Erin Allmann Updyke	"No one would believe the mischief the rabbits are doing unless they could see it. The sheep farmers have not tried to clear them and now many of the runs are so bare that there's not grass enough to feed the rabbits, let alone the sheep. The consequence is that the rabbits are traveling in thousands in search of food. Last Friday morning soon after sunrise I met a swarm coming from the hills. I never saw such a thing before. The ground was scarcely to be seen for about a mile in length. Five weeks since I could not find a rabbit on my land but since then we have killed thousands. When the sun is hot, you can go along the fences or any place where it is shady and kill hundreds with a stick. Today has been cool but still I several times killed 2 or 3 at a blow. The paddocks stink with the dead ones."
Erin Welsh	"Immediately prior to the liberation of myxomatosis, a combination of circumstances had led to the build up of rabbits to very high levels over much of most of their range and the situation in many areas could only be described as desperate. The change has been almost miraculous. The landscape in some areas has been virtually transfigured. Hills that had been grazed to the soil for decades and whose slopes appeared gray and red on the horizon are now clothed in grass. The broad margins of the country roads lying outside the boundary fences of grazing properties tended to carry dense rabbit populations and as often as not showed it in the poverty of their ground cover. It is now usual to see tall grass to the road's edge. Looking over the fences it is now very rare to see a paddock without a dense and healthy pasture."
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Wow.
Erin Allmann Updyke	I love it. And those two passages just got me so excited for this episode.
Erin Welsh	It's very interesting to kind of see very clear before and after quotes. Yeah. Those two quotes I lifted from a book called 'The Biological Control of Vertebrate Pests'. And they are both about the topic of today's episode, myxomatosis.
Erin Allmann Updyke	Myxomatosis.
Erin Welsh	The Radiohead song. So we're going to talk in this episode all about Thom Yorke and what inspired him to write the song Myxomatosis.
Erin Allmann Updyke	I have no idea what you're talking about.
Erin Welsh	(laughs) Erin! Okay, myxomatosis is actually the topic of today's episode but it's a virus that affects rabbits and it also happens to be the title of a Radiohead song.
Erin Allmann Updyke	Wow, I definitely did not know that last part.
Erin Welsh	I listened to it in prep for the recording today.
Erin Allmann Updyke	Nice. We should try and get the rights.
Erin Welsh	Bloodmobile, can you write us a knockoff? I feel like I should introduce myself before we begin the rest of this introduction. This is all over the place.
Erin Allmann Updyke	Maybe we should.

Erin Welsh	Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	Yes it is, welcome. If this is your first time here we usually do things in a different order.
Erin Welsh	And maybe a little bit more clean and a little bit more organized, yeah.
Erin Allmann Updyke	We're just so excited about myxomatosis and I think you were really excited to tell me about Radiohead.
Erin Welsh	I really was. I really was.
Erin Allmann Updyke	Did you know that I wasn't going to know? I feel like you did.
Erin Welsh	I gave it about a 55/45.
Erin Allmann Updyke	Okay, okay.
Erin Welsh	Yeah.
Erin Allmann Updyke	But yes, a rabbit viral disease is what we're talking about today. It's going to be great even if you think you don't like animal viruses or you don't like rabbits or you do like rabbits, you're gonna love this episode.
Erin Welsh	I think so too. This is like if you just clicked on this out of sheer curiosity and you're like, 'Okay, now I'm having my doubts. This is a rabbit disease?'
Erin Allmann Updyke	Yeah.
Erin Welsh	I promise, I think this is one of the most interesting and important stories about disease that we have covered on this podcast.
Erin Allmann Updyke	Agreed.
Erin Welsh	Because it covers so many different topics, so many different concepts.
Erin Allmann Updyke	Yeah. It is such a good story, promise.
Erin Welsh	It is. But we have some business to take care of.
Erin Allmann Updyke	We do. It is first quarantini time.
Erin Welsh	It is. What are we drinking this week?
Erin Allmann Updyke	We're drinking Bunny's Bug. Get it?

Erin Welsh	Yeah. Bunny's Bug is a tasty little drink that has hop water because bunnies hop. I don't know if we needed to explain that.
Erin Allmann Updyke	I like it though, I like the explanation.
Erin Welsh	It has lime juice, it has mescal, it has simple syrup and it has some grapefruit juice.
Erin Allmann Updyke	Yum. Delish. We'll post the full recipe for that quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com and all of our social media channels.
Erin Welsh	Oh, is it my turn to do the website information now?
Erin Allmann Updyke	It is.
Erin Welsh	Okay. On our website you can find transcripts, you can find our bookshop.org affiliate account, you can find our Goodreads list, you can find links to music by Bloodmobile, you can find all of the sources for each one of our episodes, you can find links to the promo codes that we mention in our ads.
Erin Allmann Updyke	Merch we've got, transcripts we've got. Yeah, we got it all. Check it out.
Erin Welsh	That's gotta be it. Okay.
Erin Allmann Updyke	Well then, should we get into it?
Erin Welsh	Let's do it.
Erin Allmann Updyke	Okay. We've hyped it enough, you think?
Erin Welsh	I hope we haven't overhyped it.
Erin Allmann Updyke	Let's find out right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	Fair warning listeners, I am starting off this biology section kind of intentionally withholding details for later dramatic effect. So let us begin. Myxomatosis is a disease caused by the myxoma virus which is a member of a family we are familiar with here on the podcast, it is a pox virus, as in smallpox. I don't think we've covered any other pox viruses.
Erin Welsh	I was just gonna ask.
Erin Allmann Updyke	I can't remember. Oops. But anyways, yeah. This is a different genus of pox virus, this is a Leporipoxvirus and smallpox is an Orthopoxvirus if anyone cares. But all of the pox viruses are double-stranded DNA viruses, they have pretty big genomes, and the virus itself if you look at it under a microscope is shaped like a brick which I just think it's funny that every single paper described it as a brick-shaped virus.
Erin Welsh	Interesting.

Erin Allmann Updyke	It is. The pox virus, Myxoma virus, replicates in the cytoplasm of cells and it's a really fascinating virus because it has a lot of proteins that interact with the host immune response that become really important in terms of how much disease we actually see in its various hosts. And Myxoma virus causes disease only in rabbits, it infects a large number of species of rabbits. But as far as I can tell it doesn't cause clinical disease in any of the other hosts that it has been tested in other than rabbits and I think one species of hare.
Erin Welsh	Yeah.
Erin Allmann Updyke	Which are all called lagomorphs. I learned so many new words researching this episode. But Myxoma virus interestingly can replicate in vitro, like in a Petri dish or a cell culture bottle, in cells from many, many different host species including human cancer cells which it turns out are particularly good at letting Myxoma virus in and letting it replicate.
Erin Welsh	Interesting.
Erin Allmann Updyke	Very. And I'm throwing that little tidbit out there and then just going to leave it to dangle and circle back to it at the very end of the episode.
Erin Welsh	Okay. I was all poised to ask a question but I will restrain.
Erin Allmann Updyke	I could tell, yeah. Okay but today we're talking about rabbits. So this Myxoma virus causes the disease known as myxomatosis in rabbits and hares and specifically it causes the severe disease that we know of as myxomatosis in the European rabbit Oryctolagus cuniculus, if I'm saying that right.
Erin Welsh	Do you remember the books Bunnicula?
Erin Allmann Updyke	No.
Erin Welsh	It was like a vampiric rabbit that sucked the juices out of vegetables.
Erin Allmann Updyke	(laughs) I do not, I've never read that book.
Erin Welsh	Really?
Erin Allmann Updyke	Yeah.
Erin Welsh	It was a series of books for kids. But I remember when I saw the scientific name of the European rabbit, I was like oh my gosh that's where Bunnicula comes from.
Erin Allmann Updyke	That's very funny. I have not read those books, I'll put them on my Goodreads list.
Erin Welsh	They're wonderful.
Erin Allmann Updyke	Okay so let's go over what this disease looks like in this European rabbit. So the incubation period tends to be about 4 days and the initial symptoms, I'll kind of go over what this progression of disease looks like. Initially after that, about 4 days after infection, the symptoms are generally redness in the eyes, so kind of a conjunctival inflammation, and an elevated body temperature. What temperature are rabbits' bodies normally you may ask?

