, Sweden, Bulgaria, Brazil, Kenya. Basically everywhere like within I don't know how many years exactly but everywhere was reporting outbreaks of hand, foot, and mouth disease. As the distribution of this disease spread and as the case numbers climbed, researchers quickly realized that this was not the mild mannered, predictable virus that they had assumed at the beginning.
	For one, the 1960 discovery that a different virus, coxsackievirus A5, there's my shout out, was responsible for a small outbreak, changed it from the hand, foot, and mouth virus to the hand, foot, and mouth viruses with more to be added to that over the following decades. And the mild nature of this disease was called into question with the report that two infants had died during the 1959 outbreak in California. Over the decades since the discovery of hand, foot, and mouth disease, it continues to surprise us. Epidemics involving hundreds of thousands or even you talked about one that was over a million people have occurred.
Erin Allmann Updyke	Yeah.
Erin Welsh	Those are huge numbers.
Erin Allmann Updyke	Yeah.
Erin Welsh	Strange outbreaks, quote unquote "strange", I'll call them atypical, strange is not a very scientific word I suppose, that target teenagers or older adults rather than young children have also happened. Like I read about one at a university, I think Loyola maybe. Anyway, new virus stereotypes have been linked to more virulent forms of the disease. Viral recombination has also thrown a wrench in the predictability of this disease.
Erin Allmann Updyke	Yeah.
Erin Welsh	Researchers are investigating the potential effect of climate change on shifting or expanding hand, foot, and mouth disease season in certain regions.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	I mean because like you talked about how the environment can play a big role in how long it can survive, not survive but how long it can stay viable on surfaces.
Erin Allmann Updyke	Yeah. I saw one paper that was investigating how long they can live and accumulate in clams.
Erin Welsh	Oh boy.
Erin Allmann Updyke	Which was actually something that my lab was studying in my masters.
Erin Welsh	That's pretty cool.
Erin Allmann Updyke	It's terrifying actually.

Erin Welsh	Yeah, yeah. I think like as I was reading it started to feel more and more like a tip of the iceberg situation with hand, foot, and mouth disease.
Erin Allmann Updyke	Yeah.
Erin Welsh	And I know that you're going to talk about where we go from here, vaccines, changing epidemiology of outbreaks, research on prevention, whatever else there is to talk about in terms of the current and future world of hand, foot, and mouth disease. But I still need to talk about where this came from.
Erin Allmann Updyke	Yeah.
Erin Welsh	Of course now that we've learned about the many players involved or possibly involved in hand, foot, and mouth disease, you could understand why that might be a little bit of a tricky question to answer. If you interpret that question as where does this group of viruses that cause hand, foot, and mouth disease come from? We can say that enteroviruses are an ancient group and they're RNA viruses so it's easy to underestimate the timescale of viral evolution and they recombine with each other so it's also difficult to trace evolutionary relationships. There's not very much specific research that I could find on enteroviruses. So I don't know where, when, how, those sorts of steps unfortunately.
	But you could also interpret that question, where does this thing come from, as where does the name hand, foot, and mouth disease or the name coxsackievirus come from? We know the answer to the first, the 1959 outbreak. And the second is that coxsackieviruses were named after a small village on the Hudson River south of Albany where two children lived from whom coxsackieviruses were first extracted or isolated in 1948 by Gilbert Dalldorf, a director in the New York State Department of Health. So there's a town called Coxsackie in New York. Yeah.
Erin Allmann Updyke	How funny.
Erin Welsh	Right? Or a village. I don't know the difference. But for the rest of this history section, I am choosing a third interpretation of your question.
Erin Allmann Updyke	Ooh okay.
Erin Welsh	Not where does this disease or where do the viruses that cause it come from? But where do viruses come from?
Erin Allmann Updyke	Stop it.
Erin Welsh	What do we think the very first viruses looked like, acted like? Did they predate cells or did they come from cells? How do we even begin to form hypotheses around the origins of viruses? Should I go back to grad school to get a degree in paleovirology? Because I kind of want to.
