Erin Welsh	"I was so overcome by sadness that as soon as we completed capturing the required electron micrograph images, I requested Dr. Cropp to use the phone in CDC and called up my head in Malaysia. I managed to get him at home. I still remember vividly what I told him over the phone. Professor Lam, Chua here, calling from CDC Fort Collins. Professor listen, listen carefully. Under the electron microscope the virus has the morphology of a paramyxovirus. For god's sake, please do not talk about Japanese encephalitis anymore. I'm quite sure now it's a paramyxovirus. Most likely it is a new paramyxovirus. The control measures for paramyxovirus are totally different from Japan encephalitis virus. Please, I want you to urgently pass this message to the Ministry of Health to stop all the Japanese encephalitis control measures and switch over to the following control measures. Professor, listen carefully. You must pass the information of what I have just said to the Ministry of Health as soon as possible. I'll get Dr. Bruce Cropp to process the electron microscopy photograph and fax it to you as soon as it is ready. There was a fairly long silence and he did not reply to my words."
TPWKY	(This Podcast Will Kill You intro theme)
Erin Allmann Updyke	Wow, Erin.
Erin Welsh	Wow. Yeah. So that was from a paper titled 'The Discovery of Nipah Virus: A Personal Account' written of course by Chua, Kaw Bing. Dr. Chua who, well, you'll hear later from him more in the episode, played a really pivotal role in the discovery of Nipah virus. And I just... Like this paper, it's a personal account of his experience. It's amazing.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so this is just a small little excerpt from it. But really the whole thing is so invaluable because I think it shows what was he feeling, what was he thinking every sort of step of the way. What was it like to be there?
Erin Allmann Updyke	Right.
Erin Welsh	And we don't really get that very much.
Erin Allmann Updyke	Yeah. To understand from a first person account of someone who was actively working on this during this outbreak, on this infection, trying to help, trying to figure out what was going on. Like what? Yeah. What did that feel like? What was that like? We don't get to see that very much anymore.
Erin Welsh	We don't. And that's why I just, I love it. Go read 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	Welcome to today's episode today.
Erin Welsh	To today's episode today on Nipah virus.
Erin Allmann Updyke	Nipah virus!

Erin Welsh	Yeah. At least a few of you have suggested this. It's been on our list for a really long time and it's been really interesting to kind of finally dig into... Like I knew what it was. I'm like oh yeah, okay, this really deadly virus spillover, etc. Bats, whatever. But then to actually read about it, I'm like oh.
Erin Allmann Updyke	Right. Yeah, to actually get to spend the time to dig into it.
Erin Welsh	Yes.
Erin Allmann Updyke	It's going to be a great episode. I'm super excited.
Erin Welsh	It's going to be a great episode also because we are going to be chatting with an expert guest later in the episode.
Erin Allmann Updyke	Our favorite thing to do!
Erin Welsh	It is.
Erin Allmann Updyke	We haven't done it yet this season.
Erin Welsh	I know, I know. And also we're gonna ask them to pick up the slack that we will be dropping when it comes to talking about the ecological factors that contribute to outbreaks of Nipah virus.
Erin Allmann Updyke	Yeah.
Erin Welsh	So Dr. Clif McKee who is a research associate at Johns Hopkins' Bloomberg School of Public Health will be joining us to talk about the dynamics of pathogen spillover events from bats to humans. So excited.
Erin Allmann Updyke	I'm so excited. I can't wait.
Erin Welsh	Me too. But we have a lot to cover before we get there, including-
Erin Allmann Updyke	It's quarantini time.
Erin Welsh	It is. What are we drinking this week?
Erin Allmann Updyke	We're drinking When Pigs Fly, which will make sense, it'll make sense later in the episode.
Erin Welsh	It will, it will, it will. Bats, pigs, whatever. We'll get there. And the quarantini itself is quite a delicious one. It has rum, it has mangoes, it has lime, passionfruit. It's tasty and we will post the full recipe on our website thispodcastwillkillyou.com as well as on our social media channels, which if you're not following us on there, you really should because we're coming up with some pretty fun content. Who doesn't love some short form media? We've got some reels for you if you're interested.
Erin Allmann Updyke	We're trying really hard.
Erin Welsh	We are. We're trying to be cool and keep up with the kids.

Erin Allmann Updyke	It's gonna be hard. We're elder millennials, we don't really know what we're doing.
Erin Welsh	True. It's very true.
Erin Allmann Updyke	On our website though, thispodcastwillkillyou.com, you can find lots of other non short form content. You can find the sources from all of our episodes, you can find bookshop.org affiliate account and our Goodreads list for lots of deep reading. You can find Bloodmobile who does the music for every single one of our episodes. You can find our transcripts, you can find our merch. We have some pretty great merge right now.
Erin Welsh	We do.
Erin Allmann Updyke	You can find our Patreon. You can find anything that you want. We've got a firsthand account form if you would like to submit your firsthand account or request an episode. Just check it out, check it out. It's great, it's great. And that's it, that's all I got. Oh and rate review and subscribe if you haven't done that already.
Erin Welsh	Oh yeah.
Erin Allmann Updyke	If you have, thank you so much. We really, really appreciate it. It helps us keep making the pod.
Erin Welsh	It's true. Let's get started, Erin.
Erin Allmann Updyke	Okay. Right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	So Nipah virus is an RNA virus in the family Paramyxoviridae, which a longtime fans of the pod might be familiar with because we've actually covered some other paramyxoviruses on this podcast before. Measles is a paramyxovirus, mumps is a paramyxovirus. Other ones you might have heard of include the parainfluenza viruses which cause common colds. Can't forget about rinderpest, Erin.
Erin Welsh	Rinderpest. I think one of my favorite episodes, a great success story when it comes to public health or wildlife health or veterinary health... One health.
Erin Allmann Updyke	Health. One health.
Erin Welsh	That's the thing. One health.
Erin Allmann Updyke	Also Hendra virus, which we have not yet covered but we will someday, is the most closely related to Nipah virus. So Nipah virus and Hendra virus are both in the family Paramyxoviridae and the genus, they kind of have their own, which is called Henipavirus. I think it's a combination of Hendra and Nipah virus.
Erin Welsh	Stands to reason.

Erin Allmann Updyke	Not that creative. Now I don't want to bury the lead here too much for anyone who didn't request Nipah virus who's maybe never heard of this thing and is wondering why the heck we're covering this virus that they've never heard of. Nipah virus has been named one of the top 10 highest priority pathogens for the World Health Organization to focus on in terms of the development of countermeasures. That means focus on vaccines, focus on developing treatments, focus on prevention. And the reason is because Nipah virus has huge pandemic potential. So not to jump ahead too much but not only is this virus capable of spreading person to person, not only has it continued to pop up and spread to new places year after year as we'll talk about but Nipah virus is also one of the most fatal infections that we've seen in humans. Case fatality rates on the low end tend to be around at least 40% and in many outbreaks they've been upwards of 90% of cases.
Erin Welsh	It is unreal.
Erin Allmann Updyke	It is terrifying in all honesty.
Erin Welsh	Yeah. Yeah.
Erin Allmann Updyke	Yeah. So it's a big deal virus and you're going to learn all about it today. So Nipah virus primary reservoir is bats. So in nature in the wild, it lives specifically in bats in the genus Pteropus. Taro-pus? Pteropus. I think I decided it's Taro-pus.
Erin Welsh	We had a conversation about this.
Erin Allmann Updyke	Yeah.
Erin Welsh	And I have forgotten what we landed on.
Erin Allmann Updyke	I looked it up several times and then I pronounced it wrong the first time. I just said it, it's Pteropus. These are flying foxes, fruit bats, right. There's a few different species but for much of the distribution of Nipah virus that we've studied so far, it's predominantly Pteropus medius that's been implicated in Nipah transmission thus far. And Nipah has caused outbreaks in humans in a number of different countries across South and Southeastern Asia and the Pacific, including India, Malaysia, Singapore, the Philippines, and Bangladesh. But the bats that carry these viruses are distributed really widely across Asia, the Pacific, Australia, even parts of Africa.
	The majority of cases thus far, like by far, have occurred as the result of spillover events. So this is a zoonotic disease primarily. And most of the spillover events have happened either from bats to humans like a little bit directly or from bats to domestic animals, especially pigs, and then to humans. But like I mentioned, this virus has also shown that it is entirely capable of being transmitted person to person as well. So let's get into a little bit more detail about how this virus makes its way into humans. What's interesting is that so far in different geographic areas where we have seen Nipah, there seems to be different modes of transmission that kind of predominate. And maybe we'll ask Dr. McKee a little bit more detail about the ecology of this. And it also might have to do with the viral strains because there's two different major viral strains. In Malaysia where Nipah was first detected, and I know you're going to talk all about it, Erin-
Erin Welsh	How dare you? No.
Erin Allmann Updyke	How dare I mention that this was first detected at some point in time.