Erin Welsh	I would ask, yes.
Erin Allmann Updyke	Yeah. Well I did google it. It's about 102 to 103 Fahrenheit which is 38.9 to 39.4 Celsius. So they run a little hot, this virus makes them a little hotter. And then following after a few more days after initial infection, after these kind of red eye symptoms, these secondary lesions appear. They're often called cutaneous papular lesions, basically just little lumps, little skin-colored lumps on the rabbits that appear kind of throughout their body but most prominently at the bases of their ears. They also get swelling in the anogenital region almost universally. And then they begin to have discharge both kind of a clear, like serous discharge as well as a mucopurulent or kind of pus-filled discharge from the nose and the eyes.
	And then by days 8-10 these poor little rabbits will have a very, very swollen face, droopy ears because of all the swelling at the base of their ears, they'll have severely swollen eyelids and really goopy eyes and goopy noses that get so filled with gunk that their tiny little nasal passages get clogged and then all across their body, like throughout their body, they'll have these little anywhere from a few millimeters to a few centimeters, these little skin swellings across their body. And their anogenital region will become really, really swollen, especially the testicles. And then their breathing will become more difficult and labored, they'll have this kind of stridor which is that gasping inhale. And they generally die between 8-12 days following infection.
Erin Welsh	And so that's 8-12 days after they first get exposed.
Erin Allmann Updyke	Right.
Erin Welsh	So it's only a period of 4-8 days?
Erin Allmann Updyke	Yeah, 4-6 days.
Erin Welsh	Wow.
Erin Allmann Updyke	4-8 days, yeah. It's a very, very rapid course of disease. And myxomatosis, this disease classically has an almost unbelievably high mortality rate in the European rabbit, 99.8-100% mortality. This is along the lines of I think just rabies and prions are the only to diseases two that match this kind of mortality that we've ever covered.
Erin Welsh	Yeah, that we've covered so far.
Erin Allmann Updyke	Yeah. And so the virus, this Myxoma virus, is present in all of those goopy secretions as well as in all of those skin lesions and it's very easily transmitted to other rabbits potentially by direct contact but mostly by various biting arthropod vectors. But even though this is a virus that's transmitted by vectors like mosquitoes and lice or fleas and especially in terms of epizootic or these outbreak scenarios, it does seem like vectors, especially mosquitoes, are pretty pivotal in terms of large scale transmission. Like without them these outbreaks don't really spread or don't spread as quickly.
Erin Welsh	Oh yeah.

Erin Allmann Updyke	But the virus does not rely on mosquitoes for its lifecycle or transmission. It doesn't infect or replicate in mosquitoes the way of most if not I think all of the vector-borne diseases that we've ever covered on this podcast do. What that means is that this vectoral transmission is just mechanical, right, which means that the virus has to be in very, very high titers in the cutaneous lesions, these skin lumps on the rabbits in order for the mosquito or the flea to have enough virus on its mouth parts to then transmit it to the next rabbit.
Erin Welsh	Yeah. Do you know what the infectious dose is in unselected rabbits?
Erin Allmann Updyke	Great question.
Erin Welsh	Yeah.
Erin Allmann Updyke	I don't know exactly but I do know that it seems like critical levels in the skin tissue are like 10 to 7th viral particles per gram of rabbit tissue. So that's like a little over 10 million or so viral particles per gram.
Erin Welsh	Wow.
Erin Allmann Updyke	So really, really high titers are necessary for this to be efficiently transmitted.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	And I'm assuming also that the mosquito has to bite one of the lesions or pick up where the gunk is.
Erin Allmann Updyke	Exactly, yes. And that is why it's thought that especially those base of the ear swellings might be very important for viral transmission because that's a common place for mosquitoes and other vectors to bite the rabbits. So now anyone who's listening who knows the story of myxomatosis knows that that description that I just gave of this horrifying lethal disease of the European rabbit is not the whole story. So let me dive a little bit deeper. So first off Myxoma virus is still and was first a virus of a different rabbit species entirely, many different rabbit species, specifically the Sylvilagus species rabbits endemic to South and North America. And in the Americas, in these species of rabbits, Myxoma virus causes an entirely different disease if you can even call it a disease really.
	In American rabbits of the genus Sylvilagus, Myxoma virus causes a single skin lump, a single myxoma, and that's it. That's it. That's what it causes. At the site of inoculation you get one big cutaneous lump and that's it. So right off the bat here, this virus is getting interesting because we see this huge variation in disease between host species in terms of the pathogenicity of this same virus. So that's the first part of this story. But number two is what I know you're going to talk a lot more about, Erin, in the history section but that is that Myxoma virus' virulence in the European rabbit dramatically changed over time. So this incredibly lethal version is not the only one which exists. Okay, I don't want to step on your toes too much because I think that hearing this story in its entirety for the first time for most of our listeners is going to be so good. So at this point let me ask you Erin, do you have any other questions about the transmission or details that you want to know about the path of physiology of this virus?
Erin Welsh	Yes.

Erin Allmann Updyke	Okay.
Erin Welsh	Okay. So in the European rabbit and these American rabbits, does the virus sort of enter in the same way and go through its normal replication cycle and move to the different parts of the skin or ears or whatever the body to replicate and cause lesions in the same way over the same time period? Where did the differences start to jump in?
Erin Allmann Updyke	Great question. Okay so this Myxoma virus, when it gets inoculated under the skin either from a mosquito probe or a little flea mouth or a needle in a lab, the virus first infects the rabbits skin cells, their epidermal cells or their dermal cells and it quickly rises to pretty high titers in those skin cells, in those lumps that appear. And then in addition to infecting the epidermal and dermal cells, this virus will go on to infect dendritic cells which I think we've touched on a number of times on this podcast. But these are white blood cells that hang out in our skin and from there spread to our lymphatic system and their goal is to present to other white blood cells these viral particles so that we can start to mount an immune response.
	But what happens with Myxoma virus is it begins to replicate in these dendritic cells and then when these dendritic cells spread to our lymph nodes or our bone marrow and our spleen, this virus is able to continue to replicate and infect other white blood cells. So this virus ends up being at very high concentrations in these skin lesions when they appear and importantly rabbits are not infectious until these skin lesions appear. But they also then have virus that spreads throughout their body, throughout their lymphatic system, and is able to infect a number of different organs and potentially reach relatively high loads there as well. Now to answer your question Erin, what's the difference between these different presentations? The less virulent forms of Myxoma virus and other similar Leporipoxviruses that are very closely related, some of which have been used to make vaccines against Myxoma virus, one thing that they do differently is they're not as good at or in some cases they can't at all infect those white blood cells. So what they cause is just a localized cutaneous infection causing a localized cutaneous skin findings, not causing systemic disease.
Erin Welsh	Okay. Gotcha.
Erin Allmann Updyke	And that seems to really make one big difference. So the virulence we know is at least in part related to how well this virus spreads beyond the epidermis and dermis and how well it invades and replicates within the lymphatic system and becomes a widespread infection.
Erin Welsh	Gotcha. Okay. So then that kind of leads me into my next question which is about immunity. So as we'll talk about later on in this episode, rabbits, the European rabbits that were exposed to myxomatosis, showed genetic resistance in later generations. And so they were able to be resistant to this virus separate from the virus' decreased virulence, that's a whole other part of the story, whatever.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	Basically these rabbits were able to resist getting infected.
Erin Allmann Updyke	Yeah.
Erin Welsh	Is the mechanism of resistance the same in the European rabbit? Does it lead to the same reduced disease presence as we see in the American rabbits?