Erin Allmann Updyke	Do it.
Erin Welsh	What is paleovirology? We'll get there.
Erin Allmann Updyke	I love it.
Erin Welsh	I was very excited to get to go down this rabbit hole which I have never gotten to go down.

Erin Allmann Updyke	Yeah, I feel like we've talked about it.
Erin Welsh	Yeah.
Erin Allmann Updyke	Now is the moment.
Erin Welsh	Now is the moment. I was going to say that everyone listening to this podcast is no doubt familiar with viruses. But then I remembered the last few years and so instead I will say that no doubt everyone in the world is familiar with viruses. The vast majority of the viruses that we are familiar with are pathogenic, either to humans or to humans and other animals or to animals or to plants or to bacteria, bacteriophages. And that makes sense, given that identifying those more deadly, those super harmful viruses is top of the priority list. But the world of viruses is much, much larger than just those pathogenic ones and being harmful to humans or the animals that we have or wildlife is by no means a requirement.
	Probably nobody needs this definition but just in case, a virus is simply a teeny tiny or in other words submicroscopic infectious agent made up of genetic information wrapped in a protein coat. Viruses are not considered living organisms because they rely on living cells to multiply which they do by invading a cell and hijacking the cell's machinery to make more viruses. They turn into like viral production factories. Viruses can be characterized by what type of genetic material they have, we've talked a lot about RNA viruses and we've talked about DNA viruses and also how they replicate in infected cells. The number and diversity of viruses on this planet is beyond imagination. It's just too big for us to even try to imagine. But Carl Zimmer tries in his book 'Planet of Viruses', he writes that quote "there are 100 billion times more viruses in the oceans than the grains of sand on all the world's beaches. If you lined up all the viruses in the oceans, end to end, they would stretch out 42 million light years."
Erin Allmann Updyke	It is in fact too much to comprehend.
Erin Welsh	You can't.
Erin Allmann Updyke	We need one of those grains of rice videos.
Erin Welsh	Yes.
Erin Allmann Updyke	You know?
Erin Welsh	I do know.
Erin Allmann Updyke	What?
Erin Welsh	And that's just the ocean.
Erin Allmann Updyke	That's just the ocean. Yeah, that's not even... Wow.
Erin Welsh	The biomass on land.
Erin Allmann Updyke	Planet Earth. Wow. Oh my goodness. Okay.

Erin Welsh	Since the discovery of the tobacco mosaic virus in the late 1890s which was the first to be described, I know I've mentioned that at least once or twice or three or four times on the podcast, scientists have classified and named a few 1000 species. But there are likely billions, trillions, even more viruses out there waiting to be discovered, like virus species. Viruses are found on every corner of the earth, infecting every cell you can think of. There are even giant viruses with genomes larger than scientists ever thought possible for a virus and these viruses can be infected by a virus. A virophage.
	That's like one of my favorite fun facts. Blows my mind. Research is in its infancy for sure when it comes to these giant viruses and their virophages and really research is in its infancy when it comes to viruses period. Although we may have observed and written about viral infections for thousands of years, we only made the connection between disease and infectious agent relatively recently. We are in a thrilling and sometimes terrifying time for virology research. Thrilling for how often it seems like there is a discovery made that completely upends what we thought we knew about viruses or the borders around what it means to be a virus, and terrifying for kind of the same reason, right?
Erin Allmann Updyke	Yeah.
Erin Welsh	The insidious long term effects of a viral infection, the increasing number of links made between viral infections and autoimmune conditions and cancers or other conditions. The sheer unpredictability of viruses, even when we can predict certain things about them, they still continue to surprise us.
Erin Allmann Updyke	Surprise us.