Erin Welsh	Why do I even do anything on this podcast? No, I'm just kidding.
Erin Allmann Updyke	So in Malaysia where it was first detected, outbreaks have been associated with contact specifically with intermediate hosts, mostly pigs. And it's thought that these pigs got infected by eating fruit that was mostly bitten or possibly pooped or peed on by bats. And then humans got infected via direct contact with those domestic animals, either through things like slaughterhouse work or farm work or through even contaminated meat. Then in the Philippines, we have seen outbreaks that have been associated also with an intermediate host between bats and humans but there it seems to be horses and horse meat that has been involved.
	And then in Bangladesh, as well as India to a certain extent, the primary route of transmission seems to be a little bit more directly due to bat contact but via raw date palm sap that's contaminated with either the saliva or perhaps the urine or feces from infected bats. Because apparently bats also love raw date palm sap just like humans do. So then humans essentially ingest this contaminated sap and then become infected that way. There also have been cases where humans might have come in direct contact with bats or bat feces, bat urine, something like that and gotten infected truly directly from bats.
Erin Welsh	And this is ingestion. This is through ingestion?
Erin Allmann Updyke	As far as I could tell, yeah.
Erin Welsh	Okay.
Erin Allmann Updyke	I mean it's coming in contact with this date palm sap and what you do with it is you drink it.
Erin Welsh	Right.
Erin Allmann Updyke	So yes.
Erin Welsh	But when we're thinking about pigs and stuff like that, is the contact again through... Is it respiratory? Like what?
Erin Allmann Updyke	Great question. Great question. With pigs and intermediate hosts, no, it's not necessarily ingestion. You could get infected from contaminated meat but even then it isn't necessarily from ingesting the meat because if you cook it then you're going to be killing this virus, it's heat labile. But it's getting in contact with things like respiratory secretions or bloodborne products, like anything from this animal that has virus in it could then be transmitted to people. But the part that makes this virus a BSL-4, a biosafety level four pathogen, a pathogen of pandemic potential, is that in many of the outbreaks there is also evidence of person to person transmission and this is usually with contact with respiratory secretions but it's very likely that other bodily fluids can also transmit. It's just that respiratory secretions are thought to be the main component of transmission when it's person to person.
TPWKY	(transition theme)
Erin Welsh	Question. Does the strain or the route of transmission, if it's a spillover event, does the strain then impact the ability of it to become transmitted person to person? And is that more likely from bat direct to human rather than bat-pig-human?

Erin Allmann Updyke	Excellent questions. So yes, the first part of the question. So the first part of the question is do the strains seem to make a difference in whether they're transmitted person to person? The two main strains are the strain from the kind of original outbreak or couple of outbreaks in Malaysia and then the strains that were first identified in Bangladesh. Those are kind of the two main lineages it seems. We have a lot more data on strains from Bangladesh, like sub strains or whatever from Bangladesh than we do from Malaysia. But in those initial outbreaks there was very limited evidence of person to person transmission. From what I could tell, not even definitive evidence of person to person transmission in those first Malaysian outbreaks. So is that because those strains are less likely to be transmitted person to person? Perhaps. But I don't know that we have as much evidence to say for sure.
	The strains in Bangladesh are more likely to be transmitted person to person. But I don't think that we have data, at least I didn't see any on whether it's more likely to happen, like how that primary person got infected, whether it was from date palm sap or from an intermediate host or from a bat. However it's only about 10% of people that seem to be spreading this person to person which is very interesting. Overall it's a pretty low rate of person to person transmission in the outbreaks that have been studied. However there is plenty of evidence that that chain of transmission can live on for several viral generations if that makes sense. So one person out of every 10 who gets infected is going to transmit it to someone else. But then the person that they transmit it to can transmit it to someone else as well.
Erin Welsh	So it's like there's something about that person that makes the virus like hey, this is great.
Erin Allmann Updyke	Exactly. We saw, I think everyone's familiar with the idea of a super spreader after COVID. It's that same kind of idea.
Erin Welsh	Okay.
Erin Allmann Updyke	We don't know right now. Is that a characteristic of the virus that happened to infect that person? Or is it a characteristic of certain people that makes them super spreaders? In this case, we definitely do not know.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	Yeah. So that's kind of how this is transmitted, right. It's a lot of different ways and it really does depend on the circumstances. And we'll get into more of the ecology of this virus later when we talk to Dr. McKee. But let's then talk about more of what this actually looks like when a human does get infected. And I'm focusing on humans but again, this is a zoonotic pathogen so this is infected and living amongst bats very readily. And when it infects our domestic animals, like dogs, cats, pigs, horses, it does tend to cause symptomatic disease for the most part but it really varies how sick these animals get. So I'm not going to get into detail on all of that. Let's focus on humans, shall we?
Erin Welsh	Let's do it.
Erin Allmann Updyke	Once a human gets infected, the incubation period tends to be between four days to two months which is a huge range. But over 90% of people who have symptoms will have them within two weeks. Now how many people are going to have symptoms? We have no idea. You can find numbers-
Erin Welsh	Yeah.

Erin Allmann Updyke	But this is such a rare and understudied pathogen still that estimates range between 1%-45% of people that are asymptomatic depending on what the study is. So it's meaningless.
Erin Welsh	It's the biggest range we've encountered on this podcast.
Erin Allmann Updyke	It's a meaningless range. Like it's entirely-
Erin Welsh	It's not 100%.
Erin Allmann Updyke	Okay.
Erin Welsh	It's not everyone.
Erin Allmann Updyke	We know that, this is true. So in any case, there are some proportion of people who are likely asymptomatic based on like serologic studies that we have seen. Okay? But for people that are symptomatic, this is a really terrible pathogen. Symptoms tend to start after this incubation period with pretty non-specific kind of prodrome. These are symptoms like a fever, headaches, muscle aches, maybe even vomiting but really nothing that would make you go oh this sounds like Nipah virus, right. It sounds like any other of a million infections that we've covered on this podcast or like 100 and something that we've covered on this podcast. But generally within a week, within a number of days, you start to see signs of central nervous system infection.
	So this looks like things like altered mental status. Very often we can see signs of brain stem involvement. And so you might see changes in reflexes. Usually it would be a loss of reflexes or a decrease in reflexes. But there's some literature where we can see loss of very specific reflexes that are associated with that brain stem or that lower part of your brain dysfunction. These are things like if you turn someone's head side to side, in a person whose brain stem is intact but who maybe isn't all the way conscious, their eyes should move in the opposite direction that their head is turned like those creepy dolls that you had in your grandma's house growing up. This is called the doll's eye reflex. If this doesn't happen, then the eyes just stay midline as the head moves, that's a loss of that reflex which is very severe, it suggests loss of brain stem function. There's a lot more detail to that that don't please ask me about that reflex because I learned it once.
Erin Welsh	But there are other like I guess other diseases that affect the brain stem.
Erin Allmann Updyke	Right. Yes.
Erin Welsh	What examples can you give? Yeah.
Erin Allmann Updyke	That's a good question. Any kind of meningitis that is affecting the brain stem.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay.