Erin Allmann Updyke	Great question, Erin. So the other part of the pathophysiology of this virus is that Myxoma viruses, all of the different strains, have a whole bunch, more than I could possibly list in this podcast, of proteins that regulate the host immune system in a way that facilitates infection. So they have these proteins that for example inhibit pro-apoptotic molecules. What that means, apoptosis is programmed cell death. That's one of the ways that animals' immune systems have of targeting and fighting off viruses by identifying and killing virally-infected cells, right. Well Myxoma virus has a whole bunch of proteins that it creates specifically to prevent that process from happening in a number of different ways. They also have other proteins that help to interfere with the coordination and recruitment of leukocytes, of white blood cells, basically downregulating that white blood cell response to infections. They have other proteins that block the presentation of antigens by those for example dendritic cells and other antigen-presenting cells so that they block these rabbits ability to make antibodies or even recognize the viral antigens.
	So Myxoma virus has a whole host of different mechanisms that affect a rabbit's immune response to infection that are really important in how much that rabbit is going to be able to resist or be susceptible to severe infection. So to answer your question Erin, it seems like a lot of these specific proteins and mechanisms that the Myxoma virus has evolved in the American rabbits and are kind of perfectly suited in those rabbits to reduce the immune response to a degree that allows for the establishment of an infection but does not impair the rabbit's ability to survive and thrive but also allows the establishment of an infection that's actually infectious, right, that has high enough titers in the skin so that this virus can be transmitted.
Erin Welsh	Okay. So it's like being able to tolerate and coexist.
Erin Allmann Updyke	Exactly.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. And so it's thought that then when those same kind of proteins were introduced to the European rabbit, that is what allowed for this establishment of a very severe infection because of the difference in their immune response and how these proteins interacted with that immune response. And so yes, that's one of the things that tends to change over time as rabbits evolve resistance.
Erin Welsh	It's really interesting.
Erin Allmann Updyke	I love it, I love it so much. I get so excited.
Erin Welsh	I swear this is my last one but I was just thinking about it. So in these rabbits that are resistant in some way to Myxoma virus, whether it's the American rabbits that just have the skin lesions, etc, how long does the virus persist in those hosts?
Erin Allmann Updyke	Ooh, that's such a good question and it's a really important part of the story as well. I don't know is the short answer to it. And I think it depends a lot on what species you're talking about and also what strain of the virus you're talking about. But it does tend to be the case that for example in American rabbits, they can have these lesions that persist for a really long time, these cutaneous lesions can potentially persist for weeks if not months. But again, they don't cause any systemic illness. In more resistant European rabbit populations or with less virulent virus strains, you can sometimes just see a prolonged illness where it lasts maybe 15, 20, 30 days instead of like 8-12 days. So it is variable between species and between strains of virus but it is an important part of the story.

Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. So yeah, that's Myxoma virus, Erin.
Erin Welsh	Interesting.
Erin Allmann Updyke	I think there's more to the story, I mean there's a lot more to the story. So can you tell us the story?
Erin Welsh	I will. If I think of more questions along the way I'm gonna ask you.
Erin Allmann Updyke	Oh good, sounds great.
Erin Welsh	Okay. Let's take a break and then we'll dive into the history of this virus and the European rabbit in Australia.
Erin Allmann Updyke	Okay.
TPWKY	(transition theme)
Erin Welsh	The story of rabbits in Australia, not just their arrival and spread but also Myxoma virus and then later attempts at bio control, it might be one of my favorite topics that we've ever covered on this podcast ever.
Erin Allmann Updyke	Yeah. I mean we've been talking about doing this and I've been wanting to do it for a very long time. So I am really excited.
Erin Welsh	I am too and it's like I said earlier on, this is such an incredible story because it covers so many different themes, right. You could learn about it in a veterinary class, you could learn about it in an ecology class, an evolution class, a virology class, an economics class, a pest management class, history class. There are so many different angles to this but I think it's also really fascinating when you put them all together and consider just the full picture of this story. So yeah, it's about not just how life finds a way, it also it also makes us think about why we choose to use the words 'invasive' or 'pests' to describe one species but not another and how those labels or the things defining those labels, how they shift over time. I could honestly go on and on about how excited I am and all the lessons that we're going to learn from this story but maybe I should just get to the story itself and then we can discuss the lessons as we go.
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay so the long and short of it is that rabbits were introduced to Australia, they bred like crazy, destroyed heaps of vegetation, and eventually the Myxoma virus was introduced as a method of controlling rabbit populations. All right.
Erin Allmann Updyke	That's the short version.
Erin Welsh	That's the short version, let's go to the long version. To do that we have to go to 1788. This is where the story really begins because that year the first fleet brought the first European settlers to Australia along with food tools, agricultural equipment, seeds, alcohol, medical supplies, and a few rabbits.

Erin Allmann Updyke	A few, just a few.
Erin Welsh	Just a few. And these are not the rabbits that we need to worry about. There's no records specifically describing what happened to these first fleet rabbits but they were likely domesticated rabbits and if there were any attempts to introduce them into the wild, they probably weren't successful. And the same could be said more or less for the domesticated rabbits that were brought to Australia in the decades after the first fleet's arrival. That is until 1859.
	That year, everything changed. A farmer by the name of Thomas Austin got it into his head that hunting wild rabbits on his farm would be really super fun. Not the lame domestic rabbits that were kept in hutches, those aren't those aren't fun to hunt, you want the wild ones. And he wanted the wild ones from his homeland of England. So he had his brother who was living in Liverpool send over two dozen wild European rabbits. It seems that only 13 rabbits survived the journey from what I gather but when they got to Austin's farm near Geelong in South Victoria, they were let go, free to breed so that the farm would be stocked with nice wild rabbits to hunt.
Erin Allmann Updyke	Oh gosh.
Erin Welsh	And since rabbits breed like rabbits, that's exactly what they did. So it's estimated that one female rabbit produces about seven litters a year, with an average of 4-6 bunnies in each litter. So let's say between 30-40 per year, one rabbit.
Erin Allmann Updyke	Oh gosh. Whoa.
Erin Welsh	And by the end of a breeding season those kittens - because did you know that baby rabbits are actually called kittens?
Erin Allmann Updyke	I learned that and it's one of my favorite things that I learned while researching this episode.
Erin Welsh	It cracks me up. I'm like wait a second, my whole life. Not bunnies.
Erin Allmann Updyke	Kittens.
Erin Welsh	Kittens.
Erin Allmann Updyke	It's not in any of the children's books.
Erin Welsh	No, at least not the ones I read.
Erin Allmann Updyke	Yeah.
Erin Welsh	But the kittens that were produced early in the breeding season, by the end of that same breeding season were sexually mature and breeding themselves.
Erin Allmann Updyke	Oh no.
Erin Welsh	So yeah, a lot of rabbits.

Erin Allmann Updyke	A lot of rabbits.
Erin Welsh	From 13 to who knows within one year, right. And then you could just see the growth curve on that, right.
Erin Allmann Updyke	Yeah. Exponential.
Erin Welsh	Exponential for sure. And also the change in environment from England to Australia, they're pretty different climates, environments, it didn't slow them down at all because actually the European rabbit is thought to have evolved in the Iberian peninsula and Southern France in a mediterranean climate.
Erin Allmann Updyke	Yeah.
Erin Welsh	Side note, did you know that Spain or Hispania, the name may have come from the Phoenician word meaning 'island of rabbits'?
Erin Allmann Updyke	No, I did not.
Erin Welsh	There's a lot of different proposed explanations for the etymology of Spain but that's one of them.
Erin Allmann Updyke	I love it.
Erin Welsh	Anyway so these rabbits were doing quite well on Austin's farm and off of it. By 1865, 6 years after those 13 rabbits arrived, 6 years, Austin wrote that he had killed 20,000 rabbits off his estate.
Erin Allmann Updyke	Oh my God.
Erin Welsh	And that 10,000 still remained. In the next year's hunt, this is 7 years after their arrival, he reported over 14,000 rabbits killed.
Erin Allmann Updyke	Oh my God.
Erin Welsh	The next year, 1867, Prince Alfred, son of Queen Victoria, killed over 400 in a three hour hunting session.
Erin Allmann Updyke	Oh my.
Erin Welsh	And it wasn't stopped because there were no more rabbits left. It was too hot. 400 in three hours.
Erin Allmann Updyke	Okay. I have a lot of thoughts.
Erin Welsh	I know. The scale of this is really kind of hard I think to comprehend.
Erin Allmann Updyke	Yeah.