Erin Welsh	In sometimes not so pleasant ways, right? We are learning about the world of viruses at an unprecedented rate and it has given us profound insight into/spurred debate on what it means to be alive, the surprising ways that evolution can work, the blurred line between health and harm, even what it means to be human. Because as you can probably imagine, viruses like bacteria and other pathogens, don't really turn into fossils, at least in the traditional sense. A select few can leave behind traces of infection in their host skeleton, like remnants of smallpox virus in the teeth of vikings, but even those are somewhat limited in how long they can last without degrading past the point of recognition. But there is another way that ancient viruses can be detected and studied millions of years post infection. And that is through our genome.
Erin Allmann Updyke	I'm so excited.
Erin Welsh	We've talked about retroviruses on the podcast before and the way that these viruses work is that when they infect our cells, they end up inserting their genetic material into our cells' DNA so that our cells end up replicating that genetic material and then producing a whole lot more of those viruses. But what's super cool about this is that if one of these viruses ends up infecting a germ cell like egg or sperm, that viral DNA can be inherited and then inherited and then inherited.
Erin Allmann Updyke	What?
Erin Welsh	This process, I know, right, is called endogenization. And it has happened over and over and over again in our species' history, in many, many species' history, all species' history? Some more than others, that's also very interesting. And it's estimated that up to 8% of our human genome is comprised of sequences of viral origin.
Erin Allmann Updyke	So we are all virus.

Erin Welsh	We are all virus. But we are 8% virus. Isn't that amazing? Like we're just hanging out, living life while we've got this huge amount of viral DNA in our genomes.
Erin Allmann Updyke	And it's like just being there.
Erin Welsh	Well is it?
Erin Allmann Updyke	Is it?
Erin Welsh	Is it? These sequences are called human endogenous retroviruses. But side note, apparently it's not just retroviruses that can become endogenized, that's just my own little like...
Erin Allmann Updyke	Seriously, yeah.
Erin Welsh	While most of this 8% is inactive as in it just like doesn't code for anything, it just chills there, some parts do still have an impact, from regulating when certain genes turn off or turn on or even say coding for proteins that are crucial for placental development.
Erin Allmann Updyke	What?
Erin Welsh	Yep.
Erin Allmann Updyke	Oh. We talked about that.
Erin Welsh	We talked about this.
Erin Allmann Updyke	Yeah.
Erin Welsh	Like it has played a tremendous role in placental development and many other aspects.
Erin Allmann Updyke	And that gene, that sequence, that protein is from a virus. What?
Erin Welsh	I know. So yes, not only that but Syncytin-1 and Syncytin-2 may play a role in preeclampsia and even some preliminary hypotheses on the development of other conditions unrelated to pregnancy. Other human endogenous retroviruses may affect our immune system and have been linked to various autoimmune diseases and ALS among other things.
Erin Allmann Updyke	You know I feel very conflicted about this, Erin.
Erin Welsh	Why is that?
Erin Allmann Updyke	Because I feel like on the one hand, this is the most incredible information, like my brain can't handle it. It's incredible. And then on the other hand I'm like that makes sense. I mean especially because like yeah, there are viruses that still today make their way into our DNA. We've talked about some, like the hepatitis viruses that do that, HIV can do that. And so of course it makes sense that that viruses have been doing this forever. And I mean evolution is so random that of course if that happens and there's some benefit to it, then it's going to become a part of you. But so it's so logical and so mind blowing at the same time.

Erin Welsh	It is. I think that what really blows my mind too is that some of these are still having an effect.
Erin Allmann Updyke	Yeah.
Erin Welsh	Whereas like for the most part, these viral genetic sequences have been like turned off because they were probably... So that sort of the turning off was selected for.
Erin Allmann Updyke	Okay.
Erin Welsh	It was like we're going to do better if we don't do whatever this virus is instructing us to do.
Erin Allmann Updyke	Don't do that. Yeah.
Erin Welsh	But the fact that there are many out there that do still play a role. And it's like I think it's also really probably challenging. This field, this is paleovirology, involves studying ancient viruses as well as the impact that these endogenous retroviruses and other extinct viruses have had on the evolution of their hosts. And it sounds like an incredibly cool field of research which is why I want to go back to grad school kind of and research it but will just end up reading papers about it instead. But it also seems really challenging.