Erin Allmann Updyke	But you also see things like other reflexes like your pupillary reflex or even just loss of muscle tone. You can also get instead of a loss of muscle tone, you can get these jerks, like myoclonic jerks. You can see seizures, you can see any number of these neurologic signs and symptoms which are just telling us how severe the brain infection is in this case. And people tend to deteriorate very rapidly. Nipah virus, like I said, is an incredibly fatal disease and usually within a matter of days. 40%-90% of people in most outbreaks die within a number of days.
Erin Welsh	So it's two weeks, you get infected, two weeks later you start to have these sort of-
Erin Allmann Updyke	Non specific symptoms.
Erin Welsh	Non specific symptoms. And then-
Erin Allmann Updyke	And then within a couple of days-
Erin Welsh	Involvement.
Erin Allmann Updyke	Nervous system involvement, coma, and death.
Erin Welsh	Death.
Erin Allmann Updyke	In some outbreaks there also does seem to be a substantial amount of respiratory involvement though not all outbreaks, which is very interesting. So respiratory involvement looks like a cough. It can look like an atypical pneumonia which we've talked about on this podcast, lust means that on a chest X-ray it doesn't look like a very classic pneumonia. You can have... I know these are silly words.
Erin Welsh	I feel like you can't define atypical pneumonia by saying it's just not your classic pneumonia.
Erin Allmann Updyke	So on a chest X-ray it would look like kind of patchy involvement in the whole lungs rather than one area of your lungs that's fully infected with a bacterial pathogen.
Erin Welsh	Okay.
Erin Allmann Updyke	That's what we think of when we think of pneumonia.
Erin Welsh	Of classic pneumonia, okay.
Erin Allmann Updyke	But in general, you're going to see some degree of respiratory distress if you have a respiratory involvement. But this hasn't happened in all the outbreaks so we don't really have a great sense of like when or why this is happening. And because this is such a fatal infection, we don't have that much data in all honesty on a lot of these signs and symptoms. What we do know is that in people who survive, something like 20% of them have some degree of residual neurologic dysfunction which can again really range. And some proportion in some of these outbreaks seem to also have a relapsing encephalitis. So looks like a new infection but it's just a relapse months or even years after the initial infection. How does this happen? I have no idea.
Erin Welsh	Yeah. And they've cleared the virus from their system?
Erin Allmann Updyke	That's a great question. Do we know that for sure? I don't know that we know that for sure.

Erin Welsh	Okay, okay. Two questions.
Erin Allmann Updyke	Okay.
Erin Welsh	How environmentally stable is this virus?
Erin Allmann Updyke	I knew you were going to ask.
Erin Welsh	Okay. Number two, when is someone... If someone is infectious person to person, at what point are they infectious pre symptoms, etc?
Erin Allmann Updyke	Yeah. These are really good questions. So this virus is fairly environmentally stable which is part of how it can be transmitted in things like date palm sap. This virus can persist for days outside of a host. One paper that I read said that on some fruits and juices that they have studied, it can live for up to three days and still be transmissible. In some cases in some studies where they have kept it colder like around 22 °C, it can last for up to seven days in something like a date sap. But even at higher temperatures it can survive for like a couple of hours. So it's a pretty environmentally stable virus.
Erin Welsh	Okay.
Erin Allmann Updyke	Now how transmissible are people or like when are people most transmissible? We don't really know. That's a great question. Because we know that there is some degree of asymptomatic infection, there's a really important question of if you are asymptomatic, can you still spread this person to person? I don't think that we even know that necessarily. I haven't seen a lot of data on that but it doesn't mean that it doesn't exist, it just means that I didn't see it. What we can try and look at is where is this virus replicating to try and understand where are you most likely to be able to spread it from, like where is this virus living in our cells? And even there we don't fully know. What we think is that because Nipah virus is often spread via respiratory droplets, like via respiratory secretions, it was long suspected and it seems to be the case in studies so far that the epithelial cells that line our respiratory tract are the first target for infection and viral replication. So that would mean that potentially early on if this virus is infecting the respiratory epithelium, someone could potentially be infectious relatively early in their infection, if that makes sense.
Erin Welsh	Yes. Okay.
Erin Allmann Updyke	Right? Because it's invading right there, replicating, and then potentially being able to be spread. But Nipah is also particularly adept at invading past our respiratory epithelium and specifically going into our microvasculature, so our blood vessels, and the cells that line our blood vessels, our endothelial cells. It's one of our favorite cells on this podcast.
Erin Welsh	That's true.

Erin Allmann Updyke	And that essentially means that Nipah has direct access to our bloodstream. And while we certainly don't know everything, not even most things about the pathophysiology of this virus, we do know that it induces a lot of direct viral damage and immune-related damage to these endothelial cells. Which means that as it spreads via these endothelial cells in our bloodstream, it can damage things like our heart, our spleen, our liver, our kidneys. These are all areas where our blood is going very rapidly. And it's also causing a lot of disruption to our blood-brain barrier, which is what allows for it to have such easy access to our central nervous system. So how much can this continue to spread if all of these other bodily fluids are getting infected? Potentially quite a bit. But I don't know like how infectious someone is early in the course of their infection vs late, I didn't see data on that.
Erin Welsh	Okay.
Erin Allmann Updyke	Another thing though about Nipah virus that is just so fascinating is that it's also thought that a secondary way that it's getting into our brains, into our central nervous system, is actually by traveling up our olfactory nerve. Our olfactory nerve which is obviously in our nose, it's what we use to smell, is one of the nerves that gives direct access to our brain. It's not covered by the blood-brain barrier. And so Nipah virus can essentially just hitch a ride on this and travel up and get direct access to our brain. It's thought.
Erin Welsh	What? How? Like how does it get there to our olfactory nerve? Yeah.
Erin Allmann Updyke	Well it's in our respiratory epithelium which is in our nose and our throat and our lungs. And how does it get there without causing all of the flags that our body would usually use to counter any virus?
Erin Welsh	Right.
Erin Allmann Updyke	That is what makes Nipah have such a high fatality rate. It happens to be incredibly good at evading our immune response. It has a protein and I think a number of proteins that specifically inhibit a number of our cytokines, including interferon which basically reduces the ability of our immune system to clear this infection. So that combined with the fact that it's then... Or because of that rather, who knows? Chicken and egg. But the ability to cross our blood-brain barrier and infect our central nervous system and evade our immune system so well is what results in such significant mortality.
Erin Welsh	So does our immune system ever recognize it? I know with like case fatality rates upwards of 90%, obviously at that point either that our immune system recognizes it too late or it doesn't recognize it ever. The bottom line is can a vaccine be made against this?
Erin Allmann Updyke	Yeah, great question. As far as we know, we think so. Like people do eventually mount an antibody response to it and there's a lot of work being done on vaccines. So it's very good at evading our innate immune response. But if you could have a faster onset antibody response, then perhaps you would be successful at not getting a severe infection from Nipah virus. See our episode on vaccines if you'd like to know more about these different immune responses. We did it in detail there way back when.
Erin Welsh	Way back when. What about like, yeah... Are there any immune therapies or anything like that?
Erin Allmann Updyke	Yeah. Right now we have absolutely no specific treatment for Nipah at all.
Erin Welsh	Okay.

Erin Allmann Updyke	So Nipah virus treatment is all about supportive care. And because this is an infection that causes such severe disease so quickly, supportive care is really like ICU level of care, right. Making sure that you can support someone's airway if they stop breathing, making sure that their fluid balance is good, like whatever is needed but it's very high level of care that's needed. There's a lot of research being done on things like antivirals. Sometimes there are antivirals that are used even though there's not really any evidence so far that they are effective. But it's one of those cases where medicine often feels the need to do something even if we don't have any evidence that it's effective when you have nothing else to do. But right now that's all that we have. That is Nipah virus.
Erin Welsh	It's wild. It is one of the most... I mean besides rabies, I'm trying to think of a more... Prions, I guess. Like a more deadly pathogen that we've covered.
Erin Allmann Updyke	Maybe it's prions. I mean pneumonic plague.
Erin Welsh	Right.
Erin Allmann Updyke	But yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. It's really scary. That is probably why Contagion used Nipah as a model system in the movie because it is terrifying.
Erin Welsh	Yep.
Erin Allmann Updyke	Yeah.
Erin Welsh	Truly. And I feel like we used to end episodes of this podcast with, do you remember that? How scared should we be?
Erin Allmann Updyke	We did, yeah. Yeah, I forgot about that. It's been a minute since we've done that.
Erin Welsh	I think we could bring it back for this episode.
Erin Allmann Updyke	Yeah, we could. We can talk about it at the end.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. So Erin, tell us how did Nipah come to be with us here?
Erin Welsh	I will attempt an answer right after this break.
TPWKY	(transition theme)
Erin Welsh	Peninsular Malaysia, 1997-1998.
Erin Allmann Updyke	Okay.