Erin Welsh	And Austin, the farmer, definitely helped along the spread of the rabbits or at least likely by introducing them to new areas and other people coming in and being like, 'I want rabbits too, hunting is really fun.' But honestly the rabbits didn't need that much help and it's not like anyone was actively trying to prevent their spread. Instead the arrival of the rabbits was seen as something to be celebrated.
Erin Allmann Updyke	Oh no.
Erin Welsh	I know. We can look back at that now and be completely horrified because we know how this story plays out and how so many other introduced species stories play out. But let's consider the historical context.
Erin Allmann Updyke	As we always do on This Podcast Will Kill You.
Erin Welsh	When Thomas Austin imported and released those rabbits it was during the period of large scale colonialism that was taking place around the globe from around the 1500s into the early 1900s. And during that time it was a really common practice for colonizers to bring with them things that reminded them of home or things that they used to eat or farm, basically anything they thought would make their new life easier or more pleasant. Colonialism is how so many different species traveled to new places, both intentionally or unintentionally, rats, cats, foxes, starlings, so many species of plants, pathogens, I mean like everything, everything. And the worldview that was imposed on the places being colonized was the one commonly held by most European or American colonizers at the time that plants and animals were put on this earth for humans to eat or to use for work or to simply enjoy.
	Biodiversity and the interconnectedness of species in an ecosystem, these things weren't really considered by the colonizers or even known about. A species' importance was defined by how it could be used for humans, the benefit that it gave to humans, not its ecological role. Those concepts, like the interconnectedness of all the organisms in an ecosystem and just how interdependent they were, those may have been held by some people or at least recognized a little bit by some people and some cultures but they were still decades away from being widespread.
	Ecology as a field of study didn't really even get started until the 1920s and the notion that biodiversity was important was even further in the future. And even if someone did hold those views back then, they probably weren't in a position to argue against those who were in power making these decisions because introductions of non native species like the European rabbit to Australia, they weren't just done casually by a few plant or animal enthusiasts, they were encouraged sometimes to the point of being included as a government directive. Yes. For instance, legislation from New Zealand in 1861 was passed quote "to encourage the importation of these animals and birds not native to New Zealand which would contribute to the pleasure and profit of the inhabitants when they became acclimatized and spread over the country in sufficient numbers".
Erin Allmann Updyke	Oh my God. Oh my God, it's giving me palpitations.
Erin Welsh	I know, I know, I know.
Erin Allmann Updyke	Oh my god.
Erin Welsh	There just wasn't the knowledge of... Yeah.

Erin Allmann Updyke	It's so hard to hear that though, to go back and be like oh my god, you intentionally ruined the world. I mean we've been doing it for so long but...
Erin Welsh	I was going to say so, so many stories. Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so all of this is just to say that if Thomas Austin hadn't brought over the rabbits when he did, it was probably just a matter of time before somebody else did.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	Just as certain species were valued for their potential for profit or enjoyment by humans, others were seen as hurting humans or human interests: pest species. And this term is still plenty in use today, typically in an agricultural context. And it's separate from terms used to describe a species origin, like native or non native/introduced which refers to where a species evolved, or the term invasive which describes the species that's been introduced and is detrimental to the native species in an area. So a pest species can be native or invasive and there are a lot more terms dealing with these concepts, but I don't want to overwhelm with terminology and definitions.
	But this concept of pest species is entirely defined by the meaning to humans for the most part and it has origins all the way back to the agricultural revolution 10,000-12,000 years ago when people began to interact more with the plants and animals that disrupted their crop yields or their livestock numbers and that gave rise to this term 'pest' from the Latin 'pestis' for plague. And people devised ways to deter those pest species like scarecrows, manual removal, fences, poisoning, hunting and trapping, introduction of animals to control them, etc. Some species may have been considered pests almost universally or at least wherever they were found, like mosquitoes, but for many others the label of a species as pest depended on who you asked.
Erin Allmann Updyke	Yeah.
Erin Welsh	For instance, wolves and sheep. So if you're a sheep farmer, you may consider wolves to be a pest species because they sometimes eat your sheep but for other people, sheep are the real pests, changing an ecosystem with their grazing, reducing habitat for other species. Over time the concept of pest species changed. It expanded to include things like pathogenic microorganisms and parasites and arthropods that carry disease and it also shifted as our understanding of ecology and biodiversity grew. And so species that were once viewed as pests lost that label as their importance to an ecosystem was recognized and others that were once highly valued earned the pest label and then some as they wreaked havoc on the landscape, like rabbits in Australia.
Erin Allmann Updyke	Like rabbits in Australia.
Erin Welsh	And the switch from valued animal to dangerous pest for rabbits in Australia was sudden and nearly complete.
Erin Allmann Updyke	Wow.
Erin Welsh	These guys, we need them gone. In the first few years after their arrival in 1859, people were thrilled, like I said. Hunting them was forbidden for several months out of the year to try to protect their numbers.

Erin Allmann Updyke	Oh my, oh my.
Erin Welsh	And one man was fined £10 for killing a rabbit on someone's property.
Erin Allmann Updyke	Oh my gosh.
Erin Welsh	But within 10 years of their introduction, their rapid spread at hundreds of kilometers a year and enormous population explosion was looked at in absolute horror. As the rabbits spread, they consumed any vegetation visible whether it was grass or shrubs or the bark of a tree, leaving almost nothing left for the prized sheep that many people farmed, let alone the native animal species. Millions of acres in land were forfeited in the late 1800s because they had been rendered useless by rabbits.
Erin Allmann Updyke	Wow.
Erin Welsh	And remember that guy who was fined £10 for killing a rabbit? A few years after that, his son was spending £5,000 a year to try to control the rabbits on his land.
Erin Allmann Updyke	That's so sad.
Erin Welsh	Yeah. And there was also legislation that was introduced in the 1880s requiring all farmers to control the rabbit populations. And if they didn't they would be fined.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. As rabbits spread even into areas that people had said, 'Oh there's no way they can survive here, this surely is not suitable land for rabbits.' People began to realize that physical barriers might be needed. Some stronger efforts that might need to take place. In the early 1900s construction began on a giant rabbit-proof fence in Western Australia and when fence number one was completed in 1907, it was the longest continuous fence in the world.
Erin Allmann Updyke	Wow.
Erin Welsh	It was 1833 kilometers or 1139 miles.
Erin Allmann Updyke	Wow!
Erin Welsh	Yeah. Over 1000. It's a lot.
Erin Allmann Updyke	And supposedly rabbit-proof, huh?
Erin Welsh	Well no, maybe not so much. Later it was I think named the Emu Fence and it did seem to have some effect in other "pest species", quote unquote. But rabbits not so much. When it was constructed it seems that rabbits could be found on both sides of the fence and a fence that long, it would have been really difficult if not impossible to maintain effectively.
Erin Allmann Updyke	Yeah.

Erin Welsh	There were two other rabbit-proof fences that were constructed around the same time and it brought the total length of fencing to over 3200 kilometers or 2000 miles. So a pretty substantial effort. But fences weren't the only thing that people were trying to use to control rabbit populations. Poisons, especially strychnine and arsenic which would be two potential great topics for future episodes-
Erin Allmann Updyke	Yeah, they would be.
Erin Welsh	They were a popular choice, as was ripping which was the term used for tearing up the large underground burrows or warrens that the rabbits were living in. This is one of the only species it seems that creates these large family warrens or burrows which is actually really important to the transmission of myxomatosis. Also predators were introduced like foxes and cats, two other sometimes invasive species.
Erin Allmann Updyke	Oh gosh.
Erin Welsh	But nothing seemed to put a dent in the rapid expansion of rabbits. So let's talk about some of the characteristics of these rabbits that made them so successful at establishing.
Erin Allmann Updyke	Okay.
Erin Welsh	And it's really a mixture of both rabbits themselves and the Australia they entered into in 1859. So first I already mentioned what efficient breeders rabbits are, off the charts.
Erin Allmann Updyke	Yep.
Erin Welsh	Second, many of the places in southern Australia they first moved to were similar in climate to the places they evolved, I mentioned that as well. Third, they can move surprisingly long distances, just individual rabbits but also allowing for the spread. Fourth, when they were brought over, they left most of their pathogens and parasites behind and there didn't seem to be any in Australia that could affect them.
Erin Allmann Updyke	Yeah.
Erin Welsh	So what we call parasite escape.
Erin Allmann Updyke	Always the case with invasive species.
Erin Welsh	It often is, yep. And then there was also predator escape which is something that happens also a lot with other invasive species.
Erin Allmann Updyke	Yep.
Erin Welsh	So for decades many farmers had been poisoning dingoes and other native predators who were considered pests because of livestock at that time.
Erin Allmann Updyke	Oh gosh.
Erin Welsh	And so rabbits entered into this low predator environment. And it also might have taken some time overall for predators to even recognize the rabbits as potential prey. Number six, there were already lots of burrows dug by bettongs, bilbies, and wombats-