Erin Allmann Updyke	Yeah.
Erin Welsh	Like how do we know what is a viral, like an endogenous retrovirus vs not?
Erin Allmann Updyke	That's my question.
Erin Welsh	Yeah.
Erin Allmann Updyke	How do we know? What's the tag? Do they have a little sign that they wave?
Erin Welsh	So I think that there are. And also this is now, I am like way out of my depth because I'm like okay, this is not what I prepared for.
Erin Allmann Updyke	Yeah.
Erin Welsh	But I did do like a little bit of extra reading. And so there do seem to be, there's a growing database where people have identified endogenous retroviruses and then you can look for similarities across other species that have these sort of genetic sequences.
Erin Allmann Updyke	Okay.
Erin Welsh	And I think that there might, you're right that there might be like little tags or something that indicates like this looks like a viral sequence.
Erin Allmann Updyke	Okay.
Erin Welsh	But there is a program I think that you can also, like a bioinformatic program that you can run genomes through to be like where's my endogenous retrovirus?
Erin Allmann Updyke	Oh wow.

Erin Welsh	Yeah. So I don't really know much about like at all about the mechanics and so if that was completely wrong which it very well could be, I'm very sorry, please correct me. Send an email.
Erin Allmann Updyke	Yeah, just send us info so we can read more about it. Thanks.
Erin Welsh	Yeah. So I promise you that this will definitely not be, like I'm gonna stop talking about endogenous retroviruses here, but it will not be the last time on the podcast that we go into them because I do want to take us further down the rabbit hole, like as deep as it can go with endogenous retroviruses, maybe in an episode on preeclampsia, like that seems like it would be really, I mean that's on our short list of episodes to do for sure.
Erin Allmann Updyke	Our list, yeah.
Erin Welsh	And then we can get sort of up close and personal with like what does this gene do? There are other genes that seem to be involved as well, like how do we determine the functions that they have or don't have? I mean just also like trying to tease apart regulatory functions of things...
Erin Allmann Updyke	I love it. I love it. I love it. I love it.
Erin Welsh	Very cool. Love it. Okay. Love it, kind of scared of it, seems overwhelming. That's life. Okay. But today for the rest of this history section, I want to take you even further back. By comparing endogenous retroviruses across different animal species, like who has what, how different are those sequences, we can learn a lot about the evolutionary relationships among those animals. And we can also learn a lot about the evolutionary history of those viruses. How closely do they resemble viruses or viral genes that are around today? How long ago do we think they were incorporated into the host genome? What purpose do we think this viral gene held for the virus? Like it had to have done something, it had to have benefited it in some way.
Erin Allmann Updyke	Right.
Erin Welsh	What was it doing? These endogenous retroviruses often referred to as molecular fossils, can give us valuable insight into what viruses may have looked like or how they acted millions of years in the past, even hundreds of millions of years. But millions is not billions and if we want to explore the possible origins of viruses, we're gonna need to go back billions. So let's get into some of the hypotheses on the origin of viruses. All of these hypotheses have to try to reconcile these two kind of paradoxical statements about viruses. Number one, viruses infect organisms across the three domains of life, the Archaea, the Bacteria, and the Eukarya. And some viruses, even though they infect super distantly related hosts, share some of the same proteins or very similar proteins. And this suggests to scientists that viruses emerged really early on, like before these domains split from one another, possibly before cells existed. Number two, this is the conflicting contradictory statement, viruses infect organisms, period. Like they have to infect cells in order to replicate.
Erin Allmann Updyke	Right.
Erin Welsh	So viruses both needed cells to exist and had to exist before cells to display the diversity they have. So how do we explain this?
Erin Allmann Updyke	Yeah.