Erin Welsh	At first it was just the pigs. Sick pigs were not a totally unfamiliar sight in this part of the country. There were occasional outbreaks of classical swine fever, aka hog cholera caused by a Flavivirus called Pestivirus C, in case you were interested.
Erin Allmann Updyke	I'm sorry, just like, I don't want to interrupt but why do we have to call things that are not the same thing the same thing? Hog cholera not being cholera, that's annoying.
Erin Welsh	Stomach flu?
Erin Allmann Updyke	I can't. It's a norovirus.
Erin Welsh	I can't think of anything else but yeah.
Erin Allmann Updyke	Yeah. Okay. Anyways.
Erin Welsh	Anyways.
Erin Allmann Updyke	Sorry for interrupting.
Erin Welsh	No, I totally hear you. Something called Aujeszky's disease, aka pseudorabies-
Erin Allmann Updyke	Oh my god. More.
Erin Welsh	Caused by a type of varicella virus.
Erin Allmann Updyke	Okay. Are you serious?
Erin Welsh	I'm serious, yeah.
Erin Allmann Updyke	It just gets worse, Erin.
Erin Welsh	I know, I know. And porcine reproductive and respiratory syndrome caused by a type of virus called Betaarterivirus suid 1, if you're interested. There are so many pig pathogens.
Erin Allmann Updyke	Okay.
Erin Welsh	And the disease that was making its way through pig farms in this region of peninsular Malaysia didn't seem super different than those more familiar ones. A few symptoms stood out, pronounced neurological syndrome, including agitation and head pressing; tetanus-like spasm and seizures, uncontrollable eye movements, trembling and twitches, uncoordinated gait, and generalized pain. And then in the pigs there were also some acute respiratory signs, rapid and labored breathing developing into a loud, harsh cough which later then gave the common name for the disease in pigs called barking pig syndrome. But even though there were some cases of sudden death in infected pigs, the rates of infection and mortality weren't all that high or at least not high enough to cause immediate and pressing concern. And so the new disease wasn't immediately identified or recognized to be a new disease.

	Then people started to get sick. In late September of 1998, several people who worked on pig farms in the suburbs of Ipoh, a city in the state of Perak in the northwest part of the peninsula, also began to show signs of illness. Headache, fever, drowsiness, vomiting, altered mental state, sometimes progressing to fatal encephalitis. And this, while absolutely cause for concern, it also didn't immediately throw up red flags as a new illness. Initially people thought this was an outbreak of Japanese encephalitis virus, which we have not done yet.
Erin Allmann Updyke	No. It's on our list but I don't even know if it's on our shortlist for this season.
Erin Welsh	I don't think that it is which is kind of surprising. But there's a lot. Yeah. Anyway.
Erin Allmann Updyke	There's a lot.
Erin Welsh	Yeah, there's a lot. Japanese encephalitis virus though, the relevant thing here to know is that it's transmitted through mosquitoes. And this wasn't a wild guess. Japanese encephalitis virus was present in the area. 4 of 28 samples from patients with encephalitis tested positive for antibodies against Japanese encephalitis virus. And as people continued to get sick, their serum contained not just antibodies against the virus but also Japanese encephalitis virus nucleic acids which suggested current or recent infection with the virus. Later many of these samples were actually found to be false positives so it's probably a case of like the threshold being too low for throwing up a positive sign.
Erin Allmann Updyke	Okay.
Erin Welsh	But given this evidence suggesting that the region had an ongoing Japanese encephalitis virus outbreak, the Ministry of Health took action against it to try to prevent additional cases which involved intensive fogging with insecticides in the outbreak areas; administering thousands of doses of Japanese encephalitis virus vaccine to those who lived near or worked on the pig farms because that's where the concentration of cases seemed to be happening. But after all of these measures, instead of cases dropping as you might expect if it was caused by Japanese encephalitis virus, they continued to rise.
	And making matters even scarier, the disease was no longer restricted to just the area outside of the city of Ipoh. Some of the farmers who were affected in this outbreak had sold their pigs in a fire sale which led to pigs being dispersed across the country. And these types of sales were a common occurrence in peninsular Malaysia which at the time had a pig population of 2.4 million. But unfortunately some of the pigs sold had brought with them this mysterious infection. And in December of 1998 and January of 1999, cases of encephalitis in humans began popping up elsewhere in the country, especially in an area about 300 kilometers south of Ipoh in the State of Negeri Sembilan. Still the thought was this is Japanese encephalitis virus, like it was still like well it has to be this, we just have a bad year for mosquitoes, the virus is in the mosquitoes, this is how it is.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so more prevention measures were carried out, more fogging, more insecticide, more administration of Japanese encephalitis virus vaccines. And according to a researcher involved in the outbreak, the governmental authorities seemed really intent only on confirming that this was Japanese encephalitis virus, not so much exploring other options like for instance if this was a totally new pathogen that needed completely different containment strategies than those used for Japanese encephalitis virus. By the end of February 1999, the outbreak was still raging with no end in sight. And the evidence that this probably wasn't Japanese encephalitis virus started to be too much to ignore.

	The control measures weren't doing anything to reduce the incidence of cases, infections seem to be limited to people who had direct close contact with pigs, mostly adults were getting sick. There was household clustering with multiple people in the same household getting sick, which you wouldn't necessarily expect clustering with Japanese encephalitis virus. There was a really high, in this particular outbreak, a really high disease attack rate. So most people who were infected became symptomatic. So for every one person who stayed asymptomatic, three developed symptoms is what I read. Japanese encephalitis virus on the other hand causes symptomatic encephalitis in one in 300 of those infected.
Erin Allmann Updyke	Wow.
Erin Welsh	So like very different.
Erin Allmann Updyke	Totally different.
Erin Welsh	Totally.
Erin Allmann Updyke	Totally different.
Erin Welsh	And perhaps the most glaring piece of information suggesting that this wasn't Japanese encephalitis virus was that some of the people who were getting sick and dying had already received multiple doses of the vaccine. Can you imagine how terrifying and awful, getting the vaccine and being told okay, you're safe to go back to work. And then it turns out you weren't. And some governmental authorities did actually try to explain that away by saying oh well it's because this vaccine was faulty, we need to replace this inactivated virus vaccine with the live attenuated version and then we'll have better results.
	But fortunately some public health officials and researchers were like okay, you keep working on that and in the meantime we're going to see what this actually might be because it doesn't seem to be Japanese encephalitis virus. And the lead researcher on this, Dr. Kaw Bing Chua at the University of Malaysia whose firsthand account you heard from, he would eventually make the discovery of Nipah virus. He was pretty sure at this time that it was a novel agent, not Japanese encephalitis virus. But the head of his department was convinced that it was Japanese encephalitis virus. So how could he persuade him that he needed to isolate this virus? Chua ended up saying well if it's a new genotype of Japanese encephalitis virus, that could be important, that could be really relevant to our control efforts and to determining whether the vaccine is whatever. And he got permission.
Erin Allmann Updyke	Smooth move.
Erin Welsh	A smooth move indeed. And so he got permission to run tests on the cerebrospinal fluid and serum samples from a few patients. On March 5th, 1999, so the first cases were in September of the year before-
Erin Allmann Updyke	Okay.