Erin Allmann Updyke	I'm sorry. What's a bettong and what's a bilby? I know what a wombat is.
Erin Welsh	My words alone can't do it justice. They are adorable small mammals, you should look them up. I was like these are new mammals I've never heard of there.
Erin Allmann Updyke	I feel like Australia has a lot of mammals I've never heard of. Oh my gosh, I love them.
Erin Welsh	So we just took a break so that Erin could look up bettongs and bilbies we recommend that you do the same because they're adorable.
Erin Allmann Updyke	I love them.
Erin Welsh	They are adorable.
Erin Allmann Updyke	Okay, getting back to it. So the bilbies and the bettongs built these burrows, and the wombats.
Erin Welsh	These burrows. And so then when the rabbits came in they were like, 'Oh, sweet. Free real estate. We're just going to move right in.' And that was that. And number seven, human mediated changes to the landscape like clear cutting of trees and the promotion of pasture lands, this also paved the way for rabbits. And then there's just the fact that it was, like I already said, this attitude of 'Oh we can't wait to have these rabbits, let's promote their growth. Anything that we want to have here to make our lives better is going to be great.'
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. And so all of these factors combined meant that by the time people recognized there might be a problem, it was already way too late.
Erin Allmann Updyke	Yeah.
Erin Welsh	I want to read another quote about rabbit population growth in Australia from the time.
Erin Allmann Updyke	Okay.
Erin Welsh	Quote: "Rabbits overran the town in search of water. They ate the gardens and burrowed under the houses. Shopkeepers had to wire net their premises. The servants at the hotels brushed them off the steps. The inspector of stock hunted two or three from under his bed each morning. School children killed so many on the way to and from school that the mayor had to employ a man with a cart to gather them up."
Erin Allmann Updyke	What?
Erin Welsh	It is still hard for me to imagine.
Erin Allmann Updyke	It is, it's unimaginable. I cannot picture that many little bun buns.

Erin Welsh	But also not everyone saw rabbits as this threatening menace, they were also seen as an opportunity. The profession of rabbiter sprung up when bonuses were introduced for rabbit scalps starting in the late 1800s and rabbiters did pretty well into the 1900s, even after this bonus system was scrapped. In the first few decades of the 20th century, upwards of a million rabbits were killed each year and canned for food to be sent to soldiers fighting in WWI and WWII.
Erin Allmann Updyke	Okay.
Erin Welsh	Although the rabbit industry certainly was raking in some money, the cost of lost farmland and sheep grazing areas, it vastly outweighed that sum. And in the late 1800s the governments of Australia and New Zealand, where rabbits had also been introduced, decided to search for a solution. On April 26th, 1888 these governments got together to establish the Royal Commission of Inquiry into schemes for extermination of rabbits in Australasia.
Erin Allmann Updyke	Wow.
Erin Welsh	Aka the Intercolonial Rabbit Commission. The goal of this commission was to quote "make a full and diligent inquiry as to whether or not the introduction of contagious diseases amongst rabbits for promoting their destruction will be accompanied by danger to human health or to animal life other than rabbits." Pretty interesting.
Erin Allmann Updyke	Yeah.
Erin Welsh	They offered a £25,000 award which in 1998 in Australian dollars, because that's when the book I read was from, was about $2 million Australian dollars. So that's quite a big reward.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. The Elmer Fudd reward.
Erin Allmann Updyke	(laughs) That's funny.
Erin Welsh	Thank you. You sound so surprised.
Erin Allmann Updyke	I forgot about Elmer Fudd.
Erin Welsh	So yeah, anyone who could come up with a successful and feasible strategy for the destruction of rabbits would get this money. Hundreds of people from all over the world wrote in with their different suggestions on how to kill the rabbits. One of these people was none other than Louis Pasteur.
Erin Allmann Updyke	Actually I think I saw that.
Erin Welsh	So, so exciting. And he suggested a chicken cholera virus. But no one, including Pasteur, took home the prize. He was really angry about it. He was like, 'My solution is the best, this is discrimination against the French because the people who were judging were Germans and they have this competition.'
Erin Allmann Updyke	Oh my goodness.

Erin Welsh	It was like over the top for sure. But also his chicken cholera wasn't deadly to rabbits, didn't seem to be super transmissible, and it wasn't restricted to rabbits. So he shouldn't have gotten the prize.
Erin Allmann Updyke	No, it's not a great option.
Erin Welsh	Sorry, Louis. But it was really fascinating to me to read about this introduction of this idea, the concept of using an infectious disease as a method of control, it seemed so early.
Erin Allmann Updyke	Yeah.
Erin Welsh	But actually people have been trying to use other organisms to control pest species for a long time. It's mostly been through the introduction of predators like cats and mongooses and after germ theory, some pathogens as well. And there are many potential benefits to biological control methods over traditional methods of control. For instance, they can be highly specific to just the target species, unlike poisons, they are often the only practical means for control if the species is already established in a large area and over diverse habitat, they can be self perpetuating, and the cost benefit is low, right, you just incubate some virus and release it.
Erin Allmann Updyke	Let's see what happens.
Erin Welsh	And see what happens.
Erin Allmann Updyke	Yeah.
Erin Welsh	But there are also risks. So we now know that biological methods of control are rarely effective or if they are it isn't for very long. They are self perpetuating which means difficult to control, you kind of just let them loose, and there are often unforeseen consequences which can lead to ecological cascades that have enormous long term impacts on an ecosystem.
Erin Allmann Updyke	Yeah.
Erin Welsh	So while biological control methods can potentially solve problems, they can also create new ones. For example, mongooses. This is a classic example, right. Throughout the second half of the 1800s they were introduced to many islands in the Caribbean as well as Hawaii to try to control rats in the sugar cane which were also invasive but instead they just ate iguanas and ground nesting birds and snakes and caused enormous population declines and some extinctions. And that led to a lot of indirect effects and ecological cascades.
Erin Allmann Updyke	Yep.
Erin Welsh	Yeah. I mean there are so many examples of biological control gone wrong.
Erin Allmann Updyke	Oh yeah, look at all of Hawaii.
Erin Welsh	Yeah. Any island at all pretty much is really susceptible to these types of ecological collapses caused by an introduced species.
Erin Allmann Updyke	Yeah.

Erin Welsh	Okay. But since this is the classic story of bio control gone mostly right I would say, I think it's about time that we meet the Myxoma virus in this part of the story. So the Myxoma virus was first observed in 1898 by an infectious disease researcher named Dr. Giuseppe Sanarelli in Uruguay. It's one of the very first viruses described, coming shortly after the word 'virus' was used to describe the filterable, transmissible agent causing tobacco mosaic disease which is what we always learn as the first virus, right.
Erin Allmann Updyke	Yeah.
Erin Welsh	Sanarelli had imported some lab rabbits from Brazil to run some experiments and some of them became super sick with swollen eyes and ears and faces. And he decided to name this disease myxomatosis, 'myxo' from the Greek word for mucus and 'oma' for tumor. Tumor mucus, mucus tumor. This disease seemed especially deadly to the European rabbits in the lab but not the ones native to South America. And for about 10 years after Sanarelli published his findings there was pretty much just silence on the myxomatosis front. But then interest picked up. Other researchers of course grew interested and over time we learned a lot more about the virus, the role of arthropod vectors in its transmission, the reservoirs of the virus in North and South America, how immunity worked, how specific its host range was, and importantly how lethal the virus was in some species like the European rabbit but not others.
Erin Allmann Updyke	Yeah.
Erin Welsh	One of the people who became interested in this rabbit disease was a Brazilian researcher named Dr. Henrique Aragão who spent his career at the Oswaldo Cruz Institute, think back to our Chagas episode.
Erin Allmann Updyke	Yeah.
Erin Welsh	Aragão had worked on identifying the reservoir of Myxoma virus in South America and also the role of arthropod vectors and he was so impressed with the virus' ability to cause disease that in 1918 he wrote to the Australian government saying, 'You should use this virus as a control strategy for your rabbit problem.'
Erin Allmann Updyke	Wow.
Erin Welsh	Which by then the rabbit problem was internationally famous.
Erin Allmann Updyke	Yeah.
Erin Welsh	His suggestion was considered and then dismissed mostly on the grounds that not enough research had been done to determine whether it would be effective or whether the virus could be dangerous to humans or other animals.
Erin Allmann Updyke	Okay.