Erin Welsh	Yeah. Well traditionally, three different scenarios are proposed and I'm gonna try to go through each of these but in not too much detail because I'm not a virologist by any means. And I'll also try to mention a few of the hybrid hypotheses that have been proposed more recently. And my goal with this is not to convince you of any one hypothesis or even give you what you need to draw your own conclusions, this is an area of active research where there doesn't seem to be any strong consensus. So my goal here is just to introduce some of these ideas and kind of get you to think about how cool and incredible and weird viruses are and to think about a time that you may not think about that often.
Erin Allmann Updyke	Oof. I'm excited.
Erin Welsh	Deep time, baby. Okay. The three hypotheses are virus first, escape, and reduction.
Erin Allmann Updyke	Okay.
Erin Welsh	Let's start with the virus first hypothesis which is more or less exactly what it sounds like. Under this hypothesis, viruses came before cells. They emerged from a soup of RNA molecules and had proteins to help them replicate. Once cells assembled later on, these sort of protoviruses evolved to infect them. There's wide agreement among biologists that RNA molecules existed before DNA and that they were the first replicating molecules. In which case, today's single stranded RNA viruses like the enteroviruses that cause hand, foot, and mouth disease are representatives of the descendants of these ancient, ancient viruses.
Erin Allmann Updyke	Okay.
Erin Welsh	Another thing in the support column for this hypothesis is that in a huge number of viral genomes, there are genetic sequences that aren't found in cells which might suggest that viruses came before cells rather than deriving from cells. Because otherwise, where did these genetic sequences come from?
Erin Allmann Updyke	Right.
Erin Welsh	There are a couple of problems with this virus first idea. One is that there is no gene or coding sequences found in all viruses. And another is just the mechanics of it. Like how can a virus replicate without a cell? How can it get that protective protein shell that caps it around its genetic material to find its next host and replicate more? The next hypothesis can help answer that, the escape or sometimes called vagrancy hypothesis. Under this hypothesis, cells predated viruses and viruses actually derived from cells. How did they do this? Well in the genomes of our cells, there are these super cool things called retrotransposons which are genetic elements that move around the genome, cutting and pasting genetic code. Like how? What?
Erin Allmann Updyke	They just beep bop around.
Erin Welsh	I just can't get over it. So some scientists think that viruses could have emerged from a similar process.
Erin Allmann Updyke	Right.
Erin Welsh	Where a mobile genetic element got wrapped up in a nice little protein coat and escaped the cell, like in a little vesicle or something, along with the tools that it needed to cut and paste itself into another cell's genome and make more of itself and voila, virus.

Erin Allmann Updyke	Okay, okay.
Erin Welsh	And there are viruses that have actually formed this way or are thought to have formed this way through gene escape. One of which is the human Hepatitis delta virus which can only infect humans and requires the Hepatitis B virus to replicate and it probably came from human genetic material, Hepatitis delta virus.
Erin Allmann Updyke	Oh that's so interesting because when you were talking about the viruses that infect other viruses, Hepatitis D was the first thing that I thought of because it's like it's not a virus that infects other viruses but it's a virus that requires another virus to already exist in the cell for it to be able to infect that cell.
Erin Welsh	It's like hyper dependent. Yeah, hyperparasite. Yeah.
Erin Allmann Updyke	Interesting.
Erin Welsh	So very cool, right? And with this scenario, these so-called pick pocketing or gene robbing viruses could have been formed from escaped genes from each of the domains, Bacteria, Archaea, and Eukarya, which helps to explain the existence of bacterial viruses, bacteriophages from bacterial genomes, eukaryotic viruses from eukaryotic genomes, and archeoviruses from archaeal genomes.
Erin Allmann Updyke	Okay.
Erin Welsh	But if this were the case, we shouldn't find viral genes or genes of viral origin because they would have all come from these cells. Yet we do. So here enters the third hypothesis or the reduction hypothesis. This idea was revived when in the early 2000s scientists discovered giant DNA viruses. The first of these to be described, Mimivirus because it mimics microbes, is bigger than anyone thought viruses could be. So you know how like on the podcast when we talk about the history of the discovery of viruses, we talk about how they were called filterable transmissible agents? Because you filter all the bacteria out and yet there's still something there.