Erin Welsh	On March 5th, Chua saw something unexpected in one of his samples. The virus seemed to kill the cells in a way that was very similar to that of respiratory syncytial virus. Not something that Japanese encephalitis virus does. So he ran to the head of his department and was like come look at this! And the head was like nah, it's just contamination, get rid of it, throw it away, ignore it. Chua didn't. He continued his work and he went around to get his colleagues opinions, some of whom agreed with his thought that this was something new, this was something interesting, this was not contamination. And so he ran tests that were available to see whether this was a known virus like herpes simplex virus, RSV, measles, mumps, parainfluenza virus. All negative.
	And then he was like well maybe I should check whether the patients that I've sampled have antibodies to this virus that I cultured. Because then it's like is this just contamination or is this a virus and they have antibodies against it? All positive, like perfect match. And so this time with these results he was able to convince his department head that this was probably a new virus and that they needed international help to figure out what kind of virus it was. Two days later, after he had these results, after he had done the testing of the virus against the antibodies and the patients, and this was one week after he first saw this weird cell-killing effect of this virus in his samples, Chua was on a plane, samples in hand, headed to Fort Collins, Colorado where the division of arbovirus-borne diseases branch of the CDC was located. Why Fort Collins and not Atlanta? Because the department head was still convinced in his heart of hearts that it was Japanese encephalitis virus which is an arbovirus.
Erin Allmann Updyke	An arbovirus.
Erin Welsh	Yeah. So hence Fort Collins.
Erin Allmann Updyke	Okay.
Erin Welsh	Less than 10 hours after arriving in Fort Collins, Chua was at the lab looking at the samples under the microscope. And what he saw terrified him. He saw the concrete ring-like structures characteristic of paramyxoviruses. Why was that so scary? We've kind of touched on that a bit. For one, it showed that this was not Japanese encephalitis virus.
Erin Allmann Updyke	Right. Very clearly.
Erin Welsh	Very clearly. And that confirmed that none of the control efforts that they had spent months trying had actually done anything. I mean it is possible that maybe there would have been an outbreak of Japanese encephalitis virus that they prevented from these control measures, I guess we won't know. But it didn't do anything to stop this particular outbreak.
Erin Allmann Updyke	Right.
Erin Welsh	And for two, it's because it was a paramyxovirus. These are, as we've talked about, a very scary group of viruses with clear pandemic potential. They infect a wide range of animals, they are RNA viruses which typically means for most RNA viruses they have high mutation rates and Nipah virus does indeed. They're spread through airborne droplets and close contact and they have some of the highest infection rates that we've ever encountered. Measles, as we've talked about before, has an R0 of 12-18 which still, it still blows my mind.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. And this new paramyxovirus had an incredibly high case fatality rate. Nearly 40%, which pales in comparison to some of the later outbreaks.

Erin Allmann Updyke	Right.
Erin Welsh	But still, 40% of people who were infected died.
Erin Allmann Updyke	I know.
Erin Welsh	Like that's huge.
Erin Allmann Updyke	It's also, yeah, it's really interesting to then put this particular outbreak in the context of it was not nearly as bad as it could have been based on all of the further outbreaks.
Erin Welsh	I know.
Erin Allmann Updyke	Yeah.
Erin Welsh	I know. Yeah. It's like 40%, that seems low.
Erin Allmann Updyke	And it's terrifyingly high.
Erin Welsh	It's terrifyingly high, yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	And this was incredibly terrifying, alarming, horrifying for the situation in Malaysia, the fact that it was a new virus and a new paramyxovirus. And it was also terrifying and horrifying for Dr. Chua and the other researchers who had been handling these virus samples just like without the safety measures that they warranted.
Erin Allmann Updyke	Right.
Erin Welsh	Like Nipah virus requires the highest level of biosafety precautions, biosafety level four, which the CDC in Fort Collins did not have. And so once they realized oh god, we have a paramyxovirus on our hands, we need to get these things-
Erin Allmann Updyke	Close that tube.
Erin Welsh	Yeah, close that tube. Ethanol those hands. You might need more than that, bleach those hands.
Erin Allmann Updyke	Bleach those hands.
Erin Welsh	Send the samples, bleach everything, send the samples to the CDC in Atlanta, There they can be studied safely. And in Atlanta researchers confirmed that yes, this was a novel paramyxovirus and it's one that seemed to be closely related to Hendra virus, which had been discovered just a few years earlier in 1994 in Australia.
Erin Allmann Updyke	Which is also so interesting.
Erin Welsh	Yes.

Erin Allmann Updyke	Because Hendra and Nipah are very different than other paramyxoviruses.
Erin Welsh	Yeah.
Erin Allmann Updyke	So it's very interesting that like Hendra was just discovered a few years prior and then here comes Nipah on the scene.
Erin Welsh	I know, I know. I feel like the 90s had a lot of these. We'll get into it in a second.
Erin Allmann Updyke	Okay.
Erin Welsh	The name Nipah was given to the virus after the village Kampung Sungai Nipah where the patient whose samples were used to detect the virus had lived. So it was like this person, that's where they had lived. An international team of experts traveled to Malaysia to learn more about this novel virus, how it was being transmitted, and helping with like containment measures. And they ultimately concluded that it was from the pigs. By the end of the 1998-1999 outbreak, 265 people had been infected with Nipah virus in peninsular Malaysia and 11 people in Singapore, which had imported pigs from Malaysia, and 105 people died. Which is like I said, a case fatality rate of around 40%.
	The majority of those infected, around 70% were directly involved in pig farming. And there was significant association between people who had worked closely with pigs and piglets, like giving injections or medications, assisting with birth, handling of dead pigs and so on. Just to think about this like okay, yes, it was an outbreak among people who farmed pigs. But you also have to think about these were entire communities. I watched in one video someone describing how there would be a street where, homes on a street, and every single home had a funeral happening the same week because it had hit that farm.
Erin Allmann Updyke	Right.
Erin Welsh	And all of the people who had lived on that street worked on the farm. And it's just like-
Erin Allmann Updyke	Everyone worked there. Everyone. Yeah.
Erin Welsh	Everyone. It's really awful. And it wasn't over. Once this link between the pigs and the infection was made, the government ordered all pigs in affected areas to be culled. So in total around 1.1 million pigs were killed in a process that was described as just utterly horrific. One person said I don't think that I could do this again, I could participate in this again.
Erin Allmann Updyke	It sounds absolutely awful.
Erin Welsh	Yeah. And 1.1 million pigs, that was nearly half of the pig population. And while the culling did seem to halt transmission, so 5.6% of all pig farms in peninsular Malaysia were positive for Nipah virus, it was also catastrophic for people who had made their livelihoods out of this.
Erin Allmann Updyke	Yeah.

Erin Welsh	I don't know anything about whether there was compensation for culled pigs but I did read that very few people were able to continue with pig farming after this. Maybe because like testing restrictions were too difficult to meet afterwards or the financial burden was placed entirely on the farmers and workers or maybe because they didn't want to get sick and die if there was another outbreak, maybe they had horrible like trauma from that other outbreak. Before the outbreak there were 1885 pig farms in peninsular Malaysia and by July of 1999 there were 829.
Erin Allmann Updyke	Wow.
Erin Welsh	Right? And I think an outbreak like this really shows how far the impacts of a disease can ripple outward. Like on the personal scale, people lost their lives or their loved ones, their neighbors, their support system, their livelihood. On the regional scale, this virus resulted in a major hit to an important industry which led many people to move or entirely change their way of life. And globally Nipah virus I think represented another terrifying reminder that our interactions with domestic and wild animals can have deadly consequences. Throughout the 1980s and 1990s, outbreaks of a new deadly virus spilling over from animals seemed to happen over and over again. HIV growing to pandemic levels in the 1980s, Sin Nombre virus in the Southwestern US in 1993, the Hendra virus outbreak in 1994, an incredibly deadly outbreak of Ebolavirus in 1995 with a case fatality rate of 81%, highly pathogenic avian influenza H5N1 one spilling over into humans in 1997. And I'm sure that there are others that I'm forgetting. Spillover events happen and they can be incredibly deadly and this is catching up to us.
	The 1998-1999 Nipah virus outbreak in Malaysia represented in this regard another point in the timeline, another deadly emerging zoonotic pathogen, another confirmation that this would keep happening, this will keep happening, and that we have to approach science in a new much more collaborative and interdisciplinary way if we want to have any chance at prediction, prevention, and control. And one piece of that puzzle was finding out where Nipah virus came from, how it got into pigs in the first place. Given what was known about Nipah's close relative, Hendra virus, which was transmitted from flying foxes to horses to humans, seemed like bats would be a good place to start the hunt. And long story short, that was the right call. A team of researchers collected urine samples and swabbed fruit that had been partially eaten by fruit bats, specifically those in the Pteropus, is that right? Genus.
Erin Allmann Updyke	Yeah, I think so.
Erin Welsh	And found both antibodies to Nipah virus as well as the virus itself. But how did it get from these bats into pigs? Long story short again, humans.
Erin Allmann Updyke	Humans.
Erin Welsh	The leading hypothesis seems to be that over the 1990s, pig farms in peninsular Malaysia grew quite a bit in size and density and many of these pig farms also cultivated mango and other fruit trees. And so this created opportunities for the virus to repeatedly spillover from the bat reservoirs to pigs. Deforestation is also thought to have maybe played a role too because it can drive movement and clustering of bats to the diminishing number of places with resources. So like there's only one stand of trees left, all the bats are going to go there.
Erin Allmann Updyke	All the bats, okay.
Erin Welsh	Much more pathogen exchange, etc.
Erin Allmann Updyke	Okay.