Erin Welsh	But while it got the official no at first, the idea wasn't entirely dropped, especially since some people were just getting so desperate for anything to work. And so in 1927 a series of experiments were carried out to see how transmissible and how specific it was. Could this actually be something we could use? The results weren't encouraging. Basically it didn't seem like it would spread among rabbits easily and even if it did it was likely to result in a situation where rabbits would evolve resistance or tolerance and the virus would decrease in virulence. And researchers still couldn't be sure that it wouldn't spread to the native animal species or humans and cause a huge catastrophe. All fair points. And the idea was shelved yet again.
	And that could have been the last time that we ever heard about myxomatosis if Dr. Jean McNamara hadn't come across the idea totally independently from Dr. Aragão. Dr. McNamara was a pediatrician from Australia who in 1933 was awarded a fellowship to study polio in New York. While there she visited the lab of Dr. Richard Shope whose name may sound familiar from our HPV episode. He discovered the Shope papilloma virus that had given rise to the jackalope myth and was one of the first people to link viruses to causing cancer.
Erin Allmann Updyke	Oh yeah! Jackalopes, okay.
Erin Welsh	Yeah. But at the time of McNamara's visit, Shope was working on a vaccine against Myxoma virus using the immunologically-related fibroma virus. He showed McNamara the rabbits that were infected with myxoma and when she saw how lethal it was she was like, 'This could be useful.' So she wrote home to her family, quote: "I had a lovely day out at Princeton, the branch of animal and plant pathology. There is a man there I would love to take home to work on our animal diseases. Shope is his name and he has something which kills rabbits though he has not tried ours. I'm going to send some to Ivan to give him the chance to become famous by killing off the rabbits." I love that. And so she sent some samples of the Myxoma virus, they were destroyed upon arrival because things had been ramped up a little bit more seriously, like let's not introduced species and potential pathogens.
Erin Allmann Updyke	Oh okay.
Erin Welsh	But nevertheless she persisted and eventually convinced the Australian government to set up some experiments commissioning Dr. Charles Martin in Cambridge to examine the virus' potential. Martin's experiments showed more promise than the 1927 ones but there was still a great deal of hesitation to introduce it to Australia. Not just on the grounds that it might not work but that if it did work there might be unintended consequences. But just like last time more field experiments were set up and just like last time they weren't overwhelmingly successful and maybe that really would have been the end of it.
	But the landscape which was already drastically altered by years of rabbit population growth, it had grown even more rabbit infested during WWII when so many people left to fight in the war and rabbit control on some of these farms slipped, there was no way, you just didn't have the human power to control the rabbit populations. And so by the end of the 1940s people were desperate for something to reduce rabbit numbers and McNamara was like, 'Okay, I'm gonna say it again. Myxomatosis. The last field trials were wrong, they were done in the wrong place, there were no mosquitoes there, you need to do it again.' And it turns out that the fourth or the fifth or whatever time it was, I've lost count, this time was the charm.
Erin Allmann Updyke	Oh yeah.

Erin Welsh	In 1950 field experiments were set up where rabbits in different areas were inoculated with the virus and then let loose to bring it back to the burrow and the rabbits living in there. The first year results weren't too impressive and the researchers in charge, Francis Ratcliffe and Lionel Bull, Francis Ratcliffe by the way was the author of the second quote that we read in the intro, they nearly pulled the plug. But then reports of sick rabbits began to come in from southeastern Australia in areas where the virus had been released. In some places over 90% of the rabbits had died within a month of the virus showing up.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah.
Erin Allmann Updyke	90% in a month.
Erin Welsh	In a month. It's again hard to imagine.
Erin Allmann Updyke	Yeah.
Erin Welsh	So it seems that heavy rains had led to a big mosquito season and the mosquitoes were able to pick up the slack where direct contact among the rabbits alone had failed. And around this time is when Dr. Frank Fenner, who's one of the authors of that great book that I read about this, he joined the team as the virologist. And Fenner would go on to uncover so much about viral evolution and resistance and also played a major role in the eradication of smallpox in Australia. So he was kind of a big name in microbiology out there.
Erin Allmann Updyke	Yeah.
Erin Welsh	So everything seemed to be going great with the Myxoma virus. People were celebrating over the corpses of millions of rabbits in anticipation of the return of vegetation.
Erin Allmann Updyke	Wow.
Erin Welsh	But then there was a development that almost brought the whole thing to a stop. An outbreak of encephalitis cases of unknown cause in humans appeared alongside the rise in myxomatosis in the rabbits which made people terrified that okay this virus that you introduced is now infecting and killing humans. A few researchers working on the Myxoma virus knew that it couldn't be the cause of this illness. And so to reassure the public, researchers, doctors Frank Fenner, Macfarlane Burnet, and Clunies Ross injected themselves with Myxoma virus and publicized the outcome which was nothing but a slight red spot near the site of injection.
Erin Allmann Updyke	Wow.
Erin Welsh	No encephalitis.
Erin Allmann Updyke	So what was causing the encephalitis?
Erin Welsh	It was actually found to be a relative of the Japanese encephalitis virus. It was given the name Murray Valley encephalitis virus after where the outbreak took place and it's transmitted by mosquitoes.

Erin Allmann Updyke	Okay. Mosquitoes! Which were so prevalent, which were also transmitting myxomatosis. Oh my gosh I love it, Erin. I don't love that people got encephalitis what a story.
Erin Welsh	No but all the pieces fall into place, yeah.
Erin Allmann Updyke	Oh my gosh, Erin.
Erin Welsh	Yeah. 1951 though was the first year to show real promise in myxomatosis as a control agent for rabbits. But even though things were looking good, the disease seemed to be largely restricted to areas along rivers and lakes. But the next year it exploded far beyond that. And with like you said this estimated case fatality rate of 99.8%, it obliterated obliterated any rabbit population it came into contact with.
Erin Allmann Updyke	Wow.
Erin Welsh	And within a few years of the virus' release Australia's rabbit population dropped from an estimated 600 million to 100 million.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. And this drop in population was not of course consistent or equal across the entirety of the rabbit-infested areas due to differences in climate. So mosquitoes might not breed as well in more hot and arid regions and so they didn't experience as much of a decline. And also despite how huge an impact the virus was having on the rabbits, researchers on the project knew that it was just sort of the honeymoon phase. It was only a matter of time before resistance popped up and attenuation crept in. And they were expecting it to happen eventually but it showed up a lot faster than they thought, years and years faster. By 1952 and 1953, so two and three years after the virus was introduced, less deadly strains of the Myxoma virus or attenuated strains had been discovered in some of the wild rabbits. 2-3 years after.
Erin Allmann Updyke	Whoa.
Erin Welsh	And later research showed that attenuated strains had popped up independently all over the continent during the 1950s. And so let's talk about the trend towards decreasing virulence. Why was it evolving to become less deadly? Well if you're a virus that's transmitted by direct contact and you kill your host before your host can pass it on, you won't survive as the virus. The strains that will survive are those that are less deadly where the host maybe stays alive a few days longer to infect a few more rabbits. And with the fast rabbit reproduction cycle and how many there were, this evolution happened on a much faster time scale than people expected. And for their part the severe bottleneck in rabbits meant that genetic resistance would be selected for, those were the ones that survived to reproduce and pass along resistance alleles.
	Genetic resistance in rabbits also showed up in the mid 1950s, also decades ahead of predictions. And some fascinating lessons were learned about host pathogen coevolution. In terms of the virus, although the general trend was towards decreased virulence, a study examining trends in viral evolution across Australia and Europe where it had been released showed that there were multiple different evolutionary pathways the virus had taken. Eventually all of these Myxoma virus strains seem to have evolved to be less deadly. So it converged on this phenotype of being less deadly. But if you looked at them genetically, they didn't show those same patterns of genetic alterations, right. They weren't constrained by evolution in that way.