Erin Allmann Updyke	Right.
Erin Welsh	These would get filtered out. Some of these viruses are bigger than bacteria.
Erin Allmann Updyke	What?
Erin Welsh	Yeah. Than some bacteria, bacteria range in size, whatever. But it's so cool. And this giant virus, this Mimivirus, has also an incredibly large genome which goes against this conventional idea that viruses have small genomes and they're restricted to having small genomes because the larger the genome, the more likely that mistakes are made in replication. And since they don't have proofreading abilities, those mistake-ridden large genome viruses would die out, right. So if you're like imagining typing, trying to copy a paragraph, the longer the paragraph is, the more likely you are to make mistakes.
Erin Allmann Updyke	Right.
Erin Welsh	And let's say that like you can't proofread your mistakes...

Erin Allmann Updyke	Right.
Erin Welsh	Yeah. But these giant viruses still exist and they not only have these big genomes but they also appear to have genes or forms of genes that may have coded for protein synthesis or may have been involved in protein synthesis.
Erin Allmann Updyke	It's wild.
Erin Welsh	It's wild. Also they have very low mutation rates which is really cool because you would think larger the genome, even though it's DNA, but still. And because of how much they resemble cells and rely less on hosts for replication compared to other viruses, some scientists have speculated that these giant viruses evolved from more complex ancestors, losing their free living ability. So I like to think of it as like this giant virus started out as a free living independent being just happy being itself going through eons chilling and then it met a cell and was like oh hey, you me, me you, maybe we could like form a partnership, work together. And over time that virus grew to be more and more dependent on its partner, it stopped working on itself and didn't care about living freely and eventually turned into a parasite. That's the story in my head.
Erin Allmann Updyke	I really love it.
Erin Welsh	And so it's even been proposed, I think it's pretty controversial, but it has been proposed that these giant viruses are the descendants of an extinct fourth domain of life.
Erin Allmann Updyke	Omg.
Erin Welsh	Yeah. Or maybe not. Because their genomes don't show the same degradation that obligately intracellular bacteria like Rickettsia and chlamydia do. And so it's possible some scientists think that they evolved from smaller DNA viruses through genome expansion.
Erin Allmann Updyke	Wild.
Erin Welsh	Wild. So at this point though, these giant viruses don't really seem to hold the complete answer for viral origins. Did viruses come before cells? Did they escape from modern cells about 4 billion years ago which is when the last universal common ancestor was thought to have originated? Or did they derive from more complex ancestors now extinct? These three hypotheses have been revised, championed, abandoned, revisited, and will probably continue to be debated forever. They do seem to be mutually exclusive in their traditional forms yet none explains the origin of viruses in a completely satisfactory way.
Erin Allmann Updyke	Right.
Erin Welsh	And it's possible that no single hypothesis ever will. Some people have proposed hybrids of these scenarios, like viruses evolving from ancient cells which later gave rise to modern cells, which is why we see genes or elements that are unique to viruses yet are not found in these more modern domains.
Erin Allmann Updyke	Yeah.

Erin Welsh	Or protoviruses that could replicate themselves came first and then ancient cells emerged and they stole protective proteins from those cells. So sort of like step-wise. Or that there were multiple origins of viruses, especially separately for RNA and DNA viruses. At this point it mostly seems like a philosophical question, albeit one that will keep changing the more that we learn about the viruses around us as well as those within us in our genomes. And I know that I probably gave you a lot more than you bargained for when you asked where did this thing come from? But hopefully you found this little foray into viral origins fun or at least somewhat interesting. And now I'm going to turn it over to you to bring us out of deep time into what's going on with hand, foot, and mouth disease today.