Erin Welsh	It also appears that the September 1998 cases weren't the first of Nipah virus. Samples from five people who got sick in 1997 were retested and found to be positive.
Erin Allmann Updyke	Okay.
Erin Welsh	It's possible that it's even older than that, I just-
Erin Allmann Updyke	Right. Don't have samples.
Erin Welsh	Those are the earliest samples that as far as I know have been found. How did the virus get into the bats? We've gone now back the chain of transmission. I mean it probably had been there for quite some time. Seems like it evolved with its bat hosts and doesn't really seem at least as far as I read to cause substantial disease in bats. So in that way it's similar to Hendra virus. The 1998-1999 outbreak of Nipah virus in peninsular Malaysia seems like it was the virus getting its foot in the door because nearly every year since... I was going to go through all the subsequent outbreaks one by one but it's like every single year.
Erin Allmann Updyke	Almost every single year.
Erin Welsh	Almost every single year, it's remarkable, outbreaks have happened especially in Bangladesh and India. But these outbreaks are different from the 1998-1999 outbreak in Malaysia in a couple of alarming ways and we've kind of touched on this already. The first being that the case fatality rate is substantially higher than the 40% reported in Malaysia.
Erin Allmann Updyke	Yeah.
Erin Welsh	So on average it's been around 70% with that one outbreak in 21 people in Kerala, India in 2018 reporting a 91% case fatality rate. And the second is that unlike the outbreak in Malaysia which seemed to mostly be from pigs to people, these later outbreaks involved much more human to human transmission which has set off some alarm bells in terms of epidemic or pandemic potential for this virus which after 1999 has for the most part only been involved in outbreaks in the double digits. But will it stay that way?
Erin Allmann Updyke	Right.
Erin Welsh	To help answer that question we need to better understand how these outbreaks happen in the first place. What increases the likelihood that Nipah virus will spillover into humans and what seems to reduce that risk?
Erin Allmann Updyke	Yeah.
Erin Welsh	I can't answer these questions.
Erin Allmann Updyke	How do we stop this? How do we stop this?
Erin Welsh	But luckily there is someone who can.
Erin Allmann Updyke	And we've got them here today.
Erin Welsh	We've got them here today. Let's chat with Dr. Clif McKee all about the ecological drivers of Nipah virus outbreaks.

Clifton McKee	So I'm Doctor Clifton McKee, I'm a disease ecologist and a research associate at the Johns Hopkins Bloomberg School of Public Health. I came here in 2020 to study Nipah virus in bats in Bangladesh. And before that I was a PhD student at Colorado State University studying bacterial infections of fruit bats, kind of the diversity of these bacteria and their ecology. And I've worked on kind of some other projects on bacterial infections in felines. And I think generally my research focuses on one health and trying to understand the dynamics of pathogen spillover at human animal interfaces and prevention efforts and epidemiology across scales.
Erin Allmann Updyke	Thank you so much for joining us today. We are thrilled.
Erin Welsh	Super thrilled, yeah.
Erin Allmann Updyke	Like so super excited to have an actual expert here to talk about the ecological drivers of Nipah virus outbreaks and then also some of the strategies for predicting and controlling. This is going to be such a fun time. If we can start off with the bats that are at the center of all of this Nipah virus mess, the ones in the Pteropus, the Pteropus genus, the flying foxes. What are some of the ecological characteristics of these bats that lead to spillover events of Nipah virus? And does it differ across the different species of the Pteropus?
Clifton McKee	So the the different Pteropus species that carry Nipah virus including Pteropus medius, Pteropus lylei, Pteropus hypomelanus, and Pteropus vampyrus have a lot of similarities in their ecology that could factor into spillover of the Nipah virus. All four of these species are known to roost and forage near human settlements and even in highly urbanized areas. And they commonly feed on cultivated fruit like mango, banana, and guava. And roosting sites for these species can range from sort of intact forests to a large tree in a village area or even a park in the middle of a city. And in some countries like Thailand and Vietnam, roosts are often situated on temple grounds where they receive some sort of some protection from disturbance.
	But the common denominator seems to be that these species all tolerate human presence really well and are opportunists. They feed on sort of a mixture of cultivated and wild fruit and nectar resources that are available in their area in a given season. Now there are some species that are more urbanized than others such as Pteropus medius that's found in India and Bangladesh. But I don't think we have really any indication that these species are gravitating towards humans per se or rather that land use change has stripped away sort of the native forests and the bats have found ways to adapt to this modified landscape. So the amount of potential contact between Pteropus bats and people has a lot to do with the amount of modification that's gone on in some regions vs others and maybe has less to do with the fundamental differences in their ecology.
Erin Welsh	Oh okay. Interesting. Yeah. Nipah virus outbreaks have occurred in only a fraction of the geographic range of Pteropus bats, suggesting that... Like does this suggest I guess that we're only seeing the tip of the iceberg when it comes to possible outbreaks? Or maybe a more specific question is do we know what set or sets of circumstances lead to a spillover event? And then what allows or causes a spillover event to turn into an outbreak?

Clifton McKee

Speaking first towards sort of like these sets or set of circumstances that lead to a spillover, having bats living near humans is a necessary prerequisite for spillover to happen but proximity alone really isn't sufficient. In the Nipah outbreaks that have happened in Malaysia, in Bangladesh, as well as another probable outbreak in the Philippines, there was this added element that allowed spillover to happen. I kind of think of it as a channel perhaps. In Malaysia that channel was pigs which were likely exposed when bats came to feed on mangoes and other fruits on farm premises that were doing mixed agriculture. And so these bats dropped partially eaten mangoes or fruit pits into the pig sties. In the Philippines the channel was horses which may have encountered dropped fruit or pasture grass that was contaminated with bat urine, similar to what we see with Hendra virus.

And in Bangladesh the channel is date palm sap. The sap is collected from date palm trees during the night and then it's sold fresh often with the sap seller going door to door to different households. And we know from infrared camera footage that Pteropus bats frequently come to date palm sap trees to consume the sap and probably contaminate the sap with their saliva or urine, potentially containing Nipah virus. So in all of these cases there's some novel ecological element that creates this channel for Nipah virus to get from bats into humans, either via some bridging hosts like pigs or horses that humans interact with more frequently than bats or a food item that allows humans to have direct contact with the virus.

So the absence of Nipah cases in other Asian countries that Pteropus bats live in is maybe a bit of a mystery. But I think the simplest explanation is that it's these novel ecological elements that widen this pathway for Nipah to get from bats into humans, they're missing or they might function differently than in areas with known outbreaks. And then there are other interactions with bats that could plausibly be involved with spillover including bat hunting or humans eating dropped fruit directly from the ground. In Bangladesh these exposures haven't been significantly associated with infection in case control studies, only date palm sap consumption was associated. So there's some speculation that the dropped fruit consumption is the cause of recent outbreaks in Kerala, India but there just aren't enough cases yet to draw really strong conclusions.