Erin Allmann Updyke	Yeah. They did it in like a bunch of different ways.
Erin Welsh	So they got to the end result, they took a bunch of different paths to get there. It's so interesting.
Erin Allmann Updyke	I love it, yeah.
Erin Welsh	And research in the 1990s showed that although in general there had been a trend towards less deadly strains, there were some strains that seemed to have evolved way back to super high virulence. And those highly virulent strains had apparently been selected for because they could overcome the rabbits' resistance, they were the ones that were causing lesions where the virus could spread, whereas the less virulent ones were just kind of existing in the rabbits and then petering out.
Erin Allmann Updyke	Right. Because it was this interplay between this rapidly evolving virus and an animal with a very short generation time that was rapidly evolving resistance.
Erin Welsh	It's so interesting and I think it really also makes us rethink, I feel like there's especially in COVID times been this assumption that all pathogens evolved to be less deadly, they evolved to be benign and that is absolutely not the case. It really is more about transmission.
Erin Allmann Updyke	Yeah, exactly. They evolved to be optimally transmitted which could vary depending on how something is transmitted and how their host reacts to it and how much resistance they have. Oh my goodness, Erin.
Erin Welsh	Yeah. There's no hard and fast rule which is what we love about ecology.
Erin Allmann Updyke	I know.
Erin Welsh	Okay. So all of that is super fascinating but there's also some really interesting tidbits from the rabbit side of things too.
Erin Allmann Updyke	Yes.
Erin Welsh	First, a study published in 2019 showed that in rabbit populations that had been exposed to Myxoma virus across Australia, France, and the United Kingdom over the past 60 years, the same alleles in the rabbits had been selected for and that most of the alleles were immunity-related genes.
Erin Allmann Updyke	Interesting.
Erin Welsh	Yeah. And so the rabbits showed a common genetic basis for the evolution of resistance but the virus did not.
Erin Allmann Updyke	Oh my gosh, that's cool.
Erin Welsh	Isn't that really fascinating? So there was existing genetic variation in all of these rabbit populations all around the world and that certain alleles were the ones that were present in all of these populations from the beginning were the ones selected for.
Erin Allmann Updyke	Yeah. Oh my gosh. Yeah, that is interesting.

Erin Welsh	Super cool.
Erin Allmann Updyke	Yeah.
Erin Welsh	And then there's one more thing.
Erin Allmann Updyke	Okay.
Erin Welsh	And so this is something called a sire effect and it was found about rabbit resistance in these myxomatosis rabbits. Okay. So essentially when a doe, an unselected doe, female rabbit, mated with a buck that had recovered from myxomatosis, had been infected and recovered, the kittens were more resistant than expected. The risk of death had been reduced by about 25% .
Erin Allmann Updyke	But only in that direction? Only an unselected doe and a resistant buck but not the other way around?
Erin Welsh	At least I didn't see... I would assume that there would be some maternal antibodies passed in but the doe is unselected and then the buck had been exposed and it's not just in the litter that was produced when the doe and that buck had mated but also future offspring.
Erin Allmann Updyke	Like of that doe with other bucks?
Erin Welsh	Yeah. So even if a doe later mates with a buck that was not immune, if she had previously made it with a recovered buck within 7 months of his infection, those offspring are also partially immune.
Erin Allmann Updyke	What?
Erin Welsh	I know. Okay, I'll post more papers about this. It's really fascinating and it's probably something to do with epigeneticS.
Erin Allmann Updyke	It's gotta be epigenetics.
Erin Welsh	It doesn't seem the mechanism is known.
Erin Allmann Updyke	Yeah. Oh my God, that is really bizarre.
Erin Welsh	It just shows also this is such an incredible system to have studied because there's so much known about it. You can watch these things happen in real time. Just the more you dig, the more you find, the more questions you have.
Erin Allmann Updyke	Yeah, I have so many.

Erin Welsh	Okay, so despite the increasing resistance in rabbits and decrease in virulence in the virus, rabbit populations continued to decline or at least even out throughout the 1960s. And part of that was due to the introduction of the European rabbit flea in 1966 which was even more successful as a mechanical vector than the mosquito. And it was also somewhat due to the reactivation of the virus in rabbits with lesions which allowed it to spread to rabbits who were newly susceptible. And by the 1980s rabbit populations were under pretty good control in some places, not eliminated by any means but at least more manageable maybe. But in drier and hotter regions where mosquitoes weren't as prevalent and the European flea didn't survive well, rabbits were still a huge problem. And so the Spanish rabbit flea which was adapted to that type of drier and hotter environment was introduced, also was decently successful. But the story of rabbits in Australia was not over and let's be honest, it may never be. Rabbit populations had begun to recover despite all of these interventions and by 1991 it was close to half of the pre-myxomatosis population.
Erin Allmann Updyke	Whoa.
Erin Welsh	Yeah. The rabbit hemorrhagic disease virus, a calicivirus also incredibly specific to rabbits, was explored as a possible rabbit control agent in the 1990s after first being discovered in China in 1984. And in 1995 it actually escaped into wild rabbit populations in Australia from an island where field studies were taking place. So it was like whoopsie!
Erin Allmann Updyke	Yeah.
Erin Welsh	But it had that would have been planned to be released anyway, it was just a little ahead of schedule.
Erin Allmann Updyke	A little early, yeah.
Erin Welsh	And the rabbit hemorrhagic disease virus proved to be pretty successful as a control agent especially in those hotter, drier areas where control had previously been challenging. And there have been repeated introductions of that virus since. So I've presented the story of rabbits in Australia as one of a villain, rabbits, and a hero, the Myxoma virus. But as always it's way more nuanced than that and those roles could easily be swapped in other places where rabbits aren't considered pests. It's true that these introduced rabbits did and continue to do tremendous damage to ecosystems in Australia by reducing overall vegetation and destroying new plant growth including trees, they have eliminated some plant species such as acacia trees and some species of grass in some areas, and the overall reduction in vegetation has also led to the erosion of topsoil which has impacts on the establishment of new plants, drought tolerance, potential for wind storms and wildfires, and further destruction of habitat.
	This destruction is also not equal across Australia. For instance, in arid rangelands where plants often have long lifespans and very slow growth periods, rabbits eat seedlings and destroy plants that were decades old. The recovery times for these areas is much, much longer than others and it's unclear whether complete recovery is even possible. And while initially the concern was primarily for the impact of rabbits on sheep or other livestock, many other species suffered at this destruction of habitat. Rabbits limited resources from many other herbivores and out-competed them, in some cases completely driving out native burrowing herbivores from rabbit-infested areas like bilbies, bettongs, common wombats, spectacled hare wallaby, western gray kangaroo, and southern hairy-nosed wombat.
Erin Allmann Updyke	Oh my goodness.