Erin Allmann Updyke	Oh my gosh Erin, I want to stay in deep time and just ponder.
Erin Welsh	Let's do that. Let's have a deep time hour.
Erin Allmann Updyke	Can we? That sounds great. Okay. But right now we'll take a quick break and then I'll bring us back to 2023-ish.
Erin Welsh	Don't sound so disappointed.
Erin Allmann Updyke	No, I'm excited. It's gonna be great.
Erin Welsh	Okay good.
Erin Allmann Updyke	Right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	At this point, all of these modern viruses, enteroviruses that cause hand, foot, and mouth disease have been seen pretty much across the globe. In my reading at least, coxsackievirus A6 is perhaps the newest one to be spreading and making headlines about it with epidemics that started like I mentioned in 2008 in Europe, spread throughout Asia, and made their way across the Atlantic to the US. Enterovirus 71 is also globally distributed but seems to cause the largest and most severe epidemics in Asia for reasons we don't really understand because it's not limited to Asia certainly. But across all of its range, especially in temperate regions, hand, foot, and mouth tends to be a seasonal disease. It usually occurs in summer as well as having smaller peaks in spring and fall. And across the globe, infections are by far most common in kids under 5 years old.
	It's also probably not that surprising both given how infectious this is and just the ways that it's spread, that it's really common for hand, foot, and mouth disease to cause outbreaks. Whether those outbreaks are small or incredibly large just depends on the certain set of circumstances surrounding it. But what that means is that we don't have great numbers on global prevalence. Yeah. It's also not a reportable disease for most of the globe. A lot of Asia does actually report especially enterovirus 71 infections, so we have some numbers and we can really see those seasonal trends. And from there we can see that there are tens to hundreds of thousands of reported cases during these peak seasons depending on the country that we look at. So if we extrapolate that data using not quite Erin math but just guessing, it's almost certain that there are hundreds of thousands, if not millions of cases of hand, foot, and mouth across the globe every year. This is a very common infection.
Erin Welsh	Yeah.

Erin Allmann Updyke	So then the question is why does it seem like perhaps some subtypes, especially those that maybe cause more severe infection, are on the rise?
Erin Welsh	Yeah.
Erin Allmann Updyke	Like coxsackievirus A6. I don't know.
Erin Welsh	I was waiting. I was like she's got the answers.
Erin Allmann Updyke	I don't ever have answers, Erin. But it's fun to think about. Is it because it's outcompeting the other coxsackieviruses because it's a more virulent infection somehow? Is it just that most of us haven't yet been exposed, so there's a lot more susceptible individuals in the population? Is it some combination thereof? Probably. But it's important that we try and get a handle on this, especially as we're looking at these viruses that seem to be causing more severe illness, right.
	Another thing that's interesting just about the general epidemiology of hand, foot, and mouth disease is that in addition to seasonal variation, there also tends to be these cyclical epidemics where every 2-5 years larger outbreaks and epidemics tend to happen. That may not be that surprising to anyone who listened to our poliovirus episode recently because that used to happen with poliovirus as well and it's likely related to just how many kids have been born and how many susceptible young babies you now have in a population that have never been exposed to any of these viruses.
Erin Welsh	Yeah. It's interesting. I wonder what the susceptible population requirements are in order to be sustained? I feel like we talked about this in different episodes and like our measles episode, compared to other things like chickenpox, you don't really need to have a certain threshold of individuals to maintain infection.
Erin Allmann Updyke	Right. Well at least one paper that I read, I remember seeing that they estimated that to have herd immunity you would need to have well over 80% of people no longer susceptible, so immune to the infection.
Erin Welsh	Wow. It's a lot.
Erin Allmann Updyke	It's a lot. It's not as high as for something like measles.
Erin Welsh	No.
Erin Allmann Updyke	But it's also that much more complicated because there are so many different viruses that can cause this. So yeah, so there's definitely a lot of variation within that. The good news is that even though we talked about the severe complications of hand, foot, and mouth disease, if we look at the case fatality rate of all cases from all causes of hand, foot, and mouth disease that are uncomplicated, the case fatality rate is incredibly low, between 0.06%-0.1% which is very low.