And to get to this question about sort of the tip of the iceberg part of your question, I do think there are potentially spillovers that we're missing, especially those that only cause a handful of cases. And this is because hospital-based surveillance for Nipah virus was for a long time only happening in Bangladesh. But large outbreaks of severe respiratory disease or encephalitis, I think those are hard to miss. So while I think there's probably some Nipah spillovers that are going on undetected in countries across the range of Pteropus bats, we're probably not talking about thousands or hundreds of thousands of cases that are going undetected.

And speaking to what takes a spillover to become an outbreak, this mostly depends on the epidemiological conditions that facilitate human to human transmission. So Nipah virus doesn't really transmit that well between humans. Less than 10% of cases actually transmit to another person. But in areas where there aren't good hygiene practices in hospitals, there have been outbreaks that happen inside of hospitals. And in one large outbreak in Bangladesh, person to person transmission largely centered around a local religious leader whose followers came to visit them while they were sick. So these epidemiological conditions could change in the future and open up new risk factors or even with the introduction of a new strain of the virus. But for now the major source of human cases is directly from spillover and not person to person transmission.

Erin Allmann Updyke

So you mentioned surveillance which initially was happening only in Bangladesh. And it's our understanding that the threat of Nipah virus is also not consistent year round and there was at least for a time increased surveillance or surveillance that only happened during certain parts of the year. Can you talk a little bit about the seasonality of Nipah virus in Bangladesh and how it's driven or is it driven by the ecology of flying foxes?

Clifton McKee

Yeah. So the seasonality of Nipah virus spillovers in Bangladesh is tied really closely to when date palm sap is harvested for fresh consumption. Almost all human outbreaks have happened in winter and that's between November and April and this coincides with the sap harvesting season. In areas where sap is harvested for fresh consumption, bats only have access to the sap during these winter months. And in areas where sap is harvested for other purposes like molasses production and trees are tapped year round, we do see that bats will feed on the sap in summer months because it's available but they do make more visits during winter. And we think this has to do with just the bats' opportunistic feeding behavior. But maybe they're shifting towards drinking this sap because they lack other fruits during winter, there's just not as much that's ripe during that time of year.

But going back to this idea of date palm sap being this channel, it seems like this channel for spillover is only open for a very limited time. Now what's interesting is that the bats are not more likely to be infected with Nipah virus during winter. So detections of Nipah virus and bats are pretty sporadic throughout the year. And at least in the large roosts that have been monitored for multiple years, there might even be more detections in spring and summer months. So there's this disconnect. It could be that date palm sap, this channel is just good enough or well timed enough during winter to let some trickles of virus through into humans. But there might be an alternative explanation.

We did a study where teams investigated Nipah spillovers in Bangladesh where the teams identified the nearest Pteropus bat roost to a human spillover and then collected urine samples to test for Nipah. In a handful of roosts, they were able to detect Nipah virus in bat urine often weeks after the human case had been reported. And mind you, these investigations were all happening in winter. The roosts with detected virus were not these really large bat roosts but rather smaller roosts of a few hundred bats. This indicates that bats can be shedding the virus in winter but perhaps it's happening in some of these smaller roosts. And so what we need to understand better is how bats are moving within this network of large vs small roosts, the seasonality of these movements, and the effects of Nipah virus transmission among that population on sort of a whole landscape scale.

Erin Welsh

There are so many factors I feel like that go into this, it makes it incredibly complicated. And you've kind of touched on one already which is human land use change and these other ways that humans have sort of changed the ecology or the landscape of these bats. And I was wondering if you could kind of dive a little bit deeper into that and talk about how habitat loss or deforestation, what role these play in setting the stage for a spillover of Nipah virus from bats to domestic animals or from bats straight to humans and sort of what that looks like or the different ways that could look.

Clifton McKee

Well I keep going back to this idea of channels. None of those would exist if it weren't for humans putting them there. The intensive pig farms in Malaysia or horses in the Philippines or even date palm sap in Bangladesh, none of these occur naturally. Date palm trees are native to Bangladesh but access to sap requires carving out a section of the trunk which is not something that bats can do. So a key landscape change is definitely the placement of these channels for spillover into the system, be it domestic animals acting as bridging hosts or foods that can carry the virus directly from bats to humans.

But zooming out a bit further though, these key pathways may just be sort of the the finishing touches in the process of landscape change. Historical loss of forests and conversion of land for human agriculture is really the ultimate force that's bringing humans into closer proximity with fruit bats. You take a native forest where bats feed on wild fruit and nectar, then cut those trees down and replace them with fields and places to raise domestic animals and also put in cultivated fruit trees. The bats end up just sticking around in the remaining trees and eat mangoes and other things in people's backyards. So really humans have inserted ourselves into bat habitat and the bats just tolerate it but it becomes this recipe for virus spillover.

Now I think the timeline of this process differs slightly among the outbreak countries. For Malaysia, the process of clearing land for agriculture and increasing production of pigs and mangoes was something that was ramping up a lot in the 1970s, 80s, and 90s, setting the stage for the outbreak in 1998. But in Bangladesh the majority of forests have been gone since the 1700s and date palms have been cultivated for sap and molasses production over that whole time because we know that the British colonialists in Bangladesh encouraged planting of date palm sap trees. So the conditions for spillover in Bangladesh have been present for a long time but we didn't know to look for human cases of Nipah until we knew there was a virus and we had tests to detect it.

Erin Allmann Updyke

Kind of going along with that, is there evidence that Nipah virus outbreaks are increasing in either frequency or severity? And kind of maybe zooming out even further, what are the possible effects of things like climate change on the ecology of Nipah virus or on these spillover events?

Clifton McKee

I don't think outbreaks are increasing in frequency or severity. There haven't been any more spillovers in Malaysia since the 1998 outbreak. And in Bangladesh the number of cases linked to date palm sap consumption kind of goes up and down and has been a bit slower since 2016. And the outbreaks haven't been as large as in previous years, which might speak to the effectiveness of control efforts that have gone on. But what is interesting is that the number of spillovers we see in Bangladesh is correlated well with how cold a winter season is, which likely links back to date palm sap production and consumption practices. So date palm sap collectors anecdotally report that they get higher quality sap during colder winter nights. And we also know from household surveys that consumption of sap is higher in cooler years.

Now this might be caused by something about the physiology of the trees producing more sap or higher quality sap or just that the sap is less likely to spoil in cooler weather. But something about weather is driving this system. So as climate continues to warm, this suggests that Nipah spillovers through date palm sap consumption in Bangladesh might decline. However I don't really want us to become complacent about Nipah in Bangladesh. We know that Nipah virus can take other pathways to get to humans like through domestic animals. So I think we need to remain vigilant with surveillance. Case in point is India. Those outbreaks in Kerala came out of left field in 2018 and we don't completely understand the ecology of what's happening there, the pathway that the virus took from bats into humans, and any of the effects of land use change that might be at play in India.

And of course every single spillover event is a new chance for a strain of Nipah virus that has higher transmissibility in humans, for that strain to emerge or for higher transmissibility to evolve in humans or some bridging host. And of course climate change could alter the range of Pteropus bats and cause some species to shift their roosting locations and food resources to overlap even more with humans, leading to potentially more spillovers. We honestly don't really know what's in store for us. So I think extending human surveillance efforts modeled in Bangladesh to other Asian countries that have Pteropus bats could be a first step but also sort of expanding surveillance to domestic animals, for example on large pig farms, could be a good step.