Erin Welsh	And then there are many social and cultural aspects of rabbit control. Some feel the introduction of Myxoma virus and rabbit hemorrhagic disease virus is inhumane and efforts have been made towards finding a better way to achieve reduced rabbit populations, like maybe through sterility. And there are also many people whose livelihood relies on or is supplemented by hunting rabbits for meat or pelts. And there have been calls to prevent the introduction of rabbit hemorrhagic disease virus in some areas where rabbits are used for this purpose. These aspects have led to questions of how to weigh the role of the rabbit as a resource against its role as an environmental pest which is a conflict that comes up often in questions of conservation. At this point, the war on rabbits in Australia has been going on for nearly 160 years. These introduced rabbits now occupy 70% of the continent, impact over 300 native plant and animal species, and cost an estimated 200 million Australian dollars every year in lost production.
Erin Allmann Updyke	Wow.
Erin Welsh	Myxomatosis has been used as a control agent for rabbits in several other countries and its story, as well as that of invasive rabbits, is likely far from over. But let's talk more about where we stand today with myxomatosis. What are those other rabbit populations impacted? Should we be worried? What's going on?
Erin Allmann Updyke	Let's get into all of that after a quick break.
TPWKY	(transition theme)
Erin Allmann Updyke	So Myxoma virus today. Like you said Erin, it is not only a story of Australia. Myxoma virus was also introduced in France to control rabbit populations in France and from there it spread across Europe and into the UK. So Myxoma virus is now found pretty well distributed around the world, it's endemic of course to North and South America but it's also found across Europe into the UK and of course in Australia. And at this point in much of the world where Myxoma virus has been introduced, it has sort of established itself as an endemic pathogen now. It causes occasional epizootics and primarily it is these medium virulence strains that tend to predominate. So as it turns out, as this virulent kind of decreased, it was also found that when strains became really mild where they caused very little disease and rabbits could recover really quickly, they only had transmissible titers for a very short period of time, so it wasn't very infectious.
	And like you talked about a lot Erin, when rabbits died very quickly from infection they were also really poor sources of infection which in the case of Myxoma virus isn't very surprising since something like a mosquito or a flea doesn't tend to feed from dead things and rabbits don't hang out with their dead friends' bodies for very long. So both these highly virulent strains that wipe out rabbits very quickly and these very, very mild strains where rabbits survive infection and recover, both of those tend to be poor sources of virus for transmission. And so it's these medium virulent strains, often called 3 or 4, there's a grading scale. So it's these grade 3 and 4 strains that tend to predominate.
	But at the same time more virulent strains, like you mentioned Erin, in some populations where rabbits have developed a lot of resistance or evolved a lot of resistance, these more virulent strains still exist. And so in different areas geographically, all of these different types of strains can actually coexist which is so fascinating. And if you think about it on an even larger scale, like the large scale evolution and ecology of this virus, it's not just the intrinsic virulence of the virus and the resistance of the rabbits, it's also larger scale things like weather, right. Turns out that cold weather increases effective virulence and warmer temperatures make it easier for rabbits to survive infection. Who knew?

Erin Welsh	It's just so many variables.
Erin Allmann Updyke	So many things.
Erin Welsh	Yeah.
Erin Allmann Updyke	Nutritional status of the little bun buns, whether they have any co-infections or other parasites that they're dealing with, predator abundance because especially in the wild predators are going to tend to remove sick rabbits that when you're looking at experimental trials, those rabbits might have survived for longer. It depends on seasonal influences. There are so many things that contribute to this continually evolving story of the co-evolution of Myxoma virus and rabbits.
Erin Welsh	It's so true. It really excites the little ecology part of my brain where I'm like, 'Well what about this? But what about that? How do you put this into a model?' And then I'm like no, I don't want to do any more modeling. No more.
Erin Allmann Updyke	Yes. Don't worry, lots of people are doing the modeling Erin, we just get to read about it.
Erin Welsh	Thank goodness. Thank goodness other people are doing the models. But I think this topic almost more than any other one we've covered just was such a perfect example of how this is truly a snapshot. This is constantly evolving. All of the moving parts of this are constantly evolving. What's climate change going to do to the areas...? Are things going to get hotter and drier and there are going to be no more mosquitoes at all and the Spanish rabbit flea can't survive? What's going to happen?
Erin Allmann Updyke	Yeah. Right, I know. And it does seem, you asked earlier on Erin how many other species of rabbits and hares are we talking about here? And I don't know exactly but I do know that there are more and more case reports and studies showing that for example the Iberian hare has now been found to be infected with myxomatosis and have outbreaks that have caused deaths of hundreds of Iberian hares which are a totally different species in the Iberian peninsula. And so how much more could this spread? We don't know yet.
Erin Welsh	Yeah.
Erin Allmann Updyke	Right? How do we try and keep it under control? There are vaccines which is great. It seems from what I could tell there's two different groups of vaccines that exist, both of them are live attenuated vaccines, so live virus that are grown in a lab to be not as virulent. One of them comes actually from the Shope fibroma virus which again is that related virus that doesn't cause severe disease, just causes one big fibroma, and it kind of tends to cause some cross protection against Myxoma virus. Think cowpox inoculation and smallpox protection, same idea, right. And then there are also live attenuated vaccines that are made from various strains of the Myxoma virus, these tend to produce a stronger and longer lasting immune response but because they're from Myxoma virus can also have the potential for mild disease. So from what I could gather in settings where you're raising a lot of rabbits, whether it's for domestic rabbits or for pelts or whatever it is, these two vaccines are often used in combination from what I can tell. So one dose of the Shope fibroma virus and then a few months later the Myxoma virus so that you have really good protection.

	And the last thing that I want to just briefly mention because first of all this blew my mind and I think it's incredibly cool but also I'm mentioning it because inevitably people will ask how does this relate to my life in specific as a human being who maybe doesn't care that much about rabbits? Fair enough. Let me tell you because this is incredible. So remember that little tiny spoiler I dropped at the top that Myxoma virus can replicate in a wide variety of cells in vitro and is very adept at replicating in human cancer cells? Well turns out there's a lot of research into using Myxoma virus as a cancer-fighting viral infection essentially, something that could potentially be used in combination with chemotherapy to treat various cancers.
Erin Welsh	That is fascinating.
Erin Allmann Updyke	Fascinating, Erin.
Erin Welsh	Where are we in that research?
Erin Allmann Updyke	Very early stages.
Erin Welsh	Okay.
Erin Allmann Updyke	There's also work being done to investigate Myxoma virus as a treatment for chronic rejection of things like organ transplants and other diseases that have a chronic vascular inflammatory component because of all of its immunosuppressive properties.
Erin Welsh	Oh, that's interesting. It's kind of like the way there's been research into human parasite infections.
Erin Allmann Updyke	Yes, exactly, yeah.
Erin Welsh	As immunosuppressants.
Erin Allmann Updyke	Yeah. So very early stages. Actually the paper that I found that went into this was actually kind of old at this point and I didn't find anything more up to date. But we'll post it and y'all can do your own research because I think it's really a cool future direction.
Erin Welsh	See it's one more lesson, one person's pest is another person's pet or potential cancer curing microbe.
Erin Allmann Updyke	Exactly, exactly. I love it. And that is myxomatosis.
Erin Welsh	What a journey.
Erin Allmann Updyke	Seriously. I think this has just been so interesting.
Erin Welsh	It really has been. And do you know what else is so interesting that I feel like we only talked about just a little bit in this episode?
Erin Allmann Updyke	What?
Erin Welsh	The rabbit hemorrhagic disease virus.

Erin Allmann Updyke	The rabbit hemorrhagic disease virus! We barely even got into it.
Erin Welsh	It's true, we barely did. And if you're kind of bummed that we didn't really talk about it as much as you wanted us to maybe, you're in luck because next week you can hear all about it when we interview Dr. Robyn Hall who is a veterinary virologist, what a cool title, at CSIRO Which is the Commonwealth Scientific and Industrial Research Organization in Australia.
Erin Allmann Updyke	It's going to be so awesome.
Erin Welsh	I am so excited about it.
Erin Allmann Updyke	Yeah, me too. Okay. But for now, sources?
Erin Welsh	Sources. I mentioned the book 'Biological Control of Vertebrate Pests' earlier by Fenner and Fantini. And I also watched a couple of really fascinating YouTube videos on this, one is called '160-year battle against one of Australia's worst invasives' and another is called 'The rabbit in Australia'. And I will post links to those as well as to a bunch of papers also that I read.
Erin Allmann Updyke	I have a number of papers. Two of my favorites just about the Myxoma virus itself were both by Peter Kerr one from 2012, one from 2015. I will post both of those. And then that paper, it was titled 'The current status and future directions of Myxoma virus: a master in immune evasion', that was the 2011 paper that really detailed kind of the future possible directions of Myxoma virus that I thought was so interesting. We will post the sources from this episode and all of our episodes on our website thispodcastwillkillyou.com.
Erin Welsh	We will. Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	Thank you to Exactly Right Media.
Erin Welsh	And thank you to you, listeners. We hope that you liked this one and that you thought it was interesting.
Erin Allmann Updyke	I feel like you did. I feel like you did. I hope so.
Erin Welsh	Yeah. Let us know.
Erin Allmann Updyke	And a special thanks to our patrons, we can't express how much we love your support.
Erin Welsh	It's true, we love you. Well until next time, wash your hands.
Erin Allmann Updyke	Ya filthy animals.