Erin Welsh	Yeah.

Erin Allmann Updyke	When it comes to more complicated cases that have neurologic involvement, the mortality rate can be between 10%-25% which is significantly higher. So I think that right now in terms of current research, there's a lot of interest understandably in these more severe subtypes, not only in what is causing this increased virulence with say enterovirus 71 and coxsackie A6, but also what are the drivers of this seemingly increase in outbreaks that we've been seeing year after year? There's also of course a lot of work to be done on vaccines which do exist, there are at least three that have existed, at least one that is licensed but they've only ever been licensed in China.
Erin Welsh	Okay.
Erin Allmann Updyke	The vaccine that exists only exists against enterovirus 71 which again is more common across Asia, so it's licensed in China. It does seem that it's quite effective. The study that I saw said that it's estimated to have 90%-97% efficacy even over a couple of years, which is pretty incredible. But other than that, I don't know a ton about it and I don't know the likelihood that it would be licensed anywhere else. But there's certainly a lot of research to be done.
Erin Welsh	As always.
Erin Allmann Updyke	As always. And that is hand, foot, and mouth and butt disease.
Erin Welsh	And fingernail and toenail.
Erin Allmann Updyke	And fingernail. Yeah.
Erin Welsh	We did it.
Erin Allmann Updyke	We did. I mean I really loved that deep dive, Erin. And I'm just not going to stop thinking about viruses in my body.
Erin Welsh	Well I'm glad. And if for anyone out there who wants to maybe read more and because there's so much more out there than what I even touched on at all. So go to our sources and I'm going to shout out a few right now. If you want to learn more about the history of hand, foot, and mouth disease, there are several great papers. One is by Richardson and Leibovitz from 1965. And if you want to learn more about the origin of viruses, like where to even begin, there are many different sources. One is by Durzyńska et al from 2015 called 'Viruses and cells intertwined since the dawn of evolution.' There's just a lot, there are a lot of sources for this one.
Erin Allmann Updyke	I can imagine. For the biology there was a few papers that were really nice overviews and a lot of papers that I had on enterovirus 71 specifically. So for more on that, you can check a paper in The Lancet Neurology called 'Clinical features, diagnosis, and management of enterovirus 71.' Really loved that one. And I used the American Academy of Pediatrics Red Book which had information on all of the different enteroviruses. And I even threw in a fun paper about all of the skin rashes that involve palms and soles just for fun.
Erin Welsh	Ooh. I'm gonna check that one out.
Erin Allmann Updyke	Yeah, it's pretty cool, pretty cool. Not a lot of the pathophysiology but just lists of all the different ones.
Erin Welsh	Ugh. No, I'm just kidding. It's still interesting.

Erin Allmann Updyke	Yeah. You can find the list of all of our sources, because there's many more, from this episode and all of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab.
Erin Welsh	Thank you to Libby again for sharing your firsthand account. Like oh, thank you.
Erin Allmann Updyke	Yeah. Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Welsh	Thank you to Lianna Squillace for our amazing audio mixing, thank you, we love it, you're the best.
Erin Allmann Updyke	Thank you to the Exactly Right network.
Erin Welsh	And thank you to you, listeners. For anyone out there who requested this, we hope that you got your questions answered.
Erin Allmann Updyke	Yeah, I hope so.
Erin Welsh	Yeah.
Erin Allmann Updyke	Felt validated? I don't know.
Erin Welsh	Yeah, that too.
Erin Allmann Updyke	And a special shout out to our patrons as always. Thank you so much, your support means everything to us.
Erin Welsh	It really does. Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals!
Erin Welsh	And your feet and your mouth.
Erin Allmann Updyke	Really do, really do. If you have a changing pad, scrub it!
Erin Welsh	Everywhere.