Erin Welsh	Problems like Nipah virus outbreaks really require a one health approach which is something that we love on the podcast, we're always mentioning, we're always talking about, we're such big fans. And this involves people working collaboratively across disciplines and organizations and different levels of government and with community involvement too to address the health of humans, animals, and the environment. Even though we're always talking about one health on the podcast, I don't know if we've ever really talked about what an actual one health approach looks like on the ground. And I was hoping you could talk a little bit about that. Like what does a one health strategy for Nipah virus look like and why is it so important for this particular pathogen?
Clifton McKee	Nipah virus is really kind of a perfect example of the power of a one health approach for emerging diseases. And at the heart of one health is this shared focus on human health, animal health, and environmental health. So with Nipah you have to think beyond just the human outbreaks and dig into bat ecology and the health of bats; agricultural systems and those interfaces between bats, domesticated animals, and humans; and the economic forces that are at the root of things like land use change and choices to harvest certain food products like date palm sap. Nipah touches on all of these things and you have to address them holistically. And a key part of this implementation of one health is with the formation of project teams, not only including sort of epidemiologists and virologists in investigations but also ecologists and veterinarians, anthropologists and other social scientists.
	Teams not only have to be interdisciplinary but ideally transdisciplinary with individuals on the team that have gone beyond their specialized training to work in other disciplines and can act as liaisons and facilitate this really collaborative work. And then speaking to one health approaches to Nipah in Bangladesh, in addition to ongoing human surveillance efforts at hospitals, we're also looking into the frequency that Nipah virus might be spilling over into domestic animals including cows, goats, pigs, cats, and dogs. Because this might be another pathway for the virus to jump into people outside of the winter date palm season and might not be currently captured by the existing surveillance efforts which are really optimized for spillover through this date palm sap channel.
	We also should be researching kind of more about how the health of bats varies over time and space and how much this contributes to spillovers. There's this hypothesis out there that bats might shed more viruses when they're experiencing stress, either during food shortages or during pregnancy and lactation. So if we knew more about when bats are stressed then we could inform public education campaigns about not drinking sap or ramping up surveillance on domestic animals. We could also use this information to find ways to support the health of bats, maybe by restoring forest habitat and wild food resources. And lastly I think the social sciences are crucial for implementation of prevention. For example, getting people not to drink sap has been difficult to do in Bangladesh because it's such a strong cultural practice and people perceive it to be low risk. So identifying ways to protect sap from contamination by bats using things like bamboo or plastic coverings or economic incentives to encourage sap producers to maybe shift from selling raw sap to selling molasses. Any work we can do to make these more acceptable could go a long way to prevention of Nipah virus spillovers.
TPWKY	(transition theme)
Erin Welsh	That was so great.
Erin Allmann Updyke	I loved it.
Erin Welsh	Loved it.
Erin Allmann Updyke	Yeah.

Erin Welsh	Yeah. Thank you so much.
Erin Allmann Updyke	Thank you so much.
Erin Welsh	Jinx. Dr. McKee, for chatting with us about this. It really is just so great to talk to an expert who actually is there doing the work on one health stuff.
Erin Allmann Updyke	In it. Doing, doing the thing. Thank you for your work.
Erin Welsh	Doing the thing. Thank you for your work and your time.
Erin Allmann Updyke	Yeah.
Erin Welsh	So.
Erin Allmann Updyke	So let's wrap this up, shall we, with just looking at where we stand with Nipah virus today.
Erin Welsh	Let's do it.
Erin Allmann Updyke	So the good news, there's a few good newses. Good newses? There's some good news to be had in this case. Thus far as of 2024 or I should say as of 2023 when the papers that I read were written, Nipah virus has still caused less than 700 human cases. But I think that we've also made the case through this whole episode that that doesn't mean that it's not worthy of study, this is a virus that has a lot of potential to cause quite a number of more cases than that. And because of that reason a lot of people are working on Nipah virus. Like I said at the very top, this has been named one of the top 10 high priority pathogens for the World Health Organization. Because the truth is that these spillover events are not something that is happening rarely.
Erin Welsh	Right.
Erin Allmann Updyke	Between 2001-2018 in Bangladesh alone, over 183 spillover events have happened.
Erin Welsh	That's a lot.
Erin Allmann Updyke	183 individual spillover events. And there have been additional outbreaks and spillover events that have happened in more and more places in different parts of India, in Singapore, in the Philippines. This is a virus that exists, persists, and luckily a lot of people are trying to understand it both from the one health approach that we heard about already and also vaccines and therapeutics. So while there are still not vaccines yet, this is one of the few times where I get to say that there are a lot of candidates that are moving through the clinical trials process which is really exciting. There are a few different ones that I found, two of which have started trials in humans as of the end of 2023 and early 2024. Both of these from what I can tell are mRNA-based vaccines which is kind of exciting. And there are also people who are developing vaccines for animals, for example there's already a Hendra virus vaccine for horses. And so the idea that you could use a Nipah virus vaccine to vaccinate things like pigs might be helpful in preventing spillover into domestic animal populations.
Erin Welsh	That's really cool.

Erin Allmann Updyke	Yeah. There's also a lot of work being done on additional therapeutics and antivirals and monoclonal antibodies. Right now there still aren't any that have actually come to market. But there is just so much focus I think on Nipah virus and on understanding that it can't be just one of these things. It's vaccines in combination with therapeutics, in combination with prevention strategies, in combination with a one health approach and really looking at this virus as it truly exists which is something that is in the environment that we don't have complete control over and we can never actually eradicate. So I think that this is one of the times where if we go all the way back to first season and we say how scared do you need to be? If I'm being honest, Nipah virus has scared me since 2011.
Erin Welsh	Is that when Contagion came out?
Erin Allmann Updyke	When Contagion came out.
Erin Welsh	Okay, yeah.
Erin Allmann Updyke	I think it's a very, very terrifying virus. But I think there's a lot of really incredible people that also think that this is a terrifying virus who are doing everything that they can to prevent it from ever becoming something that most people ever have to hear about.
Erin Welsh	That's such a great answer. It is, it is.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's like yeah, this is scary. A lot of people think so, that's why we're working really hard on it and hopefully we'll have therapeutics or vaccines or detection or a combination.
Erin Allmann Updyke	Right.
Erin Welsh	In case something like this does lead to a larger epidemic.
Erin Allmann Updyke	Right.
Erin Welsh	Pandemic.
Erin Allmann Updyke	Yeah. And that's Nipah.
Erin Welsh	That's Nipah.
Erin Allmann Updyke	That's Nipah.
Erin Welsh	Sources?
Erin Allmann Updyke	Sources. I've got a lot. Shall we?

Erin Welsh	I have so many. I'm shouting out just a couple here and all of the rest will be on our website. So there are several papers by Dr. Chua, one that I really liked was in Science called 'Nipah virus: A recently emergent deadly paramyxovirus', that's from 2000. And then there is a paper on the evolution and origin of Nipah virus by Presti et al from 2016 called 'Origin and evolution of Nipah virus'. And I will also on our website link to some of Dr. McKee's work on Nipah virus and sort of the bat spillover dynamics of pathogens, one health, all that good stuff.
Erin Allmann Updyke	Yeah, he's got some really great papers.
Erin Welsh	Also I referenced a paper of his in our Bartonella episode. Just got to shout it out.
Erin Allmann Updyke	What? We go way back. Just kidding. For the biology section, I had also quite a number of papers. Detail on the true biology and pathophysiology of this pathogen, I really liked a paper in the New England Journal of Medicine called 'Transmission of Nipah virus: 14 years of investigations in Bangladesh' by Nikolay et al. And honestly there were so many more and Erin, like you said, a couple by Dr. McKee that were also phenomenal. We will post all of our sources from this episode and every one of our episodes, there's some about the vaccines, there's so much, on our website thispodcastwillkillyou.com under the EPISODES tab.
Erin Welsh	Thanks again, just got to say it one more time to Dr McKee. You're a champion. Thank you.
Erin Allmann Updyke	We really appreciate it. Thank you also to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Welsh	Thank you to Tom and Lianna for the wonderful audio mixing.
Erin Allmann Updyke	Love it. Thank you Exactly Right network.
Erin Welsh	And thank you to you, listeners, for listening.
Erin Allmann Updyke	Yeah.
Erin Welsh	We hoped that you learned something new.
Erin Allmann Updyke	This is one of our first episodes this season of a real classic TPWKY.
Erin Welsh	Classic TPWKY, yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	Long time, long time coming. Yeah.
Erin Allmann Updyke	Thank you especially to our patrons as well for supporting us on Patreon. We really, really appreciate it.
Erin Welsh	We really do. Until